

# Strategic trends in the drug industry

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The promise of genomics in drug discovery, which was eagerly embraced in the mid-1990s, has not yet been fulfilled. However, the influence of modern biology on drug discovery remains viable. The promise of genomics and biology should be put in context with the two central problems of drug discovery: the search for disease-related targets, and the study of drug-protein interactions and protein-protein interactions. The first tier of the biotechnology industry has now become the most productive segment of the drug industry. It combines a high degree of innovative spirit with solid pharmaceutical professionalism. Some biotechnology firms have succeeded in addressing unmet medical needs in technologically appealing ways. In their totality, these changes will deeply alter the nature and appearance of the drug industry.

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▼ For the most part of the 20th century, the pharmaceutical industry was characterized by the following properties:

- Great individuality.
- Firm commitment to science and the ways in which science unfolds.
- Cultural and ethical standards that often seemed to be derived from those of medicine itself.

However, these qualities are about to be lost. A continuing process of consolidation, highlighted by almost 20 major mergers or acquisitions over the past 13 years, has created greater uniformity. Today, there are fewer large pharmaceutical companies and also fewer differences between the remaining companies than was the case 20 years ago.

The closeness of the industry to medical biological science and their willingness to submit to the rigor and discipline of good science is being replaced by a marketing dogma in which R&D is degraded to a tool for generating medicines that qualify as blockbusters. We define blockbusters as compounds that, at maturity, generate annual revenues of or in excess of one billion US dollars.

Finally, the ethics of successful business have replaced those of medicine. The supreme loyalty of today's companies is not primarily directed at patients and their physicians but at shareholders. Consequently, the most influential figures in today's pharmaceutical companies are no longer the heads of R&D but the heads of marketing and finance.

## Productivity of the pharmaceutical industry

As first quantified in 1995, the productivity of the pharmaceutical industry has dramatically fallen short of its own expectations. Based on data from 1993, it was predicted that the then ten leading companies of the world did not have a sufficient number of novel compounds to grow their revenues by 10% annually. The average innovation deficit per company for the top ten was forecast to amount to ~1.3 new chemical entities (NCEs) per year in 1999 and 2000 [1,2].

As recently shown in a study by Bain and Company [3], the actual figure for 2000 was 1.8 NCEs per company. According to an even more recent study published by the Center of Medicine's Research [4] the decline in productivity continues. The study is based on data from 24 leading pharma companies and shows a drastic decline of new compounds entering Phase I, II and III trials over the last five years. It also reveals a decrease in the number of submissions made to a regulatory authority [European Medicines Evaluation Agency (EMEA; <http://www.emea.eu.int>) or Food and Drug Administration (FDA; <http://www.fda.gov>)] by 35% during the same time period. The total number of compounds in development did not decline as dramatically as the number of entries into each phase, which indicated that development times have increased.

The proportion of annually admitted new NCEs that originated in biotech firms,

compared with the total number of NCEs, has increased to 20–25% in recent years [5]. It is expected to reach the 50% level within the next 5–10 years [6]. Apparently, the weights within the drug industry in general have shifted considerably. It could, therefore, be useful to delineate the major trends within the pharma and biotech worlds that have led to these changes and to describe some emerging strategies for different segments of the industry.

### Changes in big pharmaceutical companies

What are the reasons for the overall decline of productivity in the pharmaceutical industry? If we look at the total picture, not only at particular industrial segments, there are several reasons. Since 1995, the year in which the innovation deficit within the pharmaceutical industry was laid out in detail, the pharma industry has continued on a course that is characterized by the following principles:

- (1) Attempt to obtain and strengthen global reach.
- (2) Concentrate on compounds that are likely to generate sales in excess of one billion dollars per annum at peak sales or more.
- (3) Try to focus the R&D budget on the identification and development of such compounds.
- (4) Work in areas in which blockbusters are likely to emerge; discontinue work that does not satisfy the above criteria.
- (5) Overcome the influence of competitive compounds that are likely to emerge by sheer marketing power.
- (6) Put the main emphasis on fast worldwide development and on effective marketing.

