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Is pharmaceutical R&D just a game of chance or can strategy make a difference?

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The pharmaceutical industry is currently experiencing turbulent, yet exciting times. Despite widely expressed negative sentiments regarding productivity there are now signs that innovation could yet win the day and bring a fresh wave of breakthrough drugs. Nowhere is this truer than for oncology, which previously was dominated by cytotoxic drugs. Today, however, this field shows exciting progress with the emergence of kinase inhibitors, as well as various antibody-based mechanistic approaches. Similarly, new drug mechanisms have transformed HIV therapy. Are these chance events, or have they come about through strategy? Here, we argue that a complex interplay of chance and strategy is at work in pharmaceutical R&D, separated in time by 10 years or more.

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▼ Widely expressed negative sentiments about the ability of the pharmaceutical industry to innovate [1], together with many external forces, have led to great pressure on the industry. However, there are now signs of a fresh wave of drugs that could make a significant difference to healthcare. This is particularly true for oncology, which previously was dominated by cytotoxic drugs and was a quagmire for selective, mechanism-based approaches. Today, this field shows exciting progress: kinase inhibitors, such as Gleevec [2] and Iressa [3] have emerged, as well as various antibody-based mechanistic approaches. Similarly, new drug mechanisms have transformed HIV therapy since the discovery of the AIDS virus in the early 1980s.

Nowhere are strategic decisions more difficult than in industries where cause and effect relationships are separated by decades. Much has been said about the strategic dilemmas in hyper-competitive industries (see Box 1), with their extremely rapid product innovation cycles and the associated unpredictability of markets [4]. Less analysis has gone into the strategic environment of 'ultra slow' industries, such as the pharmaceutical industry, where 'the time to bring a new product to market takes many years, during which time that market may change substantially and unpredictably'. 'Ultra slow' is not the same as 'slow-cycle' industries. Slow cycle industries are those, where '*economic forces are slow to drive economic profit to zero*', and have been well discussed in strategy articles, unfortunately often using pharmaceuticals as (inappropriate) case examples. Slow cycle implies slow-moving, uncompetitive markets, which make rapid innovation cycles unnecessary. By contrast, in 'ultra slow' industries, rapid innovation cycles, even if required, are physically unachievable. Uncompetitive markets have long ceased to exist for pharmaceuticals; they are in fact highly competitive, with entry barriers gradually eroding through political interventions, and incrementalism leading to fierce competition despite patent protection of drugs.

Ultra slow industries, such as oil exploration, new aircraft designs, new medicines or large electronic weapons systems, share long product discovery and development times, which drive high costs. They also share the 'chance' element, which drives high risk and (potentially) high profit margins. In addition, they normally share an (impatient) investor or customer base. Such stakeholders often struggle to make realistic assessments of current and future performance from limited information. The main sources are imperfect surrogate markers of productivity, such as numbers and types of ongoing projects, peak sales projections, strategy statements and analyst reports.

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Given this context, any real or perceived difficulty to achieve profitable new products, can start a cycle of gloomy analyst prognoses, such as evidenced in recent years in the pharmaceutical industry. But is this so called 'innovation deficit' real? Here, we describe recent developments in fields such as oncology and HIV, and how they might be predictive of the next wave of products, derived from strategies set many years ago. We explore how strategy and luck form a complex relationship, and how strategic groups in the pharmaceutical industry use different strategies to reduce the chance element.

What is strategy?

A great variety of definitions exist of what strategy is [5]. Here, we borrow from a military definition. The late US military strategist Col. Boyd defines strategy as '*a basis for realizing some aim or purpose in an unfolding and often unforeseen world*' (Boyd, J.R. United States Armed Forces; http://www.belisarius.com). This definition speaks of two requirements so that strategy becomes more than tactics or randomness. First, there is an objective to be achieved. Second, the environment in which this is to be achieved is uncertain and changing. Such uncertainty can come from incomplete information and non-predictable events. Both are key features of ultra-slow industries as described previously. By this definition, strategy is simply those actions or decisions taken that increase the probability of achieving the desired objective(s). In turn, that means strategy is about changing those factors, which drive unfavourable odds. Undoubtedly, in high risk, high reward industries, such as the pharmaceutical sector, the ability to reduce the odds is linked to long-term survival. Therefore, more firms within strategic groups that rely on 'odds-reducing' strategies prosper long-term (such as generics houses, or big pharmaceutical firms), compared with firms in strategic groups that rely mostly on chance (such as many small biotechnology start-ups) (Figure 1).

