Strategic choices facing the pharmaceutical industry: a case for innovation

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The pharmaceutical industry was founded at a time of unusual scientific, political and economic opportunity, but now the industry finds itself facing important choices in a difficult economic and regulatory environment. Only those companies capable of improving the productivity of their R&D departments can remain important players in the future. The author discusses the different approaches to innovation that are available to the leading pharmaceutical companies and argues for the 'offensive' strategy.

After more than a century of a productive and profitable development, the industry finds itself in difficulties. On the one hand, health care, of which the pharmaceutical industry is an important part, is subject to increasing cost-containment measures in nearly all industrialized countries. On the other hand, the costs of bringing a novel medicine to the market have skyrocketed.

Some strategic choices available to the industry under these circumstances are discussed here. In particular, an innovation strategy is outlined, the main elements of which are the following:

- Collaboration with biotech companies in order to participate in the flow of recombinant proteins that will reach the market in the next few years.
- The establishment of a collaborative portfolio with academic laboratories leading to an increased flow of 'pre-incubated' projects into the industry.
- The formation of more independent research units that are responsible for one or several areas of research.
- The successful assimilation of new technologies, in particular genomics, combinatorial chemistry and high-throughput screening.

Only those companies capable of improving the productivity of their R&D departments have a chance to remain important players in the future health care environment.

Birth of a new industry

The pharmaceutical industry was founded at a time when chemistry had come of age: the effective components of many traditional drugs, such as morphine, quinine, alkaloids from ipecacuanha and others, had been isolated and could now be made available in pure form[1]. Coal tar, an abundant side product of coking, had provided synthetic chemists with a huge tool kit of building blocks for organic synthesis[2]. Pharmacology had established itself as an experimental science and chemotherapy had articulated the principles of selectivity based on the difference of chemoreceptors on hosts and parasites[3,4].

All of these technical advances were ready to be translated into practical progress. Pharmacies, which had been in charge of supplying drugs to doctors and patients, had not recognized the challenge that lay ahead[4]: to provide drugs of standardized quality to large populations. It was the perfect setting for the birth of a new industry.

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A changing environment

Over subsequent decades the industry almost monopolized drug research, development, production and distribution and was uniquely successful in doing so, both from a scientific and from a commercial perspective. But one century after its birth, the industry finds itself in a difficult situation. What happened? The multitude of societal, scientific and economic changes that are usually invoked to describe the troubles of the pharmaceutical industry can be reduced to a few major factors:

- Health care costs in industrialized countries have risen to a level that cannot be sustained without sacrificing other justified claims to public finance (such as education, welfare and the environment). Drug costs form a relatively small part of overall health care expenditures (8–20%) but represent a relatively easy target for correction.
- There is a growing public intolerance of drugs that are only repetitions of medicines already on the market with few, if any, improvements. 'Me-too' drugs are not likely to rank high among reimbursable items on the priority list of health care providers the world over[5].
- The discovery and development of novel drugs has become so expensive (about $359 million per drug, taking into account all failures along the way) that the development expenditures can only be recovered if a drug is marketed in several, if not all, of the major markets of the world[6,7].
- While the scientific prerequisites of finding and developing novel drugs are more numerous and better than ever before, they are no longer available within one industry, not to speak of single companies. In fact, they are spread between academic institutions, the biotech industry (about 2,000 mostly small enterprises worldwide) and the traditional pharmaceutical industry[8,9].

Taken together, these four factors have a very negative impact on the profitability of pharmaceutical companies. The industry cannot respond to economic pressures by raising prices as it has done quite frequently in the past[10]. It can also not react to economic pressures by developing more 'me-too' compounds. The hopes for lowering R&D costs without jeopardizing R&D productivity are not well founded, at least not in the short term. It is possible to lower development costs by improving the very complex development process, by focusing on the important questions and by negotiating better contracts with clinical investigators and hospitals. On the other hand, the inflation rate for scientific work is at least 50% higher than the general inflation rate[11]. Science is rapidly finding and establishing new processes requiring new and better instrumentation. A synthetic chemist who was perfectly happy with a 400 MHz mass spectrometer years ago would want, at least, a 600 MHz instrument today; instruments with greater resolution have become the state of the art. Transgenic and knockout mice have become an indispensable tool in studying the function of genes and in setting up models of disease that mimic human illness. However, to maintain thousands of mice has become very costly.

