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DOI: 10.1002/cmdc.200700008

Pharmaceutical Strategy and Innovation: An Academics Perspective

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The pharmaceutical industry is under increasing pressure on many fronts, from investors requiring larger returns to consumer groups and health authorities demanding cheaper and safer drugs. It is also feeling additional pressure from the infringement upon its profit margins by generic drug producers. Many companies are aggressively pursuing outsourcing contracts in an attempt to counter many of the financial pressures and streamline their operations. At the same time, the productivity of the pharmaceutical industry at its science base is being questioned in terms of the number of products and the timeframes required for each company to deliver them to market. This has generated uncertainties regarding the current corporate strategies that have been adopted and the levels of innovation being demonstrated. In this essay we discuss these topics in the context of the global pharmaceutical market, investigating the basis for many of these issues and highlighting the hurdles the industry needs to overcome, especially as they relate to the chemical sciences.

1. Introduction

1.1. Science and industry

"Science knows no country because knowledge belongs to humanity, and is the torch which illuminates the world."

Louis Pasteur (1822–1895)

Science is a cornerstone of everyday life; it embodies one of the most fundamental human desires, namely the search for greater knowledge. It also represents the one common linguistic and cultural bridge that spans our planet. Consequently our national economies and global interactions are also founded upon and continually influenced by the current state of understanding and our ability to exploit any scientific advances.

Ingenuity and inventiveness are vital components to any sustainable economy reliant on science. It is often stated that "inventiveness comes of need" and therefore we find in times of greatest hardship that the biggest advances are made. However, the historical reasons behind the discovery and the resulting technological applications of scientific knowledge do not have to be synonymous. Undoubtedly, scientific innovation has allowed us to improve our lives while using resources more efficiently, and we can now understand and manage the potential impact of these innovations on our surroundings.

One area which has seen considerable innovation is the health-care sector; the availability of prescription drugs and vaccines has revolutionised medical treatment, enabling physicians to prevent or eradicate numerous previously fatal diseases, thereby helping to increase the average life expectancy. In 2003, life expectancy at birth for women born in the UK was just over 81 years, compared with 76 years for men (average across the sexes is 78.4).[1] This contrasts with 49 and 45 years, respectively, at the turn of the 20th century. These statistics are consistent with other developed countries in which medical care is readily available such as the US, where the average accumulated life expectancy for a person at birth has increased from 49.2 years to 76.5 years during the last century.[2]

On a purely statistical evaluation, with a growing population there will evidently be a greater demand for health-care products. Also associated with this is the increasing longevity of the population and the specific conditions associated with an aging group. The prevalence of many chronic illnesses such as arthritis, osteoporosis, glaucoma, hormone imbalances, Alzheimer's disease, and circulatory defects (including associated platelet aggregation and gastrointestinal problems) are significantly increased with a mature population demographic (Table 1).[3] Therefore, with an estimated 16% of the UK population over the age of 65 compared with only 13% three decades ago, and with this particular demographic expected to continue to exponentially rise, it is becoming an increasingly important factor.[4] To exemplify this, in the years 1995 to 2000 the combined sales of antidepressant, cholesterol-reducing, anti-ulcerant, anti-arthritic, and oral diabetes medications rose from £5.7 billion to £14.5 billion.[5] A further five years on, this figure stands at a staggering £51.6 billion.[6]

In addition, the diagnoses of conditions like asthma, diabetes, and elevated cholesterol are also occurring with greater incidence. In part, this reflects the aging population but also the changing lifestyles that generate collective problems like obesity. Doctors are therefore requested to administer treatments that enable patients not just to live longer, but to lead more functional and productive lives over extended life spans. To do this, they are using a wider variety of drugs and with greater frequency. Additively many of these drugs must be taken daily over many months or years, or sometimes for life. Under such conditions, should not pharmaceutical companies be flourishing and spawning a plethora of proprietary medicinal products?

2. The Global Pharmaceutical Market

2.1. Financial growth

The pharmaceutical industry looks, if you will excuse the pun, "healthy" on first inspection. A recent study determined that the market size for worldwide human drugs consumption (including over-the-counter products) at the end of 2006 was approximately £346 billion[7a] (£287.8 billion in 2005,[7b–d] £279 billion in 2004,[8] £252 billion in 2003,[9] £231 billion in 2002,[10] and £195 billion in 2000[11]). Despite the current relatively weak global economy, the market is projected to grow to a figure of between £358 and £369 billion[12] by the end of 2007. World

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Table 1. Major causes of death by age and sex in England and Wales in 2004.

Disease	Age									
	<5	5–14	15–24	25–34	35–44	45–54	55–64	65–74	75–84	≥85
					Males					
Infectious and parasitic diseases	51	14	24	61	133	170	212	355	700	477
Neoplasms	53	104	198	341	1097	3724	10932	20427	25707	9557
Blood disorders	12	6	4	13	24	24	48	80	110	97
Endocrine, nutritional, and metabolic diseases	30	22	49	56	114	180	314	811	1143	647
Mental and behavioural disorders	2	4	98	297	293	173	129	330	1450	1791
Diseases of the nervous system	86	50	126	132	246	363	617	1238	2529	1354
Diseases of the circulatory system	34	29	96	341	1343	3930	9330	19783	35607	20816
Diseases of the respiratory system	62	36	33	90	236	635	2026	5536	12905	10228
Diseases of the digestive system	27	9	24	159	727	1487	1886	2179	3154	1745
Diseases of the skin and subcutaneous tissue	–	–	–	2	8	16	36	88	222	149
Diseases of musculoskeletal and connective tissue	1	3	5	7	32	33	113	251	462	377
Diseases of the genitourinary system	3	2	3	9	34	72	169	523	1538	1569
Hereditary and congenital malformations	141	25	60	56	61	63	105	48	62	27
Other	361	121	1370	1716	2011	1547	1199	1058	1773	2493
Total	**863**	**425**	**2090**	**3280**	**6359**	**12417**	**27116**	**52707**	**87362**	**51327**
					Females					
Infectious and parasitic diseases	64	16	24	56	95	78	150	344	906	1062
Neoplasms	39	82	152	403	1573	4171	9499	15398	21840	12761
Blood disorders	9	9	5	8	16	22	46	76	170	239
Endocrine, nutritional, and metabolic diseases	31	14	39	60	67	131	245	640	1316	1611
Mental and behavioural disorders	–	1	44	56	80	55	85	348	2791	6297
Diseases of the nervous system	67	43	67	79	187	291	542	976	2680	2916
Diseases of the circulatory system	21	19	65	170	552	1362	3541	11304	35958	46470
Diseases of the respiratory system	55	29	43	55	153	441	1410	4283	12618	18588
Diseases of the digestive system	28	8	20	94	402	807	1136	1950	4442	4695
Diseases of the skin and subcutaneous tissue	–	–	–	1	9	17	31	130	384	578
Diseases of musculoskeletal and connective tissue	–	8	13	23	35	55	149	367	1047	1458
Diseases of the genitourinary system	5	1	5	21	41	76	160	481	1815	2891
Hereditary and congenital malformations	145	20	36	37	48	64	100	60	76	43
Other	259	63	391	473	593	569	549	680	2355	9873
Total	**723**	**313**	**904**	**1536**	**3851**	**8139**	**17643**	**37037**	**88398**	**109482**
Total deaths male and female	**1586**	**738**	**2994**	**4816**	**10210**	**20556**	**44759**	**89744**	**175760**	**160809**

expenditure on drug-related health care has been growing at an average of 8% a year over the last five years, and this is expected to continue. Within the global market the single largest manufacturing base is the US pharmaceutical industry, with annual sales in 2005 of around £135.5 billion[13] (£131 billion in 2003). This can be compared with the UK, with a turnover of £13.9 billion in 2005 (£13.5 billion in 2003 and £13.4 billion in 2002).[14] Approximately 51% of world production capacity was administered in the US and Canada (Canada equates to approximately 4%),[15] equalling sales valued at £110 billion and representing 12.4% of the total health care expenditure of the US (Table 2[16]).[17] Europe as a whole is the second-largest consumer, accounting for an additional 25% of sales; interestingly, the total NHS bill for prescription medicines in 2003 was £7.2 billion, but this is dwarfed by the French system, which reportedly spent £12.6 billion over the same period.[18] Japan's population consumes an additional 12% (£28.3 billion), while Asia, Africa, and Australia combined represent a further 8% of the global market (£20.15 billion).[9]

Table 2. Total expenditure on pharmaceuticals (to June 2004).

Country	Sales [£ billion]	% of Total
United States	123.1	55.1
Japan	29.8	13.3
Germany	15.0	6.7
France	14.2	6.4
United Kingdom	9.9	4.4
Italy	9.6	4.3
Spain	6.9	3.1
Canada	5.6	2.5
China	3.6	1.6
Mexico	3.3	1.5
India	2.3	1.0
Total	**223.3**	**99.9**

As a consequence of the dominant US position regarding the preparation of pharmaceutical products, as well as being the main consumer, it might be assumed that the US would possess the full hierarchical structure of the drug-manufacture process. Indeed, the US does have a strong commercial presence. The US manufactures seven out of the top ten selling drugs (Tables 3 and 4).[6,19] The remaining three drugs are European exports, two of which are from companies operated and owned within the UK.[20] These top ten blockbuster drugs also account for a major proportion of the gross pharmaceutical industry revenue.[21] The top ten drugs had combined sales of £27.45 billion, and in addition, every one of the top 50 pharmaceutical therapies were in excess of $1

Table 3. Leading products based on US sales.