Where does the chance element in ultra-slow industries come from?

To understand how strategy and chance interact, it is important to consider the various sources that introduce unexpected risks and opportunities. The main sources are:

- Failure of products or concepts before or after they reach the market
- New discoveries, which make unfeasible projects technically feasible
- Changes in markets, which render the new product obsolete, or unexpectedly profitable
- Imperfect internal project/portfolio decisions
- Presence/absence of a project champion or key innovator
- Slow feedback loops, which make R&D more random

Box 1. Glossary of terms

- **Druggable targets:** Those molecular targets amenable to intervention by small, synthetic chemicals, (normally) designed for oral absorption.
- **Hyper competitive:** Industries, where radical innovation takes place frequently and unpredictably. This leads to economic forces, which drive profit margins of new products rapidly to zero.
- **Incrementalism:** The attempt to improve upon an existing treatment (on the market) via research and development centred on chemical modification of drugs within the same drug class (same molecular target).
- **Slow cycle:** Those industries, where economic forces are slow to drive economic profit to zero. Normally, there are high entry barriers and little competition, or monopolies.
- **Strategic group:** A cluster of firms within an industry, which follow a similar strategy, and/or share similar internal and external conditions (size, markets).
- **Strategy:** Defined here as the basis for realizing some aim or purpose in an unpredictable world.
- **Systems biology:** an integrated way, using computational models and pathway interference (experiments), of studying the effects of individual pathways (or drugs, targeting these pathways) on the behaviour of a whole organism or an organ/tissue.
- **Ultra slow:** Those industries, where regulatory or technical demands prolong the time to bring a new product to market by many years.

In light of these strategic dilemmas, it is no coincidence that size matters. Size can be used to spread risk, and allows greater flexibility through the ability to afford more than one strategic option. Flexibility is of increasing importance since strategic decisions have to be taken with incomplete information about the future environment. In this respect, ultra-slow industries resemble hyper-competitive ones, which demand a high degree of strategic flexibility and innovation. However, changing the strategic direction

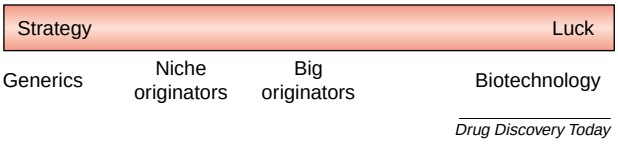

Figure 1. Location of strategic groups of the pharmaceutical industry along a continuum of reliance on luck versus reliance on strategy. The further towards either end of the continuum the firms are located, the more they are locked into specific skills bases and capital assets.

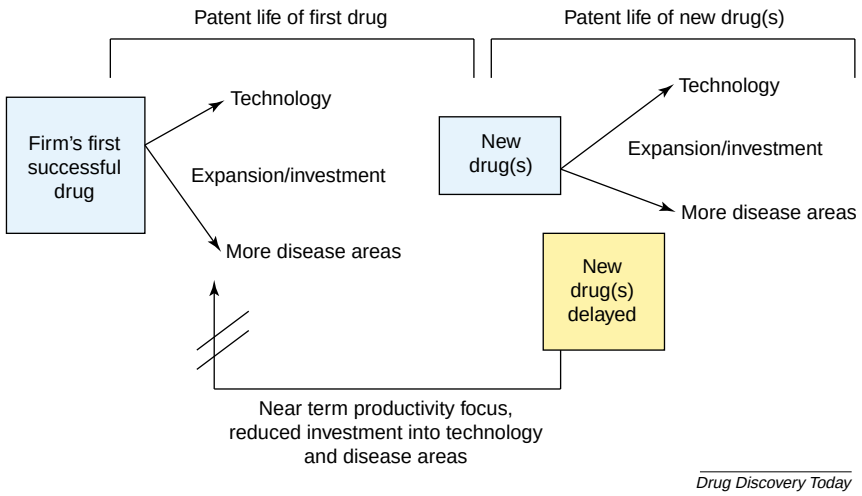

Figure 2. Expansion pattern of new pharmaceutical companies. Following the first successful product of a firm to the market, the incoming revenue stream during the patent life of the drug is normally used to invest in expansion. This expansion could be into technologies, additional disease areas, or both. These new disease areas or technologies go through a trial-and-error period, which delays the already slow R&D timelines further (by up to a decade, resulting in up to 20 years to produce a new product in a new disease area or with a new technology, such as HTS). As a result, patent life and revenue streams of the initial drug could be running out before a new product can be launched. If this happens, a downward spiral could lead to external and internal pressures that lead to a conservative, near-termist, anti-innovative environment. By contrast, if new drugs are launched successfully before revenue streams dry up, then a virtuous cycle can unfold, leading to more investment and innovation.