Other technologies may not be available in-house but will be needed in addressing a therapeutic problem to find lead substances or only to identify a good drug target. A company must therefore enter into collaborations in order to obtain the 'missing pieces' and in turn must pay for these services or make sacrifices in the form of royalties or other long-term commitments. The profit margins of the pharmaceutical industry are under pressure and some companies have reacted by putting caps on R&D expenditure. All of the leading research-based companies are trying desperately to get more mileage out of each research dollar. Cost containment is the call of the day. But is it the right call? And if so, does its common sense apply to all functional areas of a large company?

R&D productivity

The productivity statistics of the leading pharmaceutical companies are not encouraging. Almost 60 new chemical entities (NCEs) were launched annually by the global pharmaceutical industry in 1985 and 1986. Since 1987, this number has gradually declined to less than 40 per year[12]: a 'loss' of 30% (Figure 1). There are indications that the quality of the output, that is the proportion of innovative drugs to moderately novel drugs to 'me-toos', has improved when launches during 1976–1985 are compared with those of subsequent years. The output of innovative drugs was found to be only 1.5% during 1976–1985 (486 drugs) with 15% of all compounds providing some improvement and 83.5% offering no significant advantage over known therapy. In 1986 and 1987 these figures were 8.6, 14.2 and 77.2%, respectively (total 105 compounds). In subsequent years, the quality of the industrial output improved even further: 11% novel compounds for 1988 and 1989, 31 and 34%, respectively, for improved medicines and 58 and 55% for 'redundant medicines'[13]. In more recent years, these figures have remained

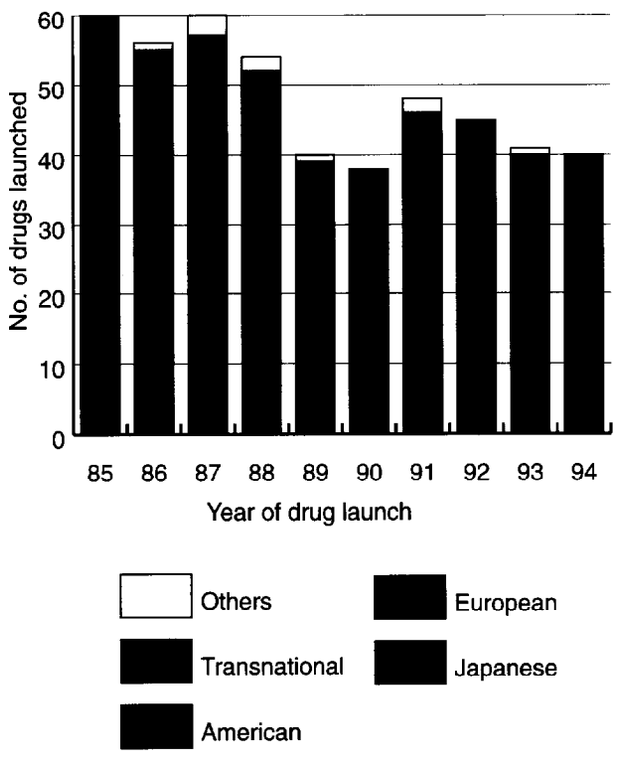

Figure 1. *New drugs launched worldwide by nationality of parent company. Source: Centre for Medicines Research, Surrey, UK.*

at about the same level – perhaps an indication that a new 'steady state' has been reached among companies who tried to be more innovative. Even if the degree of innovativeness increased further, there would always be a relatively large pool of drugs which at the time of their market introduction represent only small increments in quality when compared with the therapeutic standard[14].