US Rank	Product Name (*Compound*)	US Sales [£ billion]	Company	Class of Drug
1	Lipitor (*atorvastatin*)	4.139	Pfizer	Hypercholesterolemia (decreases cholesterol)
2	Zocor (*simvastatin*)	2.462	Merck & Co.	Hypercholesterolemia (decreases cholesterol)
3	Prevacid (*lansopyrazole*)	2.046	TAP Pharmaceutical[a]	Proton pump inhibitor (decreases stomach acid)
4	Nexium (*esomeprazole*)	2.035	AstraZeneca	Proton pump inhibitor (decreases stomach acid)
5	Procrit (*erythropoietin*)	1.717	Johnson & Johnson	Erythropoietins (treats anaemia)
6	Zoloft (*sertraline*)	1.665	Pfizer	Mental health (treatment of depression and anxiety)
7	Epogen (*epoetin alfa recombinant*)	1.609	Amgen	Erythropoietins (treats anaemia)
8	Plavix (*clopidogrel*)	1.603	Bristol-Myers Squibb / Sanofi–Aventis partnership	Anti-platelet
9	Advair/Seretide (*salmeterol & fluticasone*)	1.568	GlaxoSmithKline	Anti-asthma
10	Zyprexa (*olanzapine*)	1.521	Eli Lilly	Mental health (antipsychotic)

[a] Joint venture between Abbott Laboratories and Takeda.

Table 4. Leading products based on worldwide sales.

World Rank	Product Name (*Compound*)	World Sales [£ billion]	Company	Class of Drug
1	Lipitor (*atorvastatin*)	6.46	Pfizer	Hypercholesterolemia (decreases cholesterol)
2	Zocor (*simvastatin*)	3.18	Merck & Co.	Hypercholesterolemia (decreases cholesterol)
3	Plavix (*clopidogrel*)	2.69	Bristol-Myers Squibb / Sanofi–Aventis partnership	Anti-platelet
4	Nexium (*esomeprazole*)	2.58	AstraZeneca	Proton pump inhibitor (decreases stomach acid)
5	Zyprexa (*olanzapine*)	2.58	Eli Lilly	Mental health (antipsychotic)
6	Norvasc (*amlodipine*)	2.58	Pfizer	Hypertension (decreases blood pressure)
7	Advair/Seretide (*salmeterol & fluticasone*)	2.53	GlaxoSmithKline	Anti-asthma
8	Procrit (*erythropoietin*)	2.15	Johnson & Johnson	Erythropoietins (treats anaemia)
9	Prevacid (*lansopyrazole*)	2.05	TAP Pharmaceutical[a]	Proton pump inhibitor (decreases stomach acid)
10	Effexor (*venlafixine HCl*)	1.99	Wyeth Pharmaceuticals	Mental health (antidepressant)

[a] Joint venture between Abbott Laboratories and Takeda.

billion, with twenty three exceeding $2 billion. Consequently, the pharmaceuticals market is dominated by a small set of multinationals, with the leading companies in terms of worldwide sales, again, being American (Figure 1).[22]

Interestingly, this relationship is not maintained in the area of bulk manufacture of pharmaceutical actives, i.e., substances in drugs that perform the desired therapeutic actions. This market is estimated to be valued in excess of £38 billion, with an average annual growth rate of 9.2%. Among the top 25 suppliers worldwide for bulk pharmaceutical actives, 15 are European,[23] seven are American, and three are Japanese.[11] However, developing countries have a significant impact on this market distribution; India is now producing nearly 10% of the world's drug requirements in terms of volume,[24] and also ranks amongst the top 15 drug manufacturing countries in the world.[25] Another rapidly emerging and potentially dominant influence in terms of world supply is the Chinese pharmaceutical industry. China is the next largest producer of bulk pharmaceutical ingredients after India, with an annual production of 0.8 million kg in 2003.[26] To place this in context, the estimated production of bulk actives for 2004 was 477 million kg (this excludes large pharmaceutical in-house manufacturing capabilities).[27] However, further consideration of the market in terms of quantity of material is quite important because the volume of a bulk active is not always directly proportional to its monetary value, as many of the newer drugs have greater potency and so require smaller volumes of the active ingredient. In financial terms, the market value for these intermediates was only £854 million,[28] an almost insignificant sum in comparison with the total value attributed to the later-stage processing that results in the finished products and their ultimate sale value. However, it is this market that has the highest expected growth indicators; more companies are diversifying operations by outsourcing their initial manufacturing requirements in order to concentrate on the more lucrative downstream operations.

2.2. Additions to the new pharmaceutical industry

2.2.1. India

The profile of the world pharmaceutical market has changed drastically over the past decade. Whilst continuing to expand through classical consumer growth, intensive globalisation has impacted strongly on this sector by suddenly opening up whole new markets in addition to the emergence of new phar-

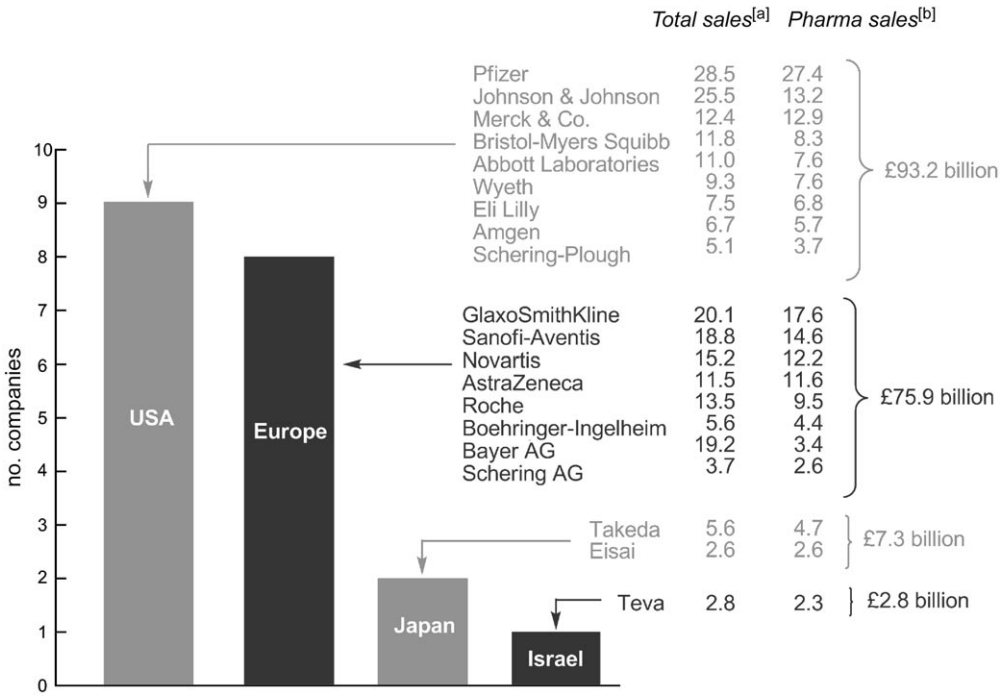

Figure 1. Origin of the top 20 companies by [a] worldwide sales and [b] pharmaceutical sales 2004–2005.

maceutical producers. It has undoubtedly been these new manufacturers that have had the most significant effect on the organisational structure and cultural perspective of the current pharmaceutical sector. Although the elevation of health care and the introduction of advanced therapeutic treatments into previously less affluent nations have been rather general, two developing countries easily stand out. The prominence of India and China as new economic powers has created a strong internal demand by their populace for improved health care products, thus rapidly establishing these new pharmaceutical markets.

At present the Indian pharmaceutical industry is highly fragmented, consisting of more than 30000 domestic manufacturers[29] of pharmaceutical-related materials; no single company has a home market share greater than ~7%, and the largest five companies make up just 20% of the total market.[26] There is a historical cause behind these figures. In 1970 the Indian government abolished the recognition of foreign drug patents, preserving only the codicil of the original legislation that protects the originator's exact manufacturing process. This automatically created a lucrative free market for trade in reverse-engineered drugs, enabling local entrepreneurs to rapidly establish businesses largely built on the discoveries of other, mainly foreign, firms. Because this type of industry structure has a low capital requirement (civil construction is £6.50 per square foot versus £40.50 in the US) and India has an extensive low-cost labour market (Indian scientists earn about a third of their Western counterparts),[29] these companies flourished. However, in order to avoid litigation due to infringing process patents, these same companies became very adept at developing alternative production methods, a definite bonus in the long term. With the renegotiation and instigation of more stringent regulatory drug patent protections (TRIPS) coming into effect in 2005, the industry has had to re-orientate its manufacturing emphasis in order to comply.

Owing to the industry's embedded skill and expertise in developing processes for preparing pharmaceutical materials at scale, it has been able to make a rapid and successful transition into the fields of bulk actives and generic drug manufacture. Indian companies have become quite proficient at manufacturing to FDA and GMP certification, thus meeting the regulatory needs of foreign companies, and marketing their bulk actives to a worldwide audience. In fact, many of the multinational pharmaceutical companies now use Indian manufacturing plants as outsourcing partners. The strength of the industry therefore lies in developing cost-effective technologies in the shortest possible time for drug intermediates and bulk actives without compromising on quality.