It is quite evident that this attitude is unsupportive of science and innovation. By emulating the pattern of blockbusters, the industry has been critically narrowing the scope and quality of its investigations. Its attitude is reflecting the false promise that research intended to identify blockbusters will indeed produce such compounds. That, of course, can only be assumed for research that is repetitive and rather unimaginative. Original drug research of the kind that the industry was supporting in the past was, and still is, full of uncertainties and surprises. Serendipitous findings are frequent, and whether such findings will lead to a new drug is almost impossible to predict. Whether drugs that emerge from open and unrestricted scientific process will be blockbusters is equally difficult to assess [7].

In fact, blockbuster status was in the past often attained against the predictions of marketing departments. Rocephin™, Roche's (<http://www.roche.com>) intravenous broad-spectrum cephalosporin surprised the company's marketing group with its eventual success. Similarly, Zyprexa™ (olanzapin; Ely Lilly, <http://www.lilly.com>), a

novel drug against schizophrenia, exceeded marketing expectations sevenfold in its first year after launch. One might even argue that only a few of the 28 blockbusters, which are expected to lose patent protection in the USA between 2003 and 2007, were selected for development because they were expected to achieve blockbuster status. Conversely, one might be in doubt whether the 14 compounds that are expected to become blockbusters after their launches between 2003 and 2006 will indeed achieve this level of celebrity. Many of these compounds could still fail or become only moderately successful. Others that are not yet in the limelight might suddenly become significant [7].

There can be no question that an open, unbiased scientific process is more productive than a 'scientific' process that is constrained by ideologies – be they commercial or political. It is not worth investing in science if one is not willing to accept the laws and dynamics of the scientific process. It can be argued that many, if not most, pharmaceutical executives are still willing to spend 15% of their revenues, or even more, on R&D. However, they want to have it their way. Relatively little of that money is supporting research that has any chance to discover truly novel mechanisms or pharmacological effects. But even if novel information emerges, it will be subjected to scrutiny, which is not dictated by the principles of scientific rigor and medical feasibility but rather by inappropriate and untimely financial considerations.

The further decline of research productivity in the big pharma companies has been predicted on the basis of behavioral patterns that were clearly recognizable in 1999 [8]. Despite more than 15 major consolidation steps in the pharma industry, the trend continues unabated. There are two sets of reasons that underlie big mergers. One is hardly ever mentioned in public, because it relates to mistakes that were made in the past. Some mergers are conceived as financial remedies to please shareholders – and analysts. These ill-conceived measures will not create any long-term value. Within 5–10 years the new company that was put together for superficial reasons will again find itself in a precarious situation.

Officially, big companies come together by mergers or acquisitions to 'strengthen their product portfolios' and their pipelines. In reality, this means, as Thomas Lönngren (Executive Director, EMEA) has testified, that a great number of assets are being lost, at least temporarily, in any consolidation event [9]. Mergers of big pharma companies are dominated by a new creed, the 'blockbuster religion'. Anything that does not fit into this religion will be either discarded altogether or will be passed on to smaller enterprises. Big pharma companies of global reach

are not likely to contribute to novel therapeutic solutions as much as they did in the past. They will, of course, develop novel compounds and they will press them into the markets, even if such marketing pressures occasionally violate the principles of the most basic imperative of medicine: 'Do no harm'.

For some time, many members of the industrial and medical communities expected the biotech industry to make up for the lagging creativity of the big pharma companies. This expectation has been met in part. Although the total number of new agents (proteins or small molecules) has not made up for the decline of big pharma's innovation deficit, the situation would be a lot worse without this contribution [10,11]. The proportion of drugs coming from biotech companies (mostly, but not all, protein products), in relation to the total number of drugs, has increased steadily over the years.

### The biotech industry

What happened to the genomic revolution which, as many people predicted, would revolutionize drug research? It would do so, the argument went, by several mechanisms. First, by elucidating the sequence of the human genome, and the genomes of various pathogenetic agents – such as bacteria and viruses – genomics would help to identify a host of novel targets for drug therapy. By using modern genetic techniques, such as gene knockouts, knock-ins, anti-sense RNA, inhibitory RNA and analysis of gene expression (expression libraries), drug researchers would be able to 'validate' these new targets. Once new targets have been validated, tests would quickly be configured, which would enable the identification of chemicals that can modify targets in a therapeutically desirable manner.