in ultra-slow industries is difficult, costly and slow to impact. Ironically, it is just as detrimental to change direction too often, as it is to not change at all. Unfortunately, the time lag between strategy and outcome means that ultra-slow industries can not assess the success or failure of their strategies easily to inform decisions on strategic direction. Nor is it likely that those who set such strategies will still be around to suffer or celebrate the results.

Strategies to reduce the odds

Taking 'attrition early' is a mantra in pharmaceutical R&D, which speaks to the need to find out with less cost, whether projects will fail. Unfortunately, finding out earlier that nothing works still leaves nothing at the end. The art of managing the risk of unfavourable chance events lies in having portfolio strategies and selection criteria that weigh the dice towards success at the outset. This means moving from a mindset of selecting losers in a war of attrition, to selecting winners before projects start, which mandates cross-functional portfolio strategies.

Big pharmaceutical companies all have similar access to science and technologies. First-mover advantage due to knowledge sharing is limited to a few years at best. The much vaunted and hyped 'technical edge' given by investment in exclusive technology or intellectual property on drugs and knowledge is actually eroded quickly in the cycle time of ultra-slow industries. Most firms perform R&D in similar disease areas. So what differentiates an individual firm? On closer inspection there are two key areas that make a company unique – how the firm is structured, and how strategic decisions are made. Large pharmaceutical companies can structure themselves as a collection of biotechnology sites, which compete with each other and external biotechnology companies to supply compounds into a centralized development organization (a model that is favoured by GSK; http://www.gsk.com), or they can form a collection of medium sized, fully integrated, semi-collaborative pharmaceutical sites (a model favoured by Pfizer; http://www.pfizer.com). Such structural choices are strategic decisions and differentiate one firm from another. Other decisions involve the portfolio. Hundreds of R&D decisions are made to get one drug to market. The seniority level, accuracy and speed with which such decisions are made, and how effective they are in reducing the odds, determines whether new investment succeeds before the revenues from existing franchise diminish (Figure 2).

Validating new mechanistic families is the lifeblood of pharmaceutical innovation, from which more and better drugs arise. Once the mine has been opened, the digging becomes easier [6]. Those firms, who follow such pioneers, can exploit the exposed seams much more strategically and at lower risk, often with much better results. It is the companies that expose the seams that carry much of the risk of the chance element of R&D. It is perhaps ironic that those strategic groups that are least able to afford failures are also those exposed to the highest odds (Figure 3). They are the small pharmaceutical and biotechnology firms, who invest a major proportion of their total capital in digging for breakthrough discoveries. Imclone (http://www.imclone.com) for instance, even though it was partnering with other, bigger partners, had a difficult time convincing its investors of the value of its lead product, Erbitux. In the end, it needed positive clinical results from a competitor compound developed against the same drug target, to restore some confidence in Erbitux. This is a classic dilemma for biotechnology firms; large pharmaceutical

partners prefer to license technologies and science that carry some evidence of validity, for reasons outlined in Figure 2. The demise of Fisons, for example, whose R&D was taken over by Astra Zeneca in 1995 (http://www.astrazeneca.com), was in large measure due to a lack of a successful pipeline, following the breakthrough drug, Intal. The ramp-up in scale following a single product to competing in several therapeutic areas is a particularly vulnerable time (Figure 2). The patent life of the single product really only allows the immediate right choice of therapeutic areas and projects (or technology) to lead to success. Many small firms simply do not make the right choices quickly enough, and some larger firms make too many wrong choices and find that time runs out.

However, not all companies are, or need to be, large to cope with risk successfully. If uncertainty can be reduced through strategy, then size can reduce proportionally. Some strategic groups consist of smaller, but also larger companies (in the case of generics), which have such strategies in play. For instance, the odds can be reduced by generic imitation, by serving more predictable niche markets with me-too proprietary products, or by specializing in elements of R&D with better odds, such as delivery technologies. Of these strategic groups, it is only the niche marketers who remain fully integrated and carry reduced risks.