2.2.2. China

As in India, the Chinese pharmaceutical industry is extremely segmented, as it consists of approximately 5000 separate companies. However, many of these survive only through substantial state intervention. The pharmaceutical sector's infrastructure within China is rather complex. Years of extensive investment by external organisations and multinational companies into low-tech manufacturing plants has created an almost exclusive single-tier industry. It is now almost impossible for many of these companies to rationalise and develop a more hierarchical structure because of the inherent manufacturing overcapacity. The situation is also exasperated by an artificially maintained environment of restricted competition, as propagated by the Chi-

nese government's command economy legacy.[30] Even under the new, more open market system of governance, a truly competitive environment has not yet been attained; problems still exist in balancing the protection of the indigenous companies with a need for further foreign investment. It is quite common for recently privatised companies to still be commercially advantaged through favourable credit terms or pricing arrangements based on previous government institutional ties. There is also a technological ceiling effect that is compounded by a stagnated skill set within the chemistry labour force, maintained because a more qualified workforce is just superfluous to the existing manufacturing requirements. This lower technological capacity is evidenced by the fact that only 15% of the domestic firms have GMP certificates.[31]

Against this backdrop is China's rapidly expanding domestic pharmaceutical market: tenth in world monetary value at present, but with the largest incremental growth of 28% in the last 12 months. This represents an annual total of £5.1 billion in sales, indicating that China is poised to become a major new market. It may therefore seem detrimental for the government to sustain such restrictive competition policies that seem to stifle its domestic pharmaceutical industry, especially when it is actively pursing health reforms aimed at improving the cost-efficiency of the health-care sector.[32] China is partway through a major restructuring programme of its hospitals that is intended to stimulate cost-efficiencies and introduce financial and administrative autonomy.[33] Again, this needs to be considered within a broader context. Despite more than 1000 synthetic medicines being produced in China, a staggering 97% of these are reportedly direct copies of registered products. However, the majority of these products are destined for home-market consumption, and China's possession of such a large-scale manufacturing capacity means that it can quite easily self-sustain its internal demand from a comparatively low-cost base. However, following a predetermined recipe does not contribute to the understanding of the chemists, as the decision-making processes are made elsewhere; the education of the chemists and the innovation introduced to the market is not amplified. This can be accepted for the synthesis of bulk generics, but does not foster the discovery of new treatments and medicines.

Another factor that will further influence the structure of the Chinese pharmaceutical industry is the importance of pricing within the generics market. Increased global competition means that we will see a gradual but continued migration of manufacturing to low-cost countries such as China and India. This is particularly likely in the context of the impending surge of the expiration of patents in the next two years, when nine major drugs are set to lose their patent protection.[34] Importantly, China has started to enshrine an IPP strategy symbolised by its accession to the World Trade Organization (including TRIPS) in 2002. This has involved the enactment of statutory regulations that extend all pharmaceutical patents to 20 years and full data-exclusivity for six years (excluding clinical data). However, despite China's reforms in recognizing the globally accepted lifespan of pharmaceutical patents, the regulatory and legal enforcement mechanisms to support this IP system lags far behind more developed countries.

3. Pharmaceutical Companies

3.1. Implications of synthesis outsourcing

For large pharmaceutical companies, outsourcing either their intermediate production or total manufacturing capabilities to these low-cost centres certainly generates immediately attainable savings. Under pressure to enhance short-term profits, such transfer options provide an easy route to satisfy investors by permitting divestment of many fixed costs, that is, by not burning money in wait time. Consequently, the major pharmaceutical companies are all involved, to varying extents, in this form of retrenchment.

With increasing rationalisation and better enforcement of IP structures, these countries have become very attractive sites for the relocation of manufacturing operations. However, it should be remembered that such a transition to external sourcing does require a considerable degree of risk management. Many companies that adopt these import procedures often have to spend considerable legal and corporate time "ring fencing" the reliable supply of their desired materials. Such basic considerations as the possibilities that the toll manufacturer may fail to meet delivery deadlines and guarding against price fluctuation often necessitate the need for the proprietary company to establish multiple supply chains.

Another issue of concern is the speed of response to fluctuations in market demand (forced turnaround issues). Extensive outsourcing reduces the primary company's ability to react to real-world conditions (point loading issues and responsive project management), especially when purchasing just-in-time manufacturing. In addition, extended supply-chain management can absorb significant human resources required to monitor the variability and duration of all the sub-processes involved, and then to ensure a smooth transition between segments. When these factors are taken into account, outsourcing can certainly equate to a more complex situation than just a simple cost-saving operation. Indeed, the decision to outsource a particular aspect of the synthesis endeavour as an isolated unit, ignoring its impact across the rest of the programme, can create deceptive economies of scale and increased total unit cost.[35]

It is probably also worth noting that the evaluation process often used in justifying many of the decisions pertaining to the exact cost savings associated with external sourcing do not always reflect the total picture. Many intangible benefits are retained by having in-house preparation facilities, such as better control of QA, process validation, and manufacturing understanding, all of which are essential for effective regulatory and license application control. Removing a company's in-house synthesis capability can also have a significant detrimental effect on the propagation of new science. Stripping a company of its large-scale synthesis workforce can reduce the

knowledge feedback that is such an important component of the integrated cyclic and iterative drug-development process. Significant external consultation regarding any formulation changes, back-up drugs, and follow-on treatments will then be required, a potentially costly and time-consuming operation. This is especially true during the period when both parties are developing their working relationship; the time required to correctly align the goals of two companies can be a significant factor when the clock is ticking on patent expiry.

Not all of the costs of outsourcing are financial or temporal in nature. The inevitable redundancies created by "streamlining" can also lead to a general fall in company-wide productivity due to the resultant ill-feeling within the workforce. Such an effect is not limited directly to the displaced scientists, but can also extend to the senior management level, where a general dissipation of focus can be felt. This lack of direction is often a precursor to a decay in inspiration and innovation, which are the cornerstones of pharmaceutical development.

On the other hand, effective outsourcing can be a positive factor; it has certainly been used to great effect in transforming the automotive and aerospace industries. These industrial sectors, which are similar to the pharmaceuticals sector in that they represent high-risk investment within highly competitive markets, have made excellent use of outsourcing. They have been able to leverage both technical excellence and lower price margins from specialist supply houses, concentrating themselves on the final-stage products and marketing aspects of the product cycles. In effect, a series of service providers representing islands of knowledge have evolved which can be accessed through a series of bespoke procurement systems. This type of model assumes companies will concentrate on their key core competencies, which, for a pharmaceutical company, is considered to be the R&D of novel drug candidates and perhaps not necessarily their synthesis.

3.2. The remodelled pharmaceutical company

The ready adoption of the new corporate mantra "Lean and Agile" by many of the 'remodelled' pharmaceutical companies has become a popular industry management style. It signifies flexibility and swiftness in regards to delivering pharmaceutical products, but it also raises a number of questions. For example, can such a strategy create the efficiency savings required within the industry or is it simply a clever accountant's shareholder-appeasement measure? Furthermore, does this form of corporate restructuring not just represent the obligatory responsiveness of these businesses towards new outside agents as opposed to an innovative business philosophy? Certainly a major external influence on the pharmaceutical industry in recent years has been the changing regulatory environment, which has forced a review of many of the industry's practices.

In addition, has a self-fulfilling reliance on outsourced materials through the erosion of internal synthesis facilities also dictated the adoption of such a corporate strategy? Hence by initially pursuing such cost-cutting measures as a speculative short-term gain, have pharmaceutical companies negated the agility they now claim to be after? Has expanding their outsourcing contracts, representing increasing amounts of their synthesis needs, made certain pharmaceutical companies enslaved to the fluctuations and reliability of a possibly temporary external market?

It is evident that the low-cost manufacturing base of such countries as India and China will erode in time, or more correctly, come into line with existing Western cost differentials. Indeed, the cost bases of these countries are already starting to escalate, closing the gap and decreasing much of the immediate financial advantages. The exact balance for each company between such toll manufacture and in-house synthesis capabilities will vary considerably, depending on the scale and complexity of the materials required. However, as previously stated, the actual associated value of the API market compared with the final manufactured drug is relatively minor, indicating that this may not be such a significant issue when considering the financial return on investment for a large pharmaceutical organisation. Therefore, moving away from in-house synthesis would seem sensible. Nevertheless, from a chemical sciences perspective of the systematic and interconnected process of drug discovery, dismembering the basic synthesis needs from the other R&D endeavours seems rather counterproductive. All scientists are aware that experiments, even the most supposedly trivial, may in many weeks, months, or even years become the inspiration for a major breakthrough. Lending credence to this reality are the repeated stories of leads for blockbuster drugs coming out of "blue sky" or unprecedented research. With this in mind, surely the core basic synthesis area of the industry is a vital component of the drug-discovery process, even if only providing a good training and tempering ground to test and evaluate new manufacturing processes that spark innovation.

The creativity and intuition of researchers is an important scientific driver. Indeed, the importance of a skilled human workforce for continued innovation is a fundamental business premise. Many studies have drawn correlations between the levels of innovative activity and the concentration of an available skilled labour force.[36] Furthermore, the value of intellectual interactions between corporate and academic researchers in R&D is widely acknowledged.[37] Obviously communication and collaborative interactions are the catalysts of such progressive thinking and cross-fertilisation of ideas. Once conceived, these new ideas may have immediate implications for novel products, while other innovations coming out of fundamental research may only trigger advances that result in a pay-off in the distant future. In all situations, any form of constraint that prevents the free flow of ideas and information will stifle the levels of creativity and innovation.[38]

Therefore, returning to our original comments regarding the prudence of large-scale chemistry outsourcing, does this form of task delegation result in decreased levels of knowledge retention and thus less innovation? Outsourcing

certainly adds new hierarchies and boundaries to communication channels, but how significantly does this affect the overall research effort and how effective is outsourcing as a strategy? Of course only time will tell, but recent indications are that a number of organisations have started to re-evaluate their outsourcing requirements because of a variety of communication problems and restrictions in the transfer of knowledge. Of further concern are the implications arising from outsourcing on maintaining an active chemical-sciences-based university and biotech innovation culture. The impact on the strategic opportunities currently available from the interplay of these two agencies could disappear under this more dispersed research and manufacturing model.