Second, and more conventionally, it was agreed that the sequencing of the human genome would greatly facilitate the identification of soluble proteins that have important physiological functions. At least several hundreds of proteins (and peptides) were expected to fall into this category and eventually be developed into drugs. Of course, the discovery and clinical use of recombinant interferons [12,13], and of many other recombinant proteins (enzymes and cytokines), had delivered early precedence for this expectation.

Third, the knowledge of the human and related genomes would help to identify alleles, which dispose people for certain multifactorial diseases, such as hypertension, diabetes mellitus, osteoporosis, cancer and many others [14]. The knowledge of the genetic base of disease would, of course, help to gain deeper insights into pathophysiological mechanisms and would, therefore, hint at possibilities to interfere with disease processes.

Fourth, knowing all human genes and understanding the most frequent haplotypes would lead to a better understanding of individual drug responses. Every physician is aware of the fact that individual patients react to a given drug in different ways. There are responders, weak responders, non-responders, and there are individuals who develop adverse events that can be a limiting and even a prohibitive factor for further treatment. The correlation of the response types with consistent patterns of haplotypes could open up possibilities for individualized drug treatment, which would be equally desirable from a medical and a commercial point of view. The status of each of these four expectations shall be briefly discussed.

### Criteria for validation

Although the hypothetical identification of novel drug targets has been relatively easy, their validation as crucial and effective points of intervention for drug therapy has been progressing at a much slower rate. It is not a trivial task to accumulate credible evidence for a novel drug target, up to the point where the institution of a full chemical program to modify this target appears justified. The number of targets (e.g. enzyme or receptor) that emerge from scrupulous biological (and sometimes chemical) research as 'validated', still amounts to a few annually (probably less than six), even in large research organizations. Statements on validation do, of course, depend on the definition of this term. In the context of drug research, a validated target should satisfy all, or at least some, of the following criteria to be judged as validated:

- Its manipulation by genetic or pharmacological means should consistently lead to phenotypic changes that are in line with the desired therapeutic effect. The induction of apoptosis in cellular models and of tumor shrinkage in animal models could, for instance, represent such changes.
- Any such effect should be dose-dependent (dose interpreted as pharmacological dose in pharmacotherapy and as gene dose in gene therapy).
- The desired phenotypic changes must be inducible in at least one relevant animal model. If possible, several animal models should be used, all of which reflect at least some important aspects of the human pathogenesis of the respective disease.
- The way in which the manipulation of a target molecule (e.g. the blocking or activation of a receptor or the inhibition of an enzyme) brings about a particular phenotype should be known. Are other gene products involved and does these bring the danger of toxic side effects?

This list is probably not complete, but it demonstrates the complexity of target validation, if that step is to go

beyond mere speculation. Therefore, it is hardly surprising that the emergence of novel targets was, and still is, a slow and gradual process. To expect sudden increases of research productivity from such a process is unrealistic. Large research organizations in the pharma industry have traditionally not generated more than a handful of validated targets annually.

In addition, we have to consider the difficulties that are inherent in chemistry. It is no trivial task to synthesize a molecule that can bring about the desired target modification in a dose-dependent and specific way. Despite many improvements in measuring protein-protein interactions, advances in protein crystallization, X-ray crystallography and molecular modeling, synthesizing and optimizing a suitable molecule could require at least two years.

#### *Further limitations*

Another difficulty compounds the limitations mentioned previously. The work that was described and outlined can best be accomplished in a co-operative mode between biotech companies [such as Human Genome Sciences (<http://www.hgsi.com>) and Millenium Pharmaceuticals (<http://www.mlnm.com>) among others] and large biotech or full-fledged pharma companies. The pieces of the puzzle are more often than not divided between these organizations. Such collaborations are, however, fraught with many considerations that are foreign to the work to be accomplished. Different perspectives on financial and legal issues, as well as on matters relating to intellectual property, can and usually do get in the way. It is, therefore, not surprising that progress has been slow.