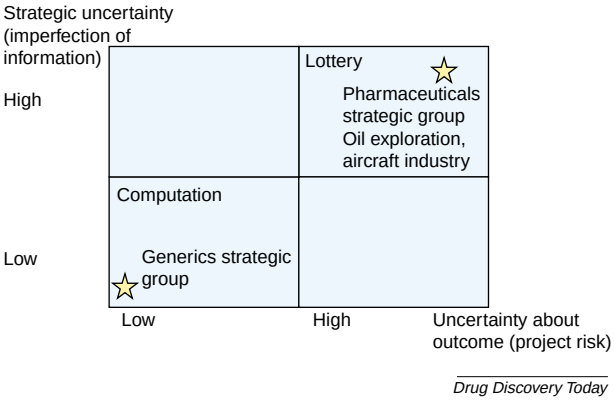

Figure 3. Clustering of different industries and strategic groups along the risk versus uncertainty axis. Ultra-low industries are faced with high strategic uncertainty caused by delayed feedback loops. At the same time they face high outcome uncertainties (changing markets, technical hurdles). Together, these factors create an environment of randomness (lottery). It is this randomness that R&D strategies try to reduce. Alternatively, it is possible to 'select' an environment, for example, by locating a business in the high certainty, low risk quadrant (e.g. generics). Adapted from reference [14].

Pharmaceutical strategies and innovation

Innovation in small companies

Small biotechnology firms are frequently regarded as being more innovative than larger companies. However, although this might be true for the combined pool of the hundreds of small ventures, the individual company is not necessarily going to produce a new medicine. The major risk such small firms carry is whether the innovative direction taken proves to be right. The large asset base required for R&D in ultra-slow industries, tend to lock such firms into one strategic direction, whether or not it is the right one. There are numerous examples of smaller innovators struggling for survival, when the one compound in Phase II fails to deliver on its promise, or larger partners can not be found to co-develop a niche (or unproven) product. Yet, the example of Genentech (http://www.gene.com) shows, that those small firms investing in a successful strategy can open new strategic groups and become a leader within it. Protein therapeutics, for instance, have proven so successful, that big pharmaceutical companies have incorporated it into their strategies. Today, such drugs (including antibodies) have a market potential greater than US$20 billion dollars per year (see http://www.i-s-b.org/business/rec_sales.htm) and growing. The ratio of protein-based drugs amongst new drug applications is also on the increase. Interestingly, the basis for this remarkable success story in recombinant drugs was laid in the 1980s, while the basic science goes as far back as the discovery of DNA in the 1940s, or even earlier (Friedrich Miescher in 1869). It has taken two decades for this new R&D strategy to truly come to fruition commercially. A key risk-reducing strategy of small companies is to reduce the cycle time, by specializing in parts of the R&D process. This has led to some firms producing mainly new drug targets, which other firms can license; others generate primarily lead molecules, or they co-develop drug candidates with partner firms. Such strategies will lead to fast cycles of only 4–5 years, instead of the 10–20 years a fully integrated firm would require to yield a product.

Innovation in large companies

Large pharmaceutical companies tend to follow more than one strategy simultaneously. Thus, the incorporation of new, successful strategies is common. Moreover, a strategic direction, for example, which therapeutic areas or diseases to focus on, becomes less crucial. R&D investment usually spans many disease areas and mechanisms. The types of R&D strategy followed in the projects of the portfolio tend to form a (varying) ratio of novelty and incrementalism, thus spreading risk. In addition, there tends to be a balance between less mature and established technologies that such companies invest in. Although this might not always be a conscious decision, it has helped to avoid locking big