3.3. Pharmaceutical spending

It could be argued that many pharmaceutical companies, in essence, are moving towards a repackaging supermarket approach towards cost efficiency, although this does not do justice to the industry by discounting the important R&D aspect of these companies. As stated previously, the household-brand pharmaceutical giants have reached such a scale that they must generate several billion pounds in additional revenue each year in order to satisfy investor expectations. New drugs, however, are becoming harder to find, and the drug businesses have accordingly responded with increased R&D spending. Relative R&D costs have been steadily escalating, while many pharmaceutical-based companies are at a relative low in terms of to-market productivity. This is despite a more than doubling of the R&D budgets of most companies in the last decade.[39] These R&D investigations are very costly; it has been estimated that on average it now costs £430 million to bring a new prescription drug to market[40] (more recent estimates place this at closer to £915 million, based on 2000–2002 data).[41] With such large overhead, only three out of every ten drugs retailed generate sufficient revenues to cover this initial expenditure.[42] In-depth industry analysis by PhRMA has attributed much of the increasing R&D costs to the extending development times (10–15 years) greatly influenced by the increased regulatory demands in today's low-risk, low-tolerance environment.[43] Furthermore, the growing complexity of the targeted diseases and their therapeutic moderators is also a significant factor. The lower-hanging fruits have all been harvested; now extended development of more complex treatments for more difficult disease indications are required. As alarming as this data is often portrayed, it should be acknowledged that many drugs are significantly cheaper to develop because of their perceived necessity, which results in decreased regulatory costs through expatiated evaluation. As examples, drugs to treat multiple sclerosis, tuberculosis, and a variety of cancers are often cited.[44] In addition, the sums quoted often incorporate the staggering monetary milestones associated with initial launches and marketing which can be significantly lower in many cases,[45] such as the recent case of Shire Pharmaceuticals' profit-sharing agreement with New River Pharmaceuticals.[46]

3.3.1. R&D spending

In real terms, R&D budgetary spending has increased from £6.84 billion in 1993 to an estimated £20.88 billion 2004,[47] with the present average R&D outlay estimated to be around 18% of a company's sales.[48] This intensification of R&D funding is still continuing (Table 5), and as a consequence it is encouraging that many new products can now be seen at advanced stages of the pipeline and indeed are starting to arrive at the marketplace (Figure 2).[49] In another sense, however, such figures may be seen as very depressing, considering the expenditure such percentages represent.

Pfizer alone spends around £82 million a week, funding more than 479 early-stage, preclinical discovery projects. However, on average, 96% of these projects will fail.[50] The cruel reality is that

Table 5. R&D spending for the top ten pharmaceutical companies in 2004.

Company	R&D Spending [£ billion]	Sales Revenue [%]
Roche	2.91	31.2
Sanofi–Aventis	5.01	29.2
Johnson & Johnson	2.80	23.5
Novartis	1.88	18.9
Merck	2.15	18.6
Wyeth	1.35	17.9
AstraZeneca	2.05	17.8
GlaxoSmithKline	2.80	16.6
Pfizer	4.04	16.3
Bristol-Myers Squibb	1.35	16.1

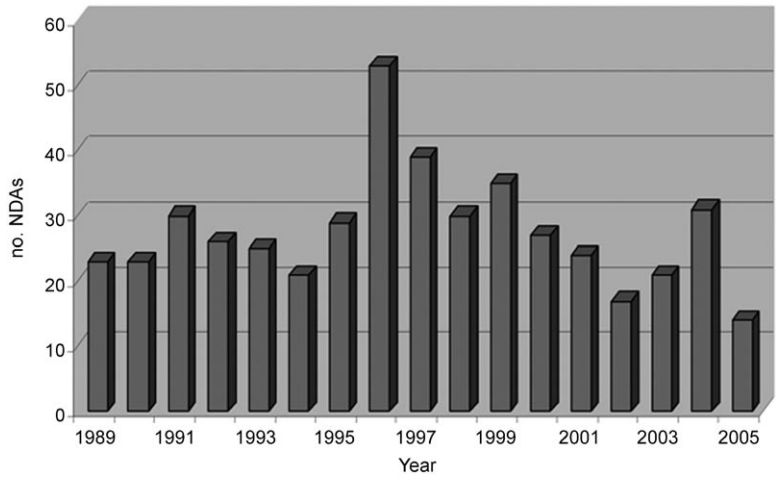

Figure 2. FDA-listed NDAs 1989–2005.

most chemical researchers will never work on a successfully commercialised drug. The commonly depicted schematics of the drug-delivery pipeline defining the exponential attrition rates of drug candidates being progressed through each stage of the evaluation process demonstrates the high-risk statistics (Figure 3).[51] With such a pyramidal structure, the clear approach is to stack the numbers by introducing more compounds to the primary screens, leading to subsequent greater numbers making it through to the next stage. This approach has been enshrined to some extent within the pharmaceutical industry, advocated by the initial investors into large compound-array combinatorial library synthesis programmes. The relative merits of such a strategy have long been contentiously debated, although history indicates that the theoretical benefits have never been realised. Despite this, adoption of large compound library HTS strategies also coincides with the start of rapidly escalating R&D spending.

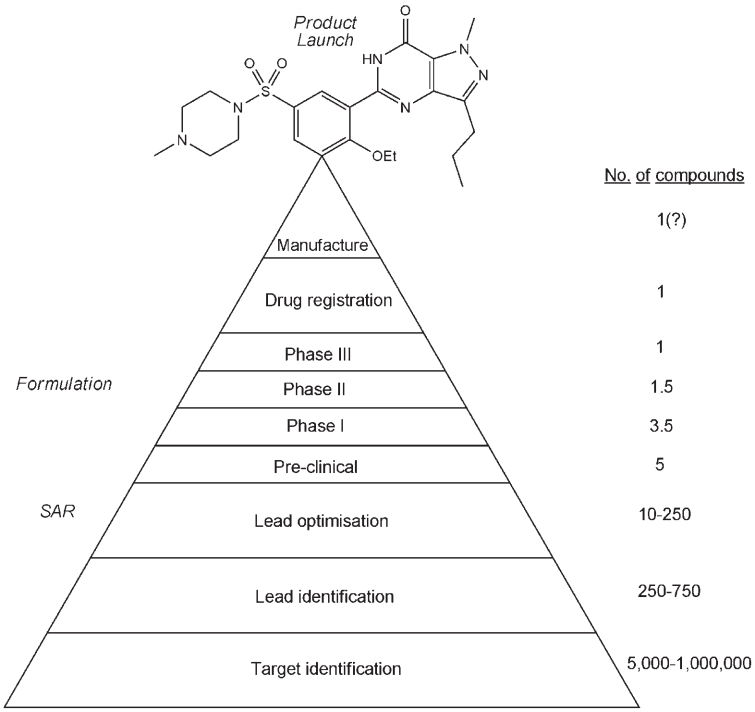

Figure 3. Simplified drug-discovery pipeline. (Chemistry functions: lead identification, HtL expansion, QSAR, lead optimisation, ADME/PK profiling, formulation, process chemistry, GLP and GMP kg-scale synthesis, stability testing, CMC support for IND filing.)

It should be noted, however, that this relatively steep R&D spending curve has not always translated into increased resources at the primary stage of compound identification and lead synthesis. From a chemistry perspective, relatively little additional funding has been allocated to this pivotal segment of the R&D pipeline (Figure 4).[52] The main area of spending is on medicinal evaluation and validation; on average, drug companies spend about 35% of their overall R&D budgets on clinical studies.[53] This is probably not a surprise, considering that drug companies that commercialise a potential blockbuster product stand to lose between £10.5 and £45 million for each month of delay in a protected market launch.

At present, clinical trials, including patient recruitment and extended studies, cost more and consume more time than any other aspect of the R&D process. As a consequence of the financial gains that can be attained through hastened com-

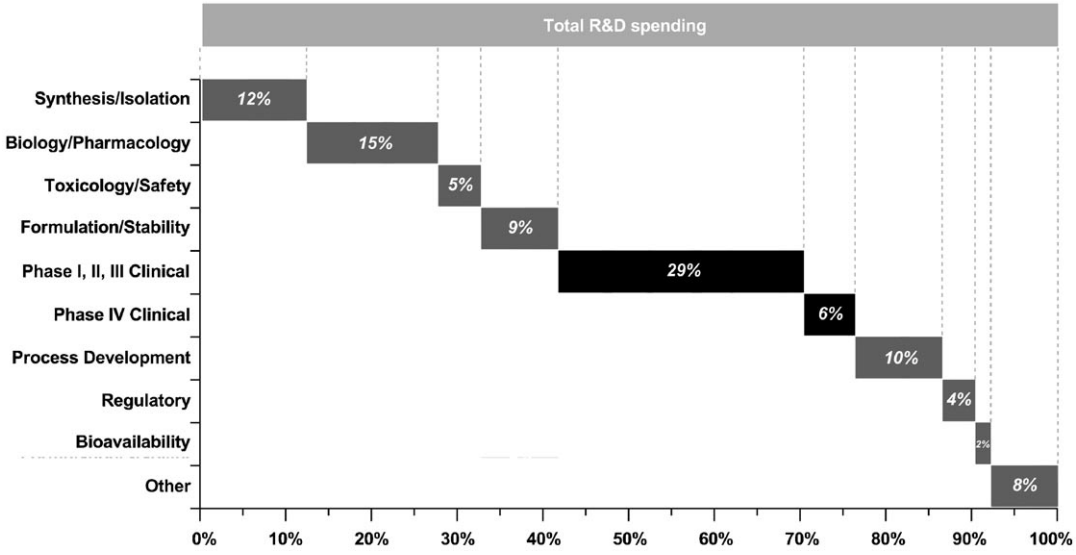

Figure 4. Breakdown of global pharmaceutical R&D budgets.

mercialisation, the pharmaceutical industry has historically attempted to expedite this phase of the process. Hence, the heightened investment aimed at accelerating clinical trials has spawned a whole new sector that has become entirely devoted to facilitating swift clinical evaluation, while simultaneously leading to a successful conclusion.[54] The clinical services industry is starting to migrate the majority of its studies towards overseas trial centres in Central and Eastern Europe, India, China, and regions of South America. In these places, it is much easier to find abundant patient populations and it is also less expensive to run the trials. Despite tapping these cheaper trial zones, the clinical testing procedure is still the major financial drain on the drug-development process and, as has been seen with a number of high-publicity withdrawals such as Merck's Vioxx and Pfizer's Bextra, the process is not infallible. However, the guidelines and protocols that have been established, when correctly followed, constitute a thorough testing regime despite recent adverse publicity.[55] Unfortunately, there will always be an inherent conflict due to the difficulty in trying to balance the financial pressures of early drug launch against a more comprehensive and exhaustive evaluation of the benefits and risks.