The second expectation, which relates to novel physiological proteins that can be used as pharmacological agents is about to be met. Again, the identification of a protein suitable to become a therapeutic agent requires time, even against the background of a wealth of genetic and genomic information. For the identification, pharmacological validation, preclinical testing and manufacturing of a novel recombinant protein or antibody, 2–4 years are needed. Clinical development will require an additional 4–6 years, depending on the nature of the compound in question and the indication selected for development. If we assume the late 1990s to be the starting point for the systemic exploitation of the human genome for the identification of novel drugs, the first compounds from this effort should reach the registration stage now or in the immediate future. A portfolio analysis of the most prominent genomic companies shows that they are on their way to provide this new wave of protein therapeutics. The chances for the eventual success of their protein drugs now in development are significantly higher than those for

small molecules in equivalent stages of development, as recently shown [15]. Again, to expect earlier successes in this particular endeavor is not realistic.

Expectations three and four (see previously) are directed towards correlating defined genetic markers (haplotypes) with disease dispositions or with drug responses. Despite the broad availability of human genetic data, the identification of crucial ‘disease’ genes or of haplotypes that can be correlated with an increased incidence of certain multifactorial diseases is still in its infancy. The same holds true for the correlation of haplotype patterns with various drug responses. There are, however, several examples that illustrate the fundamental feasibility of these approaches [12,16,17].

Although sensationally rapid developments are not likely in these fields, there can be little doubt that these applications of genomics (population genomics and pharmacogenomics) will have a deep influence on medicine and on drug therapy.

In summary, the genomics revolution has started but it has not yet progressed to the point where it could have a real impact on drug discovery. Vast territories of knowledge were staked out in the 1990s in a relatively short time. To cultivate and use these newly discovered continents will take much more time than was spent on their discovery.

#### **Biotechnology – the discovery industry?**

Many of the compounds that are shed by large pharma companies on occasion of their mergers with, or acquisitions of, other pharma companies end up in the biotech world. Often biotech companies present these leftovers from mergers and acquisitions as ‘novel’, ‘original’ or at least ‘promising’, although most of these entities offer little, if anything, new. However, in an environment that favors products over technology, anything will do, at least for a start: biphosphonates, serotonin-uptake inhibitors, cholinesterase inhibitors, another hydroxymethyl-glutaryl coenzyme A (HMGCoA) reductase inhibitor, and so on. In decorating these leftovers to make them look attractive, many biotech companies are following the doubtful example of their bigger cousins.

To make things worse, these largely unappealing compounds are now carried forward by companies who have little or no experience in preclinical or clinical development. Given the modest average quality of these ‘leftovers’ and the inexperience of their sponsors, one must remain sceptical as to the overall yield of these efforts. Of course, there are some nuggets among the many ordinary stones in this category, and some of them will eventually be brought to the market.

It has been, and will be, increasingly difficult for investors to distinguish products (and companies that develop

them) on the basis of small differences between the compounds that are mainly still in relatively early stages. Compounds that are licensed out by Novartis (<http://www.novartis.com>), GlaxoSmithKline (<http://www.gsk.com>) or AstraZeneca (<http://www.astrazeneca.com>), for example, apparently do not represent these companies' first choices to become blockbusters. As mentioned previously, the choices made by big pharma are based on a set of rather narrow criteria, among which financial expectations have the dominant role. Therefore, medicines not developed by large pharma companies might still contain attractive opportunities. They could, for instance, become important second-line therapeutics or they might be suitable for indications not addressed by the large companies. Orphan drugs could be among these drugs that serve small groups of patients but are nevertheless capable of earning money for their developers.

It is, however, difficult to identify the few precious stones among the many ordinary ones. This means, in essence, that funds to develop these compounds will only be made available in select cases.

To specialize on the development of compounds that fall by the wayside of big pharma companies is, therefore, a risky strategy, especially if it is not backed up by research efforts that, over time, can generate new drug candidates with a more original profile.