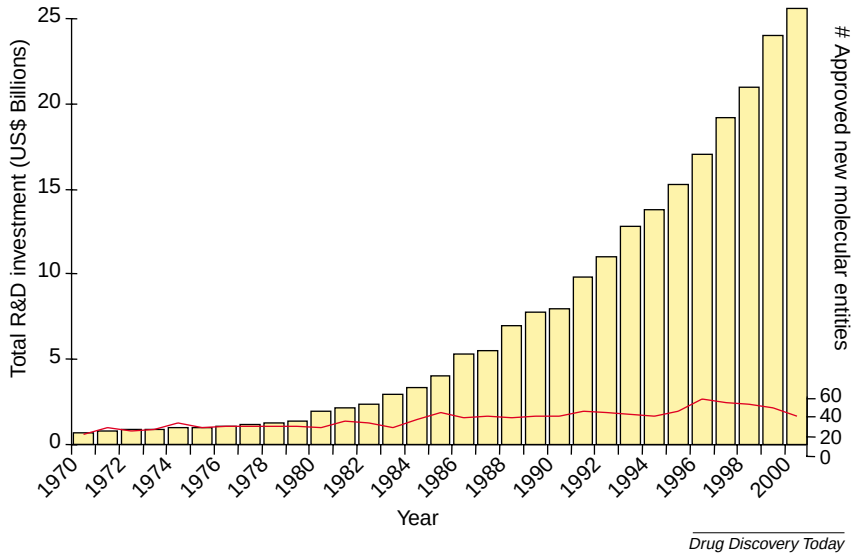

Figure 4. The number of new drug applications (new molecular entities; NMEs) depicted by the red line, versus US$ billion R&D investment (orange bars) between 1970 and 2000. (Source: PhRMA annual survey, http://www.cptech.org/ip/health/econ/rndcosts.html).

pharmaceutical companies into one strategic direction, but further obscures the relationship between strategic investment and resultant productivity (or lack thereof). A key strategy in large pharmaceutical companies also, is to attenuate risk by reducing cycle times. This can be achieved by licensing development compounds from biotechnology, or by aggressive acquisition of companies with advanced drug portfolios. Such strategies could go as far as reducing internal research and focus on developing drugs licensed from partner companies. The key risk involved in such compartmentalization of R&D is the risk of losing internal intellectual capacity, and the expertise required to assess licensing opportunities, or make sensible internal portfolio decisions. People are the most important asset an innovating industry possesses; they can be a key strategic advantage – but losing key experts, innovators or decision makers can also cause irreparable damage long-term.

There is currently a great deal of discussion about alleged innovation deficits (as measured by current numbers of new drug applications) of large pharmaceutical companies. This is discussed in the context of record levels of R&D investment today. Yet, this 'deficit' derives from the strategies set 10–20 years ago, the science base available at the time and the investments made at the time. It is important to note that they coincided with a rise in molecular biology and early experimentation with new high throughput technologies, both in chemistry and biology. Inevitably, when such new processes, science and technologies are introduced, there will be years of trial by error. In ultra-slow industries, any errors will, many years later, translate into reduced new market introductions. However, whether the deficit is real is a matter of debate – the numbers of new drug applications, which are new molecular entities, between 1970 and 2001 has not declined (Figure 4), and some fluctuations on a year-on-year basis are unlikely to be out of the ordinary [7]. In addition, the presence of many safe and effective drugs has opened new avenues. Many drugs are effective in other indications: aspirin is probably the most versatile and famous example of an (old) drug, which has recently found increasing use in a range of human diseases. The pharmaceutical industry is now investing much more in a strategy of finding new applications for existing drugs than it would or could have done 10–20 years ago. This means, the total number of new drug applications is much higher – as much as threefold, compared with Figure 4, which only lists new molecular entities. For instance, in 2000, only 27 of the 98 approved drugs were new molecular entities [8]. However, only ~30% of R&D spending is estimated to go into R&D on existing drugs [8]. Thus, although the level of investment required to discover and develop new molecular entities has risen disproportionately (Figure 4), it is debatable whether the pharmaceutical industry is suffering an innovation deficit (Figure 4). The increase in R&D investment is mandated by increasing regulatory requirements but also by the need to demonstrate differentiation in a pharmaceutical market place, which has seen many effective new drugs introduced in the 1970s and 1980s, some of which are already generic. This in turn drives much larger clinical study designs. It is estimated that the average number of patients per new drug application between 1998 and 2001 was 4380, whereas between 1985 and 1988 the figure was only 3233 patients [Tufts Center for the Study of Drug Development (1999); http://csdd.tufts.edu] a 135% rise in study size. Increasingly, bigger study sizes go hand-in-hand with the need to demonstrate improvement in outcome (mortality), and associated prolonged duration (and costs) of studies.

Changes in R&D strategies

The R&D strategies of large pharmaceutical companies have changed substantially over the decades. These changes were a direct result of successful earlier R&D strategies, which altered both market place and science base.