The industry expects the cost of such trials to continue to increase as more stringent regulation and the need for wider-ranging data sources and independent analysis are required to demonstrate greater transparency. Indeed, much of the extra regulatory framework imposed on the industry recently has been concerned with freedom of information instigated from public appeasement policies following several high-profile examples of drug complications. It has been argued that this latest clampdown should have been anticipated and that the pharmaceutical companies have existed on borrowed time in the presence of this potential time bomb for a number of years. To be fair, the appreciation of the difficulties associated with the exact "science" of drug discovery by the public has never really been addressed. A long-standing elitism propagated by pharmaceutical companies portraying themselves as the deliverers of the "magic bullets of illness" has indoctrinated the general population into expecting drugs to be entirely beneficial, and a lack of scientific literacy means the public expects medicines to be absolutely safe. The concept of balancing through design, formulation, and dosing the potential toxicity or undesired side-effects of a medicinal treatment would be an alien concept to the majority of people;[56] "Why make a drug that could be dangerous? That's just bad workmanship!"

Maybe a change of tactics involving more education rather than propaganda could help prevent the type of backlash responses of recent discoveries. The public outcries have, in these recent cases, been entirely justifiable from their standpoint; indeed the general perception of pharmaceutical industry and its reputation has been significantly tarnished. Historically, it has been difficult for the industry to communicate directly with patients because of restrictive government ordinances, creating a distance between producer and consumer. For any such industry promoting an ethical product, it's never a good time to have the ethos of its commercial intent brought into question. Establishing realistic risk–benefit profiles and then communicating them effectively to patients will help engender public trust again. In its defense, the sector has been very proactive in working with the regulatory agencies in defining new codes of practice and new ways to disseminate information, but only time will prove if this is too little and too late.

3.3.2. Advertising budgets

Another area that has seen significant growth in recent years is the advertising budgets of the main drug manufacturers. Pharmaceutical companies looking to maximise the circulation of their drugs are expending large sums on global marketing campaigns. It has been stated that marketing departments exert an excessive influence over the scientific decision-making process about which projects should move to the next stage of development and into clinical trials.[57] Over £13.6 billion was earmarked for advertising in 2003, with the majority of this £11.9 billion (87%) directed toward physicians, and the remaining £1.7 billion (13%) directed toward consumer marketing of new drug lines.[58] This indirect consumer marketing may seem unusual, but in established markets only the US and New Zealand allow direct advertising of prescription drugs to patients; thus it becomes more understandable. This restrictive advertising has been a point of contention within the industry for a long time. The industry's standpoint has been the argument that advertising provides important information to consumers—the patients—who will directly benefit from advertised products. Hence, the pharmaceutical manufacturers have campaigned and canvassed for a relaxation in the regulatory restrictions of large markets like Europe and Canada.[59]

It is certainly possible to take a cynical stance regarding the motives of the drug industry, and such advertising should be expected to increase sales, but in addition, much of the marketing is also directed towards education. As already stated, a large portion of the advertising budgets of the top companies are targeted at physicians and pharmacists who are the individuals that prescribe such therapeutics, meaning that mass advertising to this audience would seem a very logical business decision. It is this same group, however, that requires the most current and comprehensive scientific literature regarding drug dosages, compatibilities, potential side effects, biological (Prozac versus Zoloft) and chemical equivalence (Miltown and Equanil) amongst many other indicators. It has been identified that a significant cause of patient illness can be attributed to mistakes made in prescribing drugs by medicinal practitioners; in the UK this figure has been tentatively estimated at 6.5% of all accident and emergency admissions.[60] Many of these errors are due to insufficient knowledge and basic misunderstandings of the products and their application with other medications. Providing more accurate diagnosis criteria and treatment options would certainly seem to be a logical approach to combating otherwise easily avoided problems. It would also seem wise to stand-

ardise a practice for healthcare professionals enabling them to update their knowledge and skills. The question of support and sponsorship from pharmaceutical companies for such a process could be ethically mediated by a independent centralised body, possibly as an extension of the EMEA or the FDA.

3.3.3. Maintaining a product pipeline

The large pharmaceutical companies can offer unprecedented muscle in terms of marketing knowledge and resources, including validating a product with their recognised and trusted corporate name. Consequently, more of these corporations are pursuing licensing agreements to bolster their pipelines through collaborations with smaller companies as an alternative method of accessing promising late-stage candidates. Such deals are typically associated with the ongoing development and co-promotion of the therapeutic entity and its eventual introduction and distribution to the market. This can be a very profitable arrangement for both parties, providing as it does, additional market penetration and pipeline extension for the larger partner whilst also off-setting a significant proportion of the launch costs from the often more cash-restricted alliance company. The exact mechanism for financial recuperation can be varied, but is often modelled on an initial access payment from the interested organisation to the smaller inventor, with subsequent milestone rewards or percentage revenue sharing being negotiated by evaluation and sales triggers. This type of marriage of convenience is certainly beneficial, as evidenced by the 15% increase in successful licensing deals in the last 5 years.[61] In real terms, this equates to almost one fifth of the total medicinal sales of the top 20 pharmaceutical companies or a financial value of around £34 billion. Indeed, this trend is expected to continue further, resulting in these large pharmaceutical companies deriving approximately one quarter of their forecasted sales from licensed products by 2010.

In analogy to the drug pipeline of the big pharmaceutical companies, small biotech firms are often a very high-risk venture due to their significant attrition rate; however, occasionally a technological development can catapult one of these biotech companies into a prominent scientific position. This can often bring the company to the attention of the pharmaceutical giants as an acquisition target, providing as it does, both new drug avenues and the expertise to realise resultant therapies. For example, AstraZeneca has expanded its portfolio in the fields of antibody therapies and oncology by direct acquisition of Cambridge Antibody Technology and KuDOS Pharmaceuticals. It is important to emphasise the significance of how such corporate takeovers are essential to the continued development of the biotech sector. The ultimate premium stock-market valuation of the acquired company acts as an inspiration for subsequent speculative investment within this high-risk, yet potentially high-return, area. Such an approach permits the large pharmaceutical company to offset some of the risks involved in bringing a therapy to market by indirectly supporting innovation-driven drug discovery.

The debate therefore centres around the question: is the future of drug discovery really in the hands of small innovative biotechs? Furthermore, will such companies make the new drug discoveries whilst large pharmaceutical companies subsequently position and manage these candidates to the marketplace? Should more out-licensing be encouraged in order to give better opportunity for innovation, thus stimulating an increase in the development of candidates that are not industry recognised as financial blockbusters, but are effective therapeutics nonetheless?

The pharmaceutical industry has traditionally never been a conservative spending power. The corporate mentality has been that it could always buy itself out of difficulties; throw enough money at the problem and it ceases to be a problem: the pharmaceutical fix. Following such an approach as opposed to imposing cost restraints and searching for gradual improvements in efficiencies, large pharma has had to vigorously peruse the evasive blockbuster drug and its next big pay day. The industry Holy Grail has always been about getting the big product to market in the fastest way possible; this tactic is an expensive exercise and therefore self-defining in terms of corporate resource management. However, constructive managerial guidance of such a process has proven somewhat haphazard. Many managers in positions of influence have expressed relief at being "in the right place at the right time" to exploit their companies position.[62] Although it would be easy to provide reassurance to justify management decisions that enabled companies to be in opportune positions to exploit their research, industry statistics demonstrate such sporadic successes are not a readily reproducible phenomenon. New, more methodical R&D strategies centred on a streamlined discovery process and early identification and elimination of non-ideal target structures is becoming the industry standard.

3.4. New pharmaceutical approaches

Recently, the pharmaceutical industry has started to subscribe to an alternative economic philosophy based on the assumption that wasted resources equates to decreased productivity and thus reduced profits. Such thoughts have clearly been inspired by the desire to drive down costs, but also by environmental and ethical considerations.[63] A popular quality manufacturing concept is Lean, and it is a notion that all manufacturers strive for. This production monitoring process originated with the Toyota automobile production facilities in Japan, where managers discovered that removing waste from the production process increased the flow of products while additionally raising the overall quality of each product. Lean is simply about deriving increased value by eliminating activities that are considered "muda"—wasteful. As a philosophy, Lean manufacturing is a desirable principle, but in order to formulate it into a sustainable working practice it requires an analytical business construct. Consequently, Sigma, or more precisely, Six Sigma methodologies have provided the tools and techniques to improve the capacity and reduce the defects in many processes. To achieve this, Six Sigma uses a methodology known as DMAIC, an acronym of the

component methodologies. This is a cyclic iterative evaluation process that interrogates a failed or failing procedure against a set of idealised criteria; the process is then altered and tested to find out if there are any improvements. If no improvement is found, the cycle is repeated. Statistical modelling is used to determine the optimum values and identify pertinent variables.