### *Fragmentation*

A problem that is typical for technology platform companies is, of course, their fragmentation. Despite some notable exceptions, young companies usually start out as technology platform enterprises that address one, maybe two important steps in the discovery or – less often – the development process. To the extent that their technology is emulated and developed further by others, they are in danger of becoming obsolete. Some of these companies have succeeded in keeping a leading edge in their technology [e.g. Exelixis (<http://www.exelixis.com>), Genaissance Pharmaceuticals (<http://www.genaissance.com>), MorphoSys (<http://www.morphosys.de>), Telik (<http://www.telik.com>)] but sooner or later they will have to seek a broader strategic basis for themselves, which means that they have to become product-oriented companies. For a start-up enterprise that can offer elegant solutions to identify and synthesize novel compounds by new techniques, for example, 'click-chemistry' [18] or by optimized techniques of molecular modeling, this might be relatively easy. It might also be a feasible option for companies with a broad technological base in biology [e.g. GPC Biotech AG (<http://www.gpc-biotech.com>) or Axxima Pharmaceuticals (<http://www.axxima.com>)]. However, what about the

companies that offer highly sophisticated but, at the same time, specific tools that address only a narrow segment of the discovery process? The road from a technology platform company to a product company is always difficult but it could constitute a nearly impossible challenge for companies with a technology that can only be narrowly applied. The survival of most technology companies will depend on their ability to consolidate and also to maintain a technological advantage over competitors. With product-oriented companies the probability of survival rests solely in the originality and viability of their compounds. Combining the two strategies would perhaps not always double the chances of long-term survival but would, quite clearly, reduce the risk that each 'incomplete' company is carrying.

### **The difficulty of climbing higher mountains**

Whatever the company and its strategy – big pharma blockbusters, big biotech companies pursuing so-called 'high density products' [19] or small biotech firms developing 'leftovers' or offering methodology that can facilitate the identification of new molecules (small chemicals of protein drugs), one truth is there for all to see: many 'easy' targets or molecules have been found and developed. To describe the situation one can use a comparison gleaned from another field of human endeavor: mountain climbing.

Most lower and intermediate peaks that have any appeal at all have been climbed. There are still plenty of difficult peaks to be attacked. Their 'difficulty' might result from their remoteness or from their high altitude. They might be inaccessible or dangerous for whatever reason. To climb one of these peaks, one has to establish not just one base camp but many camps in between, and they all need to be connected by good lines of communication. It is possible to do this but the effort is substantial and the number of real successes might be more modest than what people were used to when the lower mountains still represented a rewarding challenge.

### **The central problems of drug discovery**

The objective of drug discovery is to find new substances that can cure, or at least contain, important diseases. Biochemistry has given us an understanding of typical alterations in chemical pathways that are linked to diseases in a causal or a phenomenological way. One could call these deviations from the normal the 'signatures' of diseases. Such biochemical patterns have helped greatly in the diagnosis of diseases, but they also have contributed to the understanding of pathophysiological mechanisms and to the identification of viable targets.



Molecular biology is teaching us that many, if not all, diseases have a genetic basis. To understand the pathways and the genetic programs that cause disease or that dispose an individual for disease must be central to drug research. At least during the past decade, this principle has been badly neglected. To hope that the knowledge of genes and their products (30,000–50,000 in the human genome) would enable major advances in drug research was too optimistic an assumption. Too little is known about the function of these genes and their specific involvement in disease processes. It will take many years, if not decades, to gather this knowledge by genetic tools, including population genetics and positional cloning, experiments involving the manipulation of the germ-line of experimental animals, differential expression and others.

It will, therefore, be necessary to place disease pathophysiology back at the forefront of our attention. In doing so, we will find that the traditional classifications of diseases, which were based on phenotypic criteria, can now be sub-classified into different genotypes. This is already happening, particularly in oncology.

### The value of technology

Even in a disease-centered approach, the identification of relevant targets will be difficult. It will, however, be easier to identify and validate important targets in this context than through the indiscriminate screening of many potential targets against an even greater number of compounds gained by the combinatorial variation of a great number of molecular scaffolds. The attempt to replace the quality of scientific arguments by the sheer quantity of data as expressed in HTS or ultra-HTS in the past has failed. An approach that is based on a much broader understanding of biochemical and genetic mechanisms of diseases appears to represent the necessary correction.