Table 1. Examples of emerging new target families (based on compounds currently in Phase III, registered or launched in recent years)

Target mechanism	Example drug(s)
Traditional technology - small molecules (medicinal chemistry paradigm)	
Thrombin (oral)	Exanta (Ximelagatran) (note: thrombin is a new drug target for oral small molecules, even though it is not new for i.v. drugs)
Renin (oral)	Aliskiren
Antifungal	Echinocandins (i.v.)
NMDA	Ebixa (Memantine)
mGluR	Fasoracetam
Maturing technology – antibodies, proteins (biotechnology paradigm)	
Adhesion molecules, e.g. ICAM-1, VCAM, etc	Alicaforsen
Cell surface receptors/ligands, e.g. VLA-4, VEGF receptor, CD28 antagonists	Avastin
Interleukins	ABT-874,
Growth factors, e.g. Nerve Growth Factor	Axokine,
Keratinocyte growth factor	Palifermin
New technology to unravel mystery mechanisms (widening of target space for traditional chemistry paradigm)	
Retinoid receptors	Alitretinoin
PPAR	Avandia (rosiglitazone)
NFkappaB	ATN-224
New technology and/or new target families	
EGF-receptor erb1 kinase	Tarceva
Farnesyltransferase	Sarasar
ACAT	Avasimibe
Caspases	Telcyta
Cyclin-dependent kinases	Alvocidib
Angiogenesis	Anecor
Neuraminidase	Tamiflu
mTOR kinase	CCI-779
P38 kinase	Doramapimod
Ornithine decarboxylase	Eflornithine
Pyruvate-dehydrogenase	Ceresine
New technologies, new treatment paradigms	
Cancer vaccines	N/A
Photosensitiser	Visudyne

Examples are listed by technology maturity. Only some of the mechanisms currently in Phase III and beyond are listed. Many new target families are directed to high medical need areas, such as cancer and inflammation. However, even in mature disease areas, such as cardiovascular, new mechanisms are emerging in Phase III. Many antibodies against cell surface receptors, and many intracellular targets are emerging. Data are derived from: Investigational Drugs database IDDB © Current Drugs Ltd (2003).

The availability of safe and effective drugs made it possible to follow a strategy of using existing drugs for new diseases. It also had effects on the demands placed on new molecular entities. They need higher and higher degrees of differentiation in three areas: safety, efficacy and convenience. This still influences R&D strategies today. It drives efforts into breakthrough discoveries (i.e. bringing entirely new mechanisms to market) but has also changed, for example, safety assays, such as cardiac potassium channel screening as a predictor for QT interval prolongation. Such assays are now more and more performed during the discovery phase to build differentiation into new molecules.

Box 2. Strategies to reduce failure rates of products or concepts before or after they reach the market

- Maximising the potential of already available, marketed chemicals through systematic searches for additional or new indications for existing drugs
- Increasing the effectiveness of drugs against multi-factorial, multi-mechanism diseases through the combination of two or more drug classes
- Removing flaws from existing drugs (e.g. QT interval prolongation, ADME limitations)
- Increasing the alignment between clinical and biology expert groups to validate novel drug mechanisms early
- Investing in predictive technologies to aid project selection
- Licensing validated compounds, technologies or concepts from more risk exposed, cash-strapped sectors, such as biotechnology

R&D strategies of big pharma from the 1970s to the 1990s

In the 1970s and 1980s, the prevailing R&D strategy was based on utilization of pharmacological disease models and medicinal chemistry that followed academic discoveries or modified naturally occurring agonists or antagonists [6]. The growth of Big Pharma in the 1980s was a direct result of exploiting this mature science base via incrementalism. Unfortunately, there was insufficient substrate available to fuel the necessary amount of incrementalism. This led to new R&D strategies in the 1980s and 1990s. The new R&D strategy centred on molecular biology and combinatorial chemistry. These novel technologies for the first time enabled blanket screening against single drug targets outside a cellular or organ system. The science and technology of this new R&D paradigm is still evolving today, but early signs of success are becoming evident, in drugs like Gleevec (which was found via subset screening of kinase inhibitors). Table 1 lists some of the exciting new mechanisms that are currently in advanced development, which show the new R&D paradigm contributing significantly to Phase III studies and, hopefully, future medicines.