In quantitative terms, the outlook for the leading 50 pharmaceutical companies is not very bright for the next few years. This statement is based on a quantitative assessment of the number of discovery projects that were pursued within 50 leading pharmaceutical companies of the world in 1993 (Ref. 15). This figure was found to be 1,271 for the 'industry'. Applying a success rate of 40% for the transition from discovery to development and of 10% for the transfer from development into the market, the total 'value' of this collective portfolio was estimated to be 51 compounds. These compounds could be launched at any time between 1999 and 2002, if one assumes the turnover time of the collective portfolio to be four years, with 13 compounds reaching the market every year. Assuming a three-year period of turnover, the number of new compounds would be 17 per year. This projection seems pessimistic, but it should be borne in mind that among the top 20 companies the number of NCEs entering the market slipped from 29 in 1990 to only 16 in 1994.

In evaluating these data, we also asked the question how this projected output would compare with the growth expectations of the industry. In particular, we calculated the number of compounds that the industry would need to generate in order to grow by an annual rate between −15 and +20%. Inevitably, such an assessment had to be based on a set of assumptions regarding the sales volume and the lifetime of the 'typical' new drug. It was found that, as a group, the pharmaceutical industry faces an innovation deficit that can be quantified and that increases with its sales expectations. For the 'total' industry (50 leading companies) and an annual compounded growth rate of 10%, this deficit or 'NCE gap' was estimated to be 30 compounds per year. These figures, of course, represent estimates that are based on certain assumptions, not only numerical ones, but also expectations with respect to factors such as regulatory environments and societal attitudes. But given the fact that the economic and political conditions for the pharmaceutical industry have tended to become harsher rather than more supportive in the past few years, these assumptions appear not to be unrealistic, at least not in the short term[16].

Innovation in the biotech industry

Of course, the output of the biotech industry will make up for part of this innovation deficit. Between 1999 and 2002, the US biotech industry will generate between 13 and 24 new recombinant proteins (including monoclonal antibodies and artificial constructs) per year[15,17,18]. Between 1993 and 1996, about 40% of the research expenditures of the biotech industry was contributed by the pharmaceutical industry[19]. Therefore, it appears logical that a proportionate number of compounds from the biotech industry and maybe as much as 50–60% of the sales from these products will flow to the pharmaceutical industry, the difference of 10–20% resulting from the pharmaceutical industry's additional investment in development, marketing and distribution of new biotech products. Even with this additional influx of new compounds, the pharmaceutical industry is likely to fall short of its own expectations. This rather bleak mid-term outlook for the industry as a whole does, of course, not exclude the possibility that individual companies can be very successful. But what is

the recipe for success? Is it enough to weather difficult times by cutting costs and hope for the arrival of new technologies? Should companies follow strategies of vertical integration by teaming up with health management organizations?

In principle, there are only two strategies, one defensive and one offensive[20]. They are not mutually exclusive but are difficult to communicate to an organization at the same time. The defensive strategy is based on the pessimistic view that the innovative power of the industry depends largely on outside factors (such as basic science and economic factors) and that it is difficult, if not impossible, to outperform competitors by innovation. So the conclusion of this strategy would be that a company must secure as wide a distribution range of its products as possible. Alliances with health care providers are a way of achieving this goal, and a number of prominent US and international companies who can certainly not be classified as weak innovators have embraced this strategy.

The alternative, which one might call an offensive strategy, argues that uniquely safe and effective medicines will meet with sympathy and societal acceptance even in times of economic constraint. While, in an increasingly regulated international environment, an innovator will not always be allowed the price he is asking for a novel drug, he will still be able to achieve a price, and therefore an income level, that will allow the company to sustain R&D and to still be profitable. The contours of this offensive strategy, a 'strategy of innovation', are outlined below.