Once a target has been identified, the central problem of drug research boils down to the task of modifying that target by either a small molecule or a protein, in many cases by an antibody. To accomplish this modification in a specific, dose- or concentration-dependent way still represents a formidable challenge. This challenge will be met by improved techniques that enable the measurement of protein-protein interactions or protein-small molecule interactions, by advances in X-ray crystallography and, in particular, molecular modeling. The protein target must – again – become the center of attention for the medicinal chemist. Opportunistic variations of scaffolds that have no obvious relationship to a validated target have failed as a strategic principle. However, perhaps they have to fail because the number of druglike molecules that can be obtained by random combinations of the nine elements that typically

constitute the structure of medicines, far exceeds the number of biological structures that need to be modified in the context of drug therapy. Today, there is little doubt that the biological space, that is the number of disease and drug relevant protein domains, is infinitely smaller than the chemical space that is at our disposal for the synthesis of new compounds. Therefore, biological structures must guide chemistry, not the other way around [20].

The value of every technology that is offered by small biotech companies, whether it is related to genomics, proteomics, chemistry, enzymes, receptors or other subjects, must be assessed by asking the following questions:

- (1) How much does the new technology help to solve one of the two central problems: the identification and validation of a disease-specific target or the identification of a molecule that can modify this target in a way that makes therapeutic sense?
- (2) How quickly can this positive effect be implemented?
- (3) How broadly can new technology be applied?

Only if a new technology enables these questions to be answered in a strongly affirmative way, does it have a chance to earn revenues for its inventors and the respective company.

### Strategies for the future

#### *Marketing and medical needs*

Most big pharma companies have embarked on strategies that aim primarily at profitability. The tool that is most prominently employed to implement this strategy is marketing. Marketing departments articulate their 'needs' on the basis of their relative positions in different world markets. Marketing determines the areas in which a company engages itself, the markets in which it wants to be strong, even the compounds that are admitted to development. The number of sales representatives is still on the increase, at least in the USA. The productivity of these sales forces as measured by the sales dollars achieved per dollar spent on the sales force has been stagnating since the early 1990s [19].

The medical needs of patients and scientific opportunities as they emerge from an open process of scientific enquiry have become secondary considerations. This attitude not only represents a reversal of the process of scientific innovation but also marks a significant deviation from the way in which pharma companies operated two or three decades ago. When asked to name the dominant objective that his company was pursuing, Yves Dunant, CEO and chairman of Sandoz (see <http://www.novartis.com>) between 1976 and 1982, mentioned the search for innovative drugs to help patients and to enrich medicine in the first place. He was quoted as saying: 'If we do this job well,

we will eventually earn money and grow.' The societal objective and the financial goals of the company [Sandoz] were inseparably linked to each other. Dunant, however, preferred the employees of the company to think about medicine and therapy first and not to be primarily concerned with revenues and profit. During the same time period, Sandoz was developing its first antifungal agents. The scientists involved in this project had occasional doubts of how well the company was able to handle these products, even if technical success would be achieved. The highly successful CEO of the major affiliate of the company dispelled these doubts in a simple way. 'If it is a good drug, we will find a way to sell it', he was quoted as saying. He turned out to be right, although it took many years for this new line of products to achieve great success. 'First things first' meant: innovative drugs first. Selling them effectively and intelligently came second.

Today, the profile of a particular drug as required from a marketing perspective often stands at the beginning of an R&D effort. R&D will then be asked to find and develop a compound that meets the desired specifications. Although this might be a logical sequence of events in line extensions, where modifications of an existing drug can be small, it clearly marks the wrong attitude in the discovery of new drugs.

The focus on projected sales rather than on the scientific novelty and the medical value of the drugs and, in particular, the obsession with blockbusters, has compromised the creative potential and the innovative power of most big pharma companies. As predicted in a monography in 1998, big pharma companies are increasingly choosing to be development and marketing machines rather than centers of innovative research [8,20].

#### *Exceptions to the rule*

There might be exceptions, notably among medium-sized pharma companies. Some of these enterprises might find ways to re-establish R&D as the main driver for new drugs. It is difficult to achieve this because heavy corporate structures, which inevitably emerge in large companies, are hostile to research creativity and innovation. There are still compounds emerging from big pharma companies that are truly innovative and highly desirable from a medical point of view,

Gleevec<sup>TM</sup> (or Glivec), Novartis' inhibitor of a cancer-related kinase, could serve as an example for such events [21]. There are some relevant success stories but they are not representative of the industry as a whole. It appears that traditional pharma companies are less likely to contribute innovative ideas to drug discovery than they were in the past.