However, most scientists will agree that the R&D strategies based on this new science were initially not successful. This might have been due to the largely non-strategic deployment of such new technologies, which were often indiscriminately used, without clear R&D objectives in mind, rather than to overcome specific project issues. Not all technologies became integrated into R&D projects, and instead were run by specialist departments. It took several years before the lack of impact became evident. From this came major strategic considerations for R&D, which aim to reduce the luck element somewhat. Examples are:

- the concept of druggable targets
- the Rule of Five (i.e. the physico-chemical properties that facilitate oral absorption of compounds [9])
- the need to establish confidence in the rationale of the target early (through animal models, organ models, or investigative clinical studies)
- the need to define structural requirements in large compound libraries, such as the avoidance of overt toxic groups [10]
- the need to develop predictive models to aid decision making (e.g. *in silico* ADME models [11], computational drug–target interaction modelling)
- the need to integrate technologies to solve specific issues of R&D projects
- the need to forecast portfolio performance into the future, based on the different risks, and technical feasibilities associated with different types of projects (i.e. using parameters determined empirically during the R&D efforts in the 1980s and 1990s).

Box 3. Increasing the speed of R&D to get faster feedback loops

- Faster, slimmer projects to key, project specific, decision points
- Accelerating and decentralising internal decision making
- Better management tools to inform decision making (computational feasibility assessment, risk models, portfolio forecasting)
- New, radical R&D models, such as faster to man proof-of-concept studies and fundamental changes in development – such as in-life trials and treatment packages (with diagnostics and monitoring)

R&D strategies of big pharma in the new millennium

Today, the amount of information and data available for pharmaceutical R&D is unprecedented. However, only small parts of this base have formed enough connectivity to enable knowledge and wisdom to evolve from it [12]. To a large extent, the outcome of R&D on novel drug targets is still based on luck. Both in drug metabolism and biology, predictive models are still evolving. For instance, systems biology has only just appeared on the horizon and has some way to travel to become useful in predicting drug efficacy. Thus, despite all progress so far, the discovery of completely new drug classes remains a difficult and costly process. Each and every one should therefore be seen as a major success, which can potentially be the basis for new, less luck-dependent strategies, which aim to improve specific