To date, the adoption of Lean and Six Sigma has been almost entirely limited to the administrative, marketing, and distribution divisions of the pharmaceutical industry. Extension to the R&D environment has been more problematic because of the creativity and fluidity of the process; defining suitable standards and then indicating limits and tolerances are involved and complex issues. The main problem has been the lack of validated statistical data on many processes; no two projects have the same starting point, and the aims and direction of the research can change daily as more information is accrued. Capturing information on the many aspects of the R&D process in an efficient and assessable form is crucial to the identification of trends and the development of best practices. However, with the pharmaceutical industry's primary task being knowledge generation, the capture mechanisms and assessment principles should already be in place, even if not fully recognised as such.

Pharmaceutical companies create and sell proprietary knowledge. This is often transcribed to a final product that is a 'pill', but these tablets represent an apparently simple solution to a complex biological problem. The understanding of the specific disease mechanism, the control and regulation strategies, the administration routes (physiology and pathology), and toxicology information, amongst many other factors all contribute to a powerful knowledge matrix. None of this information is really sold in the resultant 'pill', but without it no simple drug treatment would be viable. Harmonising and streamlining the R&D processes is obviously desirable, but determining all the parameters and formulating a coherent strategy will be a massive consolidation. However, certain tasks within the R&D cycle could derive more immediate gains from a Lean–Sigma approach. For example, the workflow process of chemical development through to pilot plant/kilogram-scale lab preparation is a relatively disjointed process and can comprise a significant number of repetitive and overlapping operations. This is inherent to the current working practice, because separate divisions are responsible for each particular synthesis requirement, that is, Medicinal Chemistry, Resynthesis, and Process. Often the synthetic route developed by one section is discarded in favour of an alternative pathway because of translational problems in scaling. However, such changes require investment in terms of both time and facilities but add no additional value to the development candidate. The same problem can be highlighted for resynthesis operations which may require the same compound to be prepared multiple times in order to complete the biological campaign. To affect these particular problems the synthesis operation as a continuum needs to be evaluated, and the basic procedures adopted at the early stages targeted. Devising new synthesis methodologies that enable smooth development and seamless scale-up opportunities will be the new challenge to industry and academia.

4. Pharmaceutical Development

4.1. The strategy

Are companies becoming too big, and hence is the industry forced to be too cost-driven because of the massive risk of failure? It is certainly hard not to justify some form of industry reorganization as the main players have evolved into diverse multinational conglomerates through repeated high-profile mergers. In the past, blockbuster drugs based on new active compounds for treating prevalent diseases that previously lacked effective therapies have generated the required sales revenues of the top pharmaceutical companies. However, few major manufacturers, if any, are now capable of meeting the financial pressures solely through the introduction of products based on entirely new therapeutic classes.

Innovation within the pharmaceutical industry varies widely, ranging from breakthrough treatments for life-threatening diseases to minor modifications of drugs that have been on the market for some time. Both the FDA and the EMEA classify all NDAs by two criteria: chemical type and therapeutic potential. The most innovative type of synthetic drugs are comparatively rare, being medicines that contain new active ingredients that provide significant clinical improvements over existing therapies. The more common drug applications are a result of the increased emphasis on incremental drug development. In order to revitalise or prolong the product life cycle and maximum sales potential, drug companies are continually screening for new therapeutic indications of their drugs. An evaluation of the top 20 best selling drugs in the US (1993) showed that within only two years almost 40% of their revenue was attained from the treatments of secondary indications.[64] Similar statistical analysis of the top 50 UK drugs showed that a significantly smaller but still substantial 25% of their sales were also derived from indications other than their initial registration.[65] This is clearly not a negative factor, as it also maximises the therapeutic benefit of the available drugs to humankind.

In addition, by fostering line extensions to existing products that use the same active ingredient, but differ from the original in some way such as increased safety, effectiveness, or more convenient dosing forms, manufacturers can extend the intellectual property protection and limit the threat of generic competition to their franchises. Such an example is AstraZeneca's asthma medication Pulmicort Respules, which was devised for young children. At the time of approval its active ingredient, budesonide, which reduces the inflammation that often precipitates an asthma attack, had been used as a maintenance therapy for over 15 years in various anti-asthma formulations worldwide. However, inhaled corticosteroid therapies required administration with an asthma inhaler, which young children were unable to use. Pulmicort Respules, by contrast,

integrated a dispersion nebuliser to convert the medication into a fine mist, which the child could then inhale through a basic face mask or mouthpiece. The new product, as the first corticosteroid to be available in a nebulised formulation, provided a solution to a previously unserved paediatric asthma population, thus gaining distribution approval and patent coverage.

Manufacturers are also formulating multiple drugs into new marketable tailored therapeutic products, namely "new combination" medicines.[66] By combining the active ingredient of various approved drug substances, new formulations can be created that offer remedies with synergistic effects, such as Bristol-Myers Squibb's Glucovance, a product containing two oral anti-hyperglycaemic drugs used in the management of type II diabetes, namely metformin hydrochloride and glyburide. Metformin hydrochloride was the active ingredient in Bristol-Myers Squibb's original anti-diabetic drug glucophage, whereas glyburide was a readily available generic. The new combination prescription demonstrated enhanced pharmacokinetic profiles over the original monotherapy glucophage and the other marketed drugs in the same therapeutic class, allowing it to be awarded market approval. Similarly, Boehringer-Ingelheim released Aggrenox to reduce the risk of repeat strokes. Aggrenox is another combination medicine composed of aspirin (antithrombotic action) and dipyridamole, a compound that inhibits the uptake of adenosine into platelets, endothelial cells, and erythrocytes. The specific dose-dependant mode of action inhibits platelet aggregation in response to various stimuli such as PAF, collagen, and ADP levels. The FDA based its approval on a study finding that Aggrenox administration reduced the risk of recurrent stroke by almost a third relative to placebo treatment, and was over 20% more effective than aspirin alone.

In other cases, compounds that are resigned to a company's sample collection library because of their insufficient potency against a previous desired target can be identified as SAR leads or interesting development candidates in subsequent library screenings. Such was the case with GlaxoSmithKline's Retrovir (zidovudine, previously named AZT), which is a synthetic thymidine nucleoside analogue reverse transcriptase inhibitor and the first drug to be approved for the treatment of AIDS. The drug was initially investigated in the 1960s within the context of potential anticancer activity, but showed only minimal promise. Following its launch in 1986, many new antiretroviral agents have been synthesised. Indeed this category of illness provides many examples of the flourishing new combination and follow-on medications.

In general, the re-evaluation of viable markets prompted by fluxional operating environments has led many key manufacturers to move away from the established blockbuster corporate models towards smaller niche markets. In order to spread the potential financial risk, many companies are forming partnerships or joint development ventures to tackle problems associated with these rare diseases.[67] Increasingly, however, such specialised targets are attracting more attention because of various charitable development grants, expedited registration, reduced clinical regulation, and very favourable tax incentives. This type of commercial transposition is aptly represented by the recent surge in anticancer therapies. In recent years many new drugs have been developed in this area and include some very successful treatments, such as Avastin (bevacizumab) for colorectal cancer growths within the large intestine and Glivec (imatinib mesylate) for leukaemia. Less prevalent cancerous conditions have also been targeted, for example bortezomib (velcade), released through a collaboration of Millennium Pharmaceuticals and Johnson & Johnson, is used to treat multiple myeloma. Such collaborations between commercial entities have clearly been a profitable endeavour. Alternatively, a possible pathfinder to new drugs may be collaborations between industrial, academic, and charitable bodies, such as is seen in the development programme announced between Sareum Holdings plc, The Institute of Cancer Research and Cancer Research Technology Ltd.[68] Further initiatives targeting killer diseases such as malaria and tuberculosis are receiving backing from organisations such as The Gates Foundation.[69] With the cost and regulation of drug discovery expected to increase further, such partnership strategies provide opportunities to pursue less commercially viable treatments. Furthermore, working in this type of research environment facilitates a greater degree of scientific freedom leading to increased levels of innovation.

4.2. Chiral compounds

Chiral drugs have also become more important to the drug industry. In 2004, chiral drug development accounted for almost a half of all the emerging and updated drug strategies and is expected to become the predominant class by 2008.[70] However, in spite of the phenomenal advances in stereogenic centre control that are available to us today, the industry still seems to actively avoid the introduction of chiral centres into drug candidates, despite the fact that biological receptors are chiral. The enhanced selectivity and function that can be delivered by chiral materials has to be medically advantageous. Odour perception is a very good example of this principal, as the enantiomers of more than 285 compounds are known to exhibit differing odours or odour intensities.[71] One of the most interesting stories of the evolution of a racemic drug into a single enantiomer equivalent is that of Omeprazole, which is used as a treatment for Zollinger–Ellison syndrome.