Strategy of innovation

Innovation, as defined by the Austro-American economist Josef Schumpeter, is a product or a process at the time of its market introduction[21]. In order to get there, this product has to be discovered or invented and subsequently developed. So there are at least two components to the innovation process as defined by Schumpeter's economic theory: the generation of novelty and the development process, which in a way amounts to a preservation of novelty.

Inventions and discoveries often occur in clusters. Therefore, a quick and efficient development process may be the mechanism that determines whether a new product is still novel when it arrives on the market. Without denying the importance of this 'preservation of novelty' through development, this review will deal exclusively with the discovery process, which appears to be the more critical element in building success. In order to survive and, moreover, to be successful, the pharmaceutical industry has to improve its discovery performance significantly. How can it do this in the short term (the next 5 years), in the mid term (5–10 years) and in the long term (more than 10 years)?

Collaborations

In the short term, there seems to be only one strategy to improve discovery output: intensive, well focused and well managed collaborations with biotech companies and with academic institutions. Any company wishing to deliver more compounds into the development pipeline within the next five years must tap into projects that are disease-oriented, that have produced model systems for testing a pharmacological hypothesis and to which a chemical effort can therefore be added within one or at most two years. Such projects exist – mostly in academic environments. To bring such projects to a point where the drug discovery process can be initiated may cost some money and take some time. The effort, however, seems relatively cheap considering the potential benefits. If a company could establish 60 such collaborations with university laboratories worldwide, and assuming a success rate of 40% (as for the transition from discovery into development and an average duration of two years per project), such a collaborative portfolio would result in $60 \times 0.4 / 2 = 12$ 'pre-incubated' projects per year. Within an additional two to three years in the company, roughly half of these projects should result in development projects. So in a steady-state situation, six additional projects could enter the development pipeline annually.

To set up a collaboration portfolio of 'pre-incubated' projects for a company takes management time. It can probably not be done quickly within existing management structures and, therefore, needs a specialized group to at least 'jump start' such an initiative. The costs would not be formidable compared with in-house expenses. If one would assume a maximum of $500,000 per year per project, the total amount would not exceed $15 million annually with a result of six new products entering into the development pipeline every year and a resulting increase in the output of new marketed compounds between 0.5 and 1 per year. While the numbers can be played in different ways, the basic strategy holds promise in the short term as well as in a longer perspective.

An additional way of enhancing the number of compounds entering the development pipeline could come from collaborations with biotech companies. 'Classical'

biotechnology, for instance the provision of new recombinant cytokines, enzymes, monoclonal antibodies or artificial constructs like fusion proteins, has come of age. The opportunities for pharmaceutical companies to participate in this process are only limited by competitive mechanisms. At the time of this writing, 29 such compounds have been marketed and 284 are in some stage of clinical development in the USA alone[22].

Research centres: attractive working environments

The productivity of research in-house depends almost exclusively on the quality of the scientists that a company can attract and hold. At least in the USA, the attractiveness of big pharmaceutical firms has suffered. This is mainly because the stability of employment that these companies could traditionally offer no longer exists in the present environment of consolidation, mergers and acquisitions. Other options such as academia and especially the biotech industry offer alternatives that, although also unstable and maybe even more so, provide a working environment and incentive structures that appeal to many scientists. In Europe, the biotech alternative does not exist to nearly the same degree as in the USA and so the problem is less pressing.

In order to improve their appeal for young and particularly gifted scientists, companies must change the internal status of their research organizations. Research centers comprising 400–800 scientists and staff should have a clear scientific and entrepreneurial mission, an incentive plan to reward success in a way that is comparable with the benefits seen in biotech companies, and more independence in determining their own course of action. A five-year plan, containing budgets, expected output, areas in which to concentrate and a reconfirmation of annual goals and budgets in each budgeting period, may be all the guidance that a research center needs.