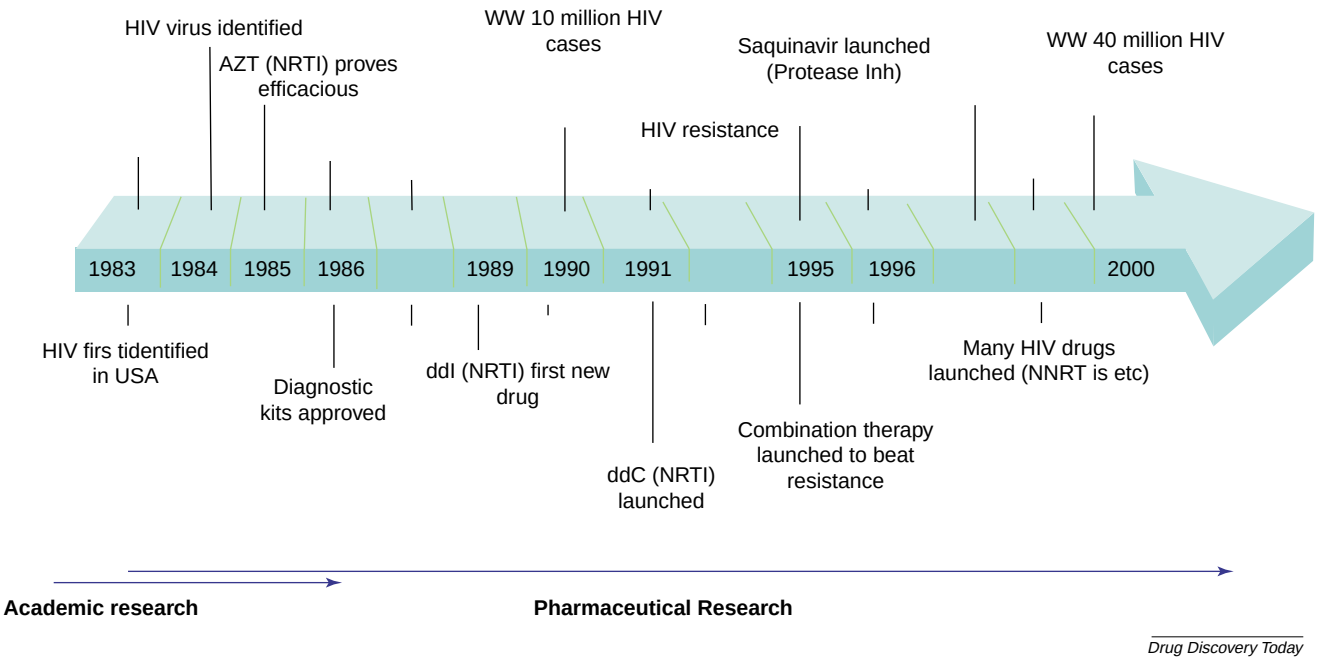

Figure 5. Interplay between academic research and pharmaceutical R&D, using HIV research as a case study. The discovery of the nature of the infectious agent, the development of diagnostics and the early, lucky discovery that AZT worked in HIV patients opened an R&D field, which is still developing today. Furthermore, the seriousness of the HIV epidemic led to an unprecedented cooperation between academia, regulators, government institutions and the pharmaceutical industry. This resulted in a concerted, strategic approach to developing new medicines and helped reduce R&D timelines to record levels. They dropped from typically 10–15 years, to 2–6 years. More recently, these timelines are on the increase again because the availability of the early agents has increased the demands placed on new medicines in terms of efficacy and safety (http://www.niaid.nih.gov/publications/discovery/thiv.htm).

flaws in the original discovery. In fact, despite such humbling admissions, the pharmaceutical industry has made significant progress in predicting the odds at the start of R&D. Today, most large pharmaceutical companies try to balance risk in their portfolios through strategies, which target some of the sources of uncertainties and which influence project selection (Boxes 2 and 3).

Conclusion

The lack of feedback on the outcome on R&D strategies in ultra-slow industries, such as the pharmaceutical industry, remains a major dilemma. Although the so-called innovation gap can be rationalized, many stakeholders find the promise of success 'just round the corner' not credible. In fact, not all strategies are, or will be, successful and for many novel strategies only time will tell about the ultimate outcome (e.g. gene therapy). What needs to be remembered, however, is that of all pharmaceutical strategic groups, big pharma is best placed to weather these strategic uncertainties.

Despite the appearance of being ultrastable monoliths, some of them are among the most flexible and responsive organisations today. Drug discovery and development have changed beyond recognition over the last decade and this trend is likely to continue. Some of the recent strategies are already successful, such as antibody-based approaches for the treatment of some cancers, or kinase inhibitors, which have originated from advances in molecular biology.

There have been many cycles of radical, often highly strategic change over the history of the pharmaceutical industry. Regulatory and political pressures in the aftermath of the Kefauver investigations and the thalidomide tragedy have changed R&D processes fundamentally in the 1960s, even, in the eyes of analysts at the time, seemingly heralded the demise of the industry [13]. But only 20 years later, the industry enjoyed one of its most fruitful eras! Undoubtedly this is to a large measure attributable to serendipity, that is, the discovery of new, efficacious drug classes in major disease areas. However, it is obvious that only those firms became top firms, which strategically used such good fortune. Thus, we postulate that strategic direction that is science driven, and therefore has depth, is an essential ingredient in R&D success.

Strategic collaborations with companies, who have invested in one strategic direction and have struck lucky, can

significantly enhance the available opportunities. In the case of HIV, the foundation of academic research has enabled the pharmaceutical industry to enter this field with more and improving drug classes. New drugs in turn help further academic research, by providing essential tools to elucidate disease pathways. Successful collaboration amongst key stakeholders to fight a life-threatening disease, can also dramatically improve the innovation cycle time (Figure 5).

It is highly likely that the pace of change will further accelerate. If these developments continue at the current pace, they might well lead to fundamental changes in what constitutes pharmaceutical R&D within the next few decades. Spotting those scientific opportunities with the greatest promise for future success, within the many influences that bear on the industry, and using them as ingredients for strategic change, has to be at the heart of R&D strategy today.

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Erratum

In the 1st December 2003 issue of *Drug Discovery Today* (Vol. 8, No. 23; 1085–1093), in the article entitled '*Confocal optics microscopy for biochemical and cellular high-throughput screening*', by Lenka Zemanová *et al.*, the author affiliations should have read:

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We would like to apologize for any confusion that this might have caused.