This potent inhibitor of gastric acid secretion[72] was first made commercially available in 1998 by AstraZeneca (premerger), and by 2000 it had become one of the world's best selling blockbuster drugs. The patents however, in the drug's biggest markets of Europe and the US, were destined to expire in 1999 and 2001, respectively. AstraZeneca was able to successfully protect its investment and market by moving to a single-enantiomer formulation. In order to gain regulatory approval and protection, the updated prescription must offer advantages in terms of patient treatment (see below). The original racemic form of Omeprazole exhibited polymorphism, resulting in reduced uptake by certain population groups. The single *S*-enantio-

mer drug was deemed therapeutically beneficial because of less individual patient variation resulting in higher average plasma levels leading to higher dose efficiency.[73–75] Introduced as the magnesium trihydrate species under the trade name Nexium (esomeprazole magnesium) this compound is still one of the most prescribed therapies for acid reflux and gastric ulcers on the market. Indeed, this molecule remains at the centre of many development programmes and patent investigations that will undoubtedly expand into a more comprehensive case study in the years to come.[76]

5. Innovation in Drug Discovery

5.1. New molecular entities

Drugs containing active compounds that have never before been approved for market use are designated by regulatory bodies such as the FDA as NMEs. During the 16-year period from 1989 to the end of 2005, the FDA approved 1152 new drug applications. Of these, only 417 or 36% were for NMEs, meaning that 735 medicines (64%) contained active ingredients that were already available in other marketed products. Many of these only differed from existing products in dosage formulation, route of administration, or were combined with other active ingredients; they were available essentially as repackaged products. However, as already pointed out, many of these modified pharmaceuticals offer major benefits to the patients, and so represent valid development routes. A commercial and possibly ethical question is when should a company follow a programme that tries to develop incremental improvements of existing products as opposed to a more adventurous programme that could lead to possibly fruitless research. Clearly from a commercial point of view this is strategically a very complex decision and normally the two approaches will be run in tandem, although the absolute resource distribution can vary greatly.[77]

A seminal paper published by Robert Solow[78] in 1956 proposed a theory that for viable and sustained economic expansion, technological progress must be embraced.[79] Recent theoretical models[80] have expanded upon this assumption, hypothesizing that specific scientific progress is a synoptic gauge of a society's R&D capabilities and is directly coupled to its economic prosperity. Empirical evidence[81] is consistent with this supposition, in that those firms and industries that perform the most innovative R&D exhibit the highest productivity and enhanced financial growth. Consequently, industries such as the pharmaceutical sector, which represent a technological focal point for several multidisciplinary cutting-edge research channels that accumulate in a high-tech end product, can generate significant economic multipliers. Such financial returns are, however, ultimately distributed back through to the support industries, invigorating further innovation of new products thus enabling additional upstream breakthroughs. For example, most of the scientific apparatus, by definition, is expected to embody significant technical progress due to the relatively high R&D intensity of such equipment manufacturers; each successive strata of R&D investment that uses the base technology should, as a result, be more productive than the last.[82]

Pharmaceutical companies with long-term vision have realised that they need to encourage and nurture new ideas that require them to reinvent and evolve in order to keep pace with the changing world and its demands.[83] The risks associated with this are high, and gambling with a company's future has become totally unacceptable to many institutional investors. Pharmaceutical giants are now perceived as a safe blue-chip investment market, but it might be argued that such consideration and expectation has translated into the industry becoming less creative and pioneering. In the same way, has the establishment of the household pharmaceutical mega-corporation meant that these companies have consequently become too reliant on consensus management sidelining the individual science drivers and inspired compound champions of old? Obviously, pharmaceutical futures lie in sustainable product pipelines, but where will these new products come from if innovation is removed from the equation?

It has already been mentioned that a major source of new therapeutics for large pharmaceutical companies is being drawn through licensing agreements from smaller concept-based startup companies that possess novel entry technology. The larger companies then act as facilitators, shepherding these compounds into the marketplace. Another substantial part of the growth experienced in the pharmaceutical industry over the last decade has come from biologicals (biotechnology-derived pharmaceuticals and fine chemical intermediates: the market grew 17% to £17.8 billion in 2005) for which there is no synthetic preparation method readily available.[84] Substances such as monoclonal antibodies and protein therapeutics are key emerging markets and are expected to account for market values of £6.46 billion and £31.75 billion, respectively, by the year 2010.[85] Although these represent an important and exponential growth area, they still only satisfy a relatively small quota of the pharmaceutical industry's requirements. Additional drivers are required to enhance the more traditional R&D routes, increasing throughput and reducing candidate attrition.[86] What are these innovative new science drivers, and how are they manifesting themselves into effecting change in R&D strategies?

5.2. Innovation in drug delivery[72]

One of the most important considerations taken by regulatory agencies for granting marketing clearance for a new pharmaceutical therapy is its proven enhancement over the established products. An increase in the drug's potency, safety profile, or efficiency of delivery is characterised as a significant and worthy development criteria. In this respect, the identification of prodrugs and drug metabolites has become an even more important consideration in modern drug-development strategies.

Drug metabolism is the process by which the body breaks down and converts a medication into either an active or passive chemical substance. Such biological mediation affects many physiochemical properties,[87] but principally it impacts on drug transport and can magnify the desired therapeutic effect of a

drug, or may cause unwanted or unexpected chemically induced side effects. Therefore, predicting essential human pharmacokinetic properties and understanding the mechanism for absorption, distribution, metabolism, excretion, and toxicology is a vital research endeavour within the drug-design process. In addition, oral bioavailability constitutes a major challenge and a highly prized property of any potentially drugable compound.[88]

5.2.1. Prodrugs

The rationale for the development of prodrugs relies upon delivery of higher concentrations of a drug to target sites relative to administration of the drug itself. Although this approach can offer tremendous advantages in terms of bioavailability, there are limitations, such as potential lack of site-specificity, which mean this approach will not always improve the therapeutic index. A more involved drug activation strategy can often lead to enhancement through site-targeting prodrugs. These molecules are pharmacologically inactive molecules that require several steps of chemical or enzymatic conversion in order to attain the active drug. The superior medicinal effect is notably achieved through enhanced drug delivery to a specific tissue distribution or organ, such as up-regulation in tumour cells. The subsequent activation is then triggered by a combination of chemical or biological processes that are highly specific to the target system, in effect, a coded release pattern.

In addition to delivery strategies, degradation and excretion pathways have also been developed. A class of pharmaceutical candidates called soft drugs operate by which the biologically active, therapeutically useful compounds undergo predictable and controllable in vivo deactivation, after fulfilling the therapeutic objective, to nontoxic, inactive compounds.

5.2.1.1. Drug conjugates

The selective in vivo metabolism of synthetic drug conjugates leading to bioactivation has also become a key drug-delivery strategy.[89] In this way, many inert functional carrier constructs such as small peptides, lipids, carbohydrates, and various polymer formulations have been devised to allow targeted and measured drug release or to optimise viral delivery.[90] This also allows the use of multi-drug combinations as well as the transport of physiologically incompatible substances and potentially toxin-masked therapeutics, termed the pharmaceutical warhead approach. Polymer therapeutics[91] based on polymer tags or polymeric micelles containing covalently bound drugs and polyplexes for DNA delivery have also started to reach the market. The versatility of synthetic polymers readily permits the tailoring of molecular properties such as weight, physical size, hydrophobicity, and incorporation of additional bioresponsive elements.[91e,92]

Classically, long-stranded polymers such as precision-manufactured PEG are employed, although newer branched or starburst dendrimers[93] are finding successful applications. Such materials that are often capable of forming protective polymeric micelles or spherical vesicles are employed, which also incorporate efficient release strategies as part of their design, permitting these polymer–drug conjugates to function as prodrugs. Another class of materials that are being developed for drug delivery are the so-called intelligent biomaterials, which use site-specific molecular recognition to trigger drug release. Encoded polymers programmed using techniques such as molecular imprinting can create drug-delivery systems that allow the slow release or extended circulation of a therapeutic. Preparation of these systems from biocompatible materials can even lead to an implantable drug-delivery device[94] that is especially useful in regulation or long-term illnesses. All of these concepts require increased investment in both chemistry and the detailed understanding that underpins the processes.

6. The Search for New Molecular Entities

6.1. Chemical and diagnostic techniques

The pharmaceutical industry has passed through a remarkable transition over the past two decades in its mission to identify novel compound structures that regulate specific control aspects of new biological targets, thus paving the way to new healing agents. The first signs of change were initially apparent in the biological field, as screening assays first reached micro- and then sub-micro-administration levels. The testing capacities were additionally bolstered by powerful automation that permitted multiple samples to be rapidly assessed; thus the foundations for high-throughput screening were laid. Indeed, given the limited initial biological information available for most therapeutic targets, HTS remains the only investigative tool that can generate lead molecules de novo in a realistic time frame. As a result, HTS is currently the industry standard for lead structure identification for a large variety of biological targets.[95] At its outset, HTS shifted the discovery bottleneck firmly to the door of the medicinal chemists. The traditional practices of single-compound bench-top synthesis could no longer satisfy the insatiable demand of the biologist, and combinatorial chemistry rapidly evolved to compensate for this shortfall. Given this ability to construct a multitude of rapidly assembled compounds, the pharmaceutical companies should have been able to reap the rewards. The problem was that although effective for delivering large numbers of compounds, combinatorial chemistry did not necessarily generate molecules commensurate with the desired biological activity. The success of HTS in mapping a new receptor site relies on access to a collection of compounds that possesses a very broad range of chemical functionality distributed across a uniquely configured three-dimensional structural template. As powerful as it is, HTS alone is not capable of identifying drugs, in that it can only effectively indicate a general compound class or lead, providing that the com-

pound screen is sufficiently large and diverse.

Combinatorial chemistry tended to generate structurally similar chemical series; in many cases target evaluation and validation was not considered to be of high importance compared with array size. Consequently, the attrition rate of potential lead candidates entering early HTS programmes was extremely high, often in excess of 80%.[96] Supplementing this high failure rate were problems associated with compound logistics in terms of controlling purity and registration of so many new compounds.