Corporate research management should help in setting goals for the short and the long term, allocate budgets, ascertain that the centers collaborate and exploit synergies, and ensure that efforts are not duplicated. Corporate management should also have the final say in concluding extensive and expensive strategic alliances that affect the overall technological and scientific situation of the company. Responsibility for smaller collaborations, especially those with academic institutions, could lie entirely with the individual research center. Such semi-autonomous centers should be liberated from the often redundant interactions with other corporate functions in order to pursue their own research agenda. It is important to communicate with members of development and marketing departments in order to solicit their 'buy in' and support of projects that come through the research pipeline. However, the innumerable meetings, sessions and presentations in which research staff often become entangled are unnecessary.

The pharmaceutical industry must understand that scientists are a special breed of people who need a special environment in order to be productive. This environment may be characterized by good science, a minimum of hierarchy, informality and high incentives for unusual achievements. If companies fail to provide this environment, they will fail to be scientifically productive, which in turn means that within the medium-to-long term they will depart from the ranks of the research-based industry.

Table 1. Number of drug targets of current therapies[23]

Indications	Drug targets	Shared drug targets									
		(a)	(b)	(c)	(d)	(e)	(f)	(g)	(h)	(i)	(j)
(a) Synaptic and neuroeffector junctional sites and CNS	139	–	4	2	7	2	0	0	0	0	0
(b) Inflammation	49	4	–	2	4	4	0	0	2	0	0
(c) Renal and cardiovascular function	47	2	2	–	0	1	1	0	1	0	0
(d) Gastrointestinal	15	7	4	0	–	1	0	0	0	0	0
(e) Uterine motility	8	2	4	1	1	–	0	0	1	0	0
(f) Hormones and hormone antagonists	55	0	0	1	0	0	–	4	0	0	0
(g) Neoplastic diseases, oncology	39	0	0	0	0	0	4	–	3	0	7
(h) Blood and blood formation	39	0	2	1	0	1	0	3	–	5	3
(i) Vitamins	10	0	0	0	0	0	0	0	5	–	0
(j) Immunomodulation	16	0	0	0	0	0	0	7	3	0	–
Total	417	Redundancy of drug targets = 54									

A long-term perspective

What else needs to be done, especially with respect to drug discovery in the long term? The single most important event affecting prospects for drug discovery is the emergence of genomic sciences. Present drug therapy (excluding antiviral, antibiotic and antiparasitic chemotherapy) addresses a total of 417 molecular targets[23] (Table 1). There are about 100,000 genes in the human genome. Each of the 100 or so important diseases for which new therapies must be sought[24] may result from 5–10 mutated genes[25,26]. So the total number of 'disease' genes, if no significant overlaps occur, may be in the range of 500–1,000. These genes are probably not good drug targets in their own right. But they will be part of biochemical pathways that will offer interesting targets for pharmacological intervention. If this number of potential targets amounts to five targets per 'disease' gene on average, the total number of targets to be identified through genomics and, subsequently, used for drug research would amount to 2,500–5,000 targets. In other words, the potential of drugs to interfere with physiological or pathophysiological processes would increase by at least one order of magnitude as compared with the present situation.

Drug researchers spent a century utilizing more than 400 drug targets that are addressed by today's therapy. How long will it take for the new targets to emerge and for chemists to find suitable compounds that can modify them? The sequencing of the human genome is expected to be completed by 2005, and maybe earlier[27]. cDNAs of most, if not all, expressed human genes are available even now. But the understanding of gene function has progressed very slowly. So far, genomic sciences have not had a major impact on drug discovery. Genomic databanks have been helpful for scientists very much in the way that libraries are helpful, but the evolution of meaningful targets for drug discovery has barely started. In 5–10 years, enough information will have evolved from genomic projects to make a difference for drug discovery but it will take much longer, maybe many decades, to gain a deep understanding of the 100,000 genes in the human cell.

Are there any shortcuts to enhanced drug discovery? Can we utilize the progress in gene sequencing without understanding gene function first? Some think we can. The argument goes as follows. Genes can be classified according to structure. There are G-protein-coupled membrane receptors, tyrosine protein kinases, serine protein kinases, phosphatases, proteases and other enzymes, integrins, adhesion proteins, nuclear hormone receptors and many other genes (proteins) that can be classified and that could be potential drug targets. Scientists could select a limited number of such targets. They could then explore the expression patterns of these genes (proteins) in different tissues, at different times, during health or disease, under the influence of various environmental factors or of drugs. They could subsequently select those targets that they suspect to be of possible importance in relation to certain diseases that they might want to treat. Subsequently, by screening high-diversity combinatorial libraries against these targets, compounds that reproducibly bind to the targets with high affinity could be identified and screened in cell-based assays and in animal models. At present, it is uncertain whether this approach will help to find drug candidates and, eventually, lead to the identification of new drugs, but given the high number of targets and compounds involved, it appears to be worth trying.

Thus, two major avenues to drug discovery will emanate from genomic sciences. One will follow the classic route of gene identification and determination of gene function by various methodologies, including the use of developmental biology and the creation of large libraries of knock-out cells and mice[28,29]. This approach will take many years and possibly several decades to leave its imprint on drug discovery. The second technology-based approach relies on our ability to classify proteins according to their hypothetical role as drug targets, on the development of combinatorial chemistry and on novel methods of high- or ultra-high-throughput screening – and beyond that on serendipity. A company that makes product innovation its major strategic thrust will need both of these approaches, and these must be balanced against one another over time. The 'blind' approach requires a very balanced build-up of genomics (access to annotated sequence databases and bioinformatics), combinatorial chemistry and techniques for high-throughput screening. It does not make sense to spend a lot of money on high-throughput screening methods if the number of targets to be tested is still small or if the number of compounds that can be tested is limited to a few hundred thousand. But building and, at the same time, balancing target identification, combinatorial chemistry, assay development and high-throughput screening may indeed represent a powerful strategy for increased drug discovery in the mid-to-long term.

Summary

A strategy aiming at a significant improvement of a drug company's innovation output would be based on the following principles:

- A large number of collaborative projects with academic laboratories should be built up. The focus should be on the elucidation of relevant pathophysiological mechanisms, the identification of drug targets, development of assays and/or animal models. Also, companies should try to participate in the flow of recombinant drugs that is now underway through agreements with biotech firms.
- Research organizations within large pharmaceutical companies should obtain a high degree of operational autonomy. Creating research centers that have the status of relative independence within a corporate framework of goals, resource allocations and strategic collaborations appears to be a reasonable way to achieve this objective.
- Genomic sciences have to be built in-house and in collaboration with biotech companies. The emphasis should be on the exploration of gene function rather than the determination of sequences. At the same time, a well-coordinated exploitation of sequence data, combinatorial chemistry, assay development and high-throughput screening can contribute to the identification of new drug candidates.

While some of these proposals, especially the establishment of large collaborative portfolios with universities, will help to contain research expenditures, others will require additional resources. Cost savings can be made in drug development but will be more difficult to achieve in drug discovery. In spite of the cost pressures described above, the global pharmaceutical industry has continued to invest heavily in R&D: in 1994, the figure provided by the Centre for Medicines Research (CMR) amounted to 15% of sales, in 1995, it seems to get closer to 17.5%[30]. In the USA, the estimated R&D spending for 1996 will be nearly 16% of sales in the pharmaceutical industry[31]. Globally, R&D expenses still seem to grow a little faster than sales. While most of this increase appears to result from more collaborations rather than from a strengthening of research organizations in-house, these are encouraging signs. However, they will only help to maintain the research-based pharmaceutical industry if the money invested in R&D is spent more productively than in the past. The wave of consolidations will continue, and which organizations represent the dominant few pharmaceutical companies of the future will largely depend on their power to innovate.

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