Modern strategies in high-throughput chemistry are now primarily focused on quality rather than quantity, with stringent purity standards (>85% or even >95% for certain compound types) having been established to avoid the emergence of false leads in HTS; almost every pharmaceutical company now applies repeated purification procedures and analysis to their archived compound libraries.[97]

More effort is also expended to prepare high-quality lead structures that serve as optimum starting points for lead optimisation. Compound libraries are now designed to exert both lead and druglike properties through fit-to-target approaches.[98] The move towards the creation of smart combinatorial libraries through the extrapolation of preferred features defined by precedence and any SAR information, as well as guides from computational analyses has resulted in a more rational approach. Additional strategic approaches to compound design through greater knowledge of bioisostere-, pharmacophore-, and chemotype-morphing concepts have also aided chemists in redefining or opening novel chemical space, thus expanding the drugable universe. The other major change in strategic approach has been the enhanced emphasis placed upon previously late-stage assessment of physicochemical, pharmacokinetics, and toxicological properties (ADMET) to access the drugable characteristics of the molecules.[99] The importance placed upon such characteristics can be seen in the fact that most major companies now apply significant pre-screening filters to identify undesirable features.[100]

The days of searching for the most active molecule possible are gone, with the game now being a balance between the safety profile of the compound and its potency. In this respect, establishing a set of suitable and reliable HTS follow-up screening cascades to support HtL development has become of paramount importance. Confirmation that the observed hit activity is real and thus tractable as a target is an essential starting point.

HTS methods coupled with HT chemistry provides the ability to make and test tens of thousands of compounds. However, this approach generates enormous volumes of biological test data, which needs to be analysed in order to generate predictive QSAR models.[101] Often this is required to guide further rounds of compound selection, synthesis, and testing through a series of evolutionary molecule developments using hereditary synthesis and screening methodologies (parent-to-child as a part of HtL). This has been enabled by the emergence of intelligent data examination systems.[102] Informatics applying the techniques of neural networking and artificial intelligence can be used to predict which molecules within a large set are most likely to display the biological profile specified by a particular drug-discovery programme. Therefore, virtual libraries composed of large data sets are regularly subjected to diversity analysis to determine the minimum acceptable number of compounds for subsequent synthesis and testing that should display all of the biological activity for the whole library. However, the analysis of these greatly escalating stores of chemical data and biological information does not necessarily equate to the discovery of the perfect drug. New technologies that facilitate the rapid synthesis of these compounds are also required.

6.2. The modern laboratory

Historically, laboratory design has been conducted with a specific function in mind, with synthesis, analysis, or biological screening as separate endeavours. The basic infrastructure such as plumbing, ventilation, and bench installations have dictated the floor plan and generated the specific working environments. New labs need to be built with both the short- and long-term occupancy and use in mind; such high-tech environments require the intimate interaction of scientists, engineers, and architects at all stages of laboratory construction, not just towards the end, when ideas can often be overlooked because they do not conform to the aesthetic plan.

The modern laboratory needs to be able to respond rapidly to a multitude of challenges that are presented. A higher level of intrinsic flexibility needs to be built in, especially if it is to support emerging technologies such as microarrays or microfluidic devices for the early capture of biological data within the synthesis environment. The laboratory also needs to be responsive to the ergonomics of efficient molecule synthesis by bringing together a wide range of synthesis and analysis equipment in a functionally adjacent manner, with a minimum footprint, maximising the vertical over the horizontal space. The traditional fume hood must change to a potentially mobile and easily reconfigured unit that becomes an integral part of the information- and data-capture process; in silico avatars and other synthesis enhancement technologies need to be integrated into the new style of working, and away from the synthesis silos of the past. Such design criteria will require a commercial balance of flexibility, functionality, and configuration stacked against the development costs that will, however, ultimately stimulate the necessary levels of innovation and productivity.

A key driver of future working practices will be the closer collaboration between more scientific disciplines such as engineering and informatics. A focussed interdisciplinary approach coupled with more efficient usage of laboratory space and time will clearly enhance output. This is even more important considering that the majority of drug developers are multinational companies spread across various sites around the world. This globalisation means that the classical 9-to-5 working environment or interaction is stifling to the current and future discovery culture. Rather, a switch that allows a laboratory to be available on a

24/7 basis will be needed, with the whole research site becoming a form of "science hotel".

Regardless of the exact setup, the laboratory should always endeavour to foster creativity and serendipitous discoveries. However, the specific catalysts and mechanisms by which such ambiguous targets can be achieved are clearly almost impossible to define and implement, meaning that each laboratory construction equates to an experiment in architectural optimisation.

6.3. Emerging technologies: a personal perspective

With the new focus in synthetic medicinal chemistry being the delivery of high-quality compounds in high-purity states, the next hurdle for chemists to surmount has become a mounting purification bottleneck. To some extent, solid-supported reagents and scavengers[103] have become an industry standard to expedite synthetic transformations, enabling the preparation of complex molecules[104] without the requirement for conventional purification procedures.

However, the synthetic protocols pertaining to these operations have conventionally been batch procedures involving dispensing and filtration of the solid-phase species. In most cases, such repetitive operations have been the labour-intensive aspect of the synthesis procedure. While this has, in part, been offset by the introduction of automated systems capable of solid handling, the conceptual shift of moving from a situation of sequential addition and filtration steps to a fully integrated flow-through system represents a significant operational advance. In fact, such a change in working practice actually facilitates a more effective approach to synthesis in the way we design and conduct chemistry because of the greater degree of knowledge that can be harvested about a reaction in real time.

When conducting batch chemistry each optimisation is a significant investment in synthesis time and resources; even working in parallel, we still tend to only investigate indications or definition sets of best guesses. Employing powerful design of experiment analysis software[105] does not improve the situation greatly; we still conduct optimisation in a similar manor to the way we search for a lead compound that possesses a particular function or property. We inevitably devise or use sets of conditions or look for a molecular architecture that best displays or covers the synthesis space. This tends to be an ineffective practice because we are selecting from an infinite matrix of possibilities. This is especially true when we embark on the optimisation of a specific chemical reaction for which it is possible to simultaneously evaluate different reaction conditions and synthetic approaches to the target functionality. The situation can become even more compounded by attempts to generate generic conditions, which are then applied to library synthesis using a diverse set of reactants. Such an approach will often lead to high levels of failure, especially with respect to the purities of the compounds derived from these procedures. The application of flow processing by which we can monitor the transformation using the data to feedback into the reaction to effect direct modifications provides a way of conducting synthesis where failure could potentially be entirely eliminated. For example, a self-optimising system can be constructed that includes various back-end analysis devices, such as an HPLC system, which are used to interrogate the flow path.[106] This generates a vast quantity of analytical data that can be evaluated and immediately used in the continued development of the chemistry. The ready ability to monitor each transformation in real time enables the construction of telescoped sequences of multiple synthetic steps into a single continuous operation, thereby permitting the preparation of complex targets within a drastically reduced timeframe.[107]

Once the technological capability has been developed to prepare high-quality molecular entities comprising all the desired members of a compound library in an on-demand fashion, the only question that remains is what to synthesise next. This question can be addressed in an iterative fashion by using the results from the testing of the initial library to determine the next chemical series. A logical extension to this scenario is to directly couple the synthetic flow stream into an on-line biological screen. In the same way that conducting chemistry in a flow domain can expedite the synthetic procedures of the chemist, a similar parallel could be drawn to the screening protocols of the biologist. Making this a rapid integrated iterative looping mechanism creates a very powerful and versatile discovery platform.

7. Final Remarks

It is relatively easy to be critical of an institution or industry from the outside; however, we as academics consider ourselves to be part of the same scientific community as the pharmaceutical industry and therefore feel our comments may be of value in initiating discussion. It would be equally interesting to discuss the global issues affecting university research and education with respect to the future impact this will have on the pharmaceutical industry.

Although serendipity will always be part of the drug-discovery process, the greatest impact will be made by smart ideas and outstanding people who are able to build upon the resultant science. Contemporary pharmaceutical researchers are working at the frontiers of chemistry, biochemistry and biology, pharmacology, toxicology and medical science, combining the latest knowledge with well-educated guesses. However, the advantages provided by many of today's powerful drug-hunting technologies are sometimes offset by what is seen as a loss of freedom and the inability to properly explore novel ideas. The general inflexibility of the current system in its hierarchically controlled and restrictive attitude to drug discovery creates a questionable level of individuality in an industry that survives on the creativity of its workforce. Providing the scientific base with the freedom to innovate within the corporate structure will develop a more diverse and inspired discovery platform.

While as academics our focus is primarily on scientific discovery, whereas industry is perceived to be about the application of science to the benefit of humankind, these two drivers cannot and

should not be pursued independently. Good processes and procedures are important, but we believe it is good science that should be the fundamental driver for the discovery of a good drug.

8. Glossary

ADP	adenosine diphosphate
API	active pharmaceutical ingredients
ADME	absorption, distribution, metabolism and excretion
ADMET	absorption, distribution, metabolism, excretion and toxicology
AZT	azidothymidine
CMC	chemistry, manufacturing and controls
DMAIC	define opportunities, measure performance, analyze opportunity, improve performance, control performance
EMEA	European Agency for the Evaluation of Medicinal Products
FDA	US Food and Drug Administration
GLP	good laboratory practice
GMP	good manufacturing practice
HtL	hit-to-lead
HTS	high-throughput screening
IND	investigational new drug
IPP	intellectual property protection
NDAs	new drug applications
NHS	UK National Health Service
NME	new molecular entities
PAF	platelet activating factor
PEG	poly(ethylene glycol)
PK	pharmacokinetics
QA	quality assurance
QSAR	quantitative structure–activity relationship
R&D	research and development
SAR	structure–activity relationship
TRIPS	trade-related aspects of intellectual property rights

Acknowledgements

We thank colleagues in the pharmaceutical industry for their stimulating feedback on the manuscript during preparation. We gratefully acknowledge financial support from the RS Wolfson Fellowship (to I.R.B. and S.V.L.), the Natural Sciences and Engineering Research Council of Canada for a postdoctoral fellowship (to G.K.T.), Novartis for funding (to J.J.H.), and the BP endowment and the Novartis Research Fellowship (to S.V.L.).

Keywords: academia · biotechnology · chemistry · drug discovery · pharmaceutical industry

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Received: January 12, 2007
Published online on April 26, 2007