Fortunately, other organizations are in the process of filling the void left by the large pharma companies. At present, the big biotech firms appear to be the center of drug innovation. Companies like Amgen (<http://www.amgen.com>), Biogen (<http://www.biogen.com>), Genentech (<http://www.gene.com>), Genzyme (<http://www.genzyme.com>), MedImmune (<http://www.medimmune.com>), and Immunex (<http://www.immunex.com>), have recently made important contributions to drug therapy. Moreover, ~350 biotech products are presently in some stage of chemical development [19]. According to a recent analysis, the attrition rates for these products are likely to be considerably lower than the corresponding rates for new small molecules [4].

Occasionally, research-based biotech companies will produce a blockbuster, such as recombinant erythropoietin [Epogen<sup>TM</sup> (Amgen); Procrit<sup>TM</sup> (Ortho)] or G-CSF [granulocyte colony-stimulating factor; Neupogen<sup>TM</sup> (Amgen)]. Typically, however, their products fall into a category that has been termed 'high density products.' Characteristically, such products are presented as second-line therapy, which is administered by specialists rather than by general practitioners. Many of these substances are proteins, notably monoclonal antibodies or derivatives thereof [19]. It appears likely that peptides will complement, or even replace, some of these proteins. There are techniques by which peptides can be tailored to fit the binding sites of proteins and to exert similar effects [22,23]. They are also cheaper to manufacture and easier to store. Although the number of big and profitable biotech companies is still small, there are some larger companies with solid pipelines – or even with one product already launched. The big biotech tier of the drug discovery industry will grow in the near future and will, for some time at least, continue to be the most innovative segment of the drug industry. It seems that these companies have succeeded in preserving the entrepreneurial and scientific spirit that brought them into life. But they also have acquired a high degree of pharmaceutical professionalism. In this sense, they combine the best of both worlds.

#### *The future for biotechnology*

A large segment of the biotech industry, mostly represented by small companies, is in dire need of further consolidation. Companies must offer more complete technological solutions to drug discovery than most of them do at present. If possible, they also should have products. What could result from carefully targeted mergers between biotech companies is the emergence of several specialized small pharma companies that show greater productivity than most big pharma companies in relation to their size.

**Table 1. Initial Public Offerings (IPO) class of 2000 – biopharmaceutical companies. Post IPO performance versus peers and Nasdaq Biotech Index (NBI)**

Company	IPO date	Market cap at IPO (US\$)	Market cap 29 Aug 2002	Change IPO to 29 Aug 2002 (%)	Change versus NBI
Telik	11 Aug 2000	152.4	384.2	152.1	210.4
Intermune	3 Mar 2000	419.0	742.0	77.1	145.2
Versicor	2 Aug 2000	242.0	289.6	19.7	77.0
Atherogenics	8 Aug 2000	183.5	200.3	9.2	67.9
Adolor Corp.	15 Nov 2000	402.7	437.3	8.6	66.2
Esperion Therapeutics	9 Aug 2000	216.2	165.1	–23.6	35.0
Antigenics	3 Feb 2000	436.0	302.7	–30.6	22.4
Pain Therapeutics	13 Jul 2000	310.0	187.4	–39.5	20.6
Allos Therapeutics	27 Mar 2000	411.0	223.5	–45.6	11.2
Kosan Biosciences	4 Oct 2000	334.2	152.4	–54.4	3.7

Biotech companies that increased their market capitalization values after their IPOs in 2000 (upper five) against market trends or did better than the Nasdaq Biotech Index (NBI). Telik (<http://www.telik.com>); Intermune (<http://www.intermune.com>); Versicor (<http://www.versicor.com>); Atherogenics (<http://www.atherogenics.com>); Adolor Corp. (<http://www.adolor.com>); Esperion Therapeutics (<http://www.esperion.com>); Antigenics (<http://www.antigenics.com>); Pain Therapy (<http://www.paintrials.com>); Allos Therapeutics (<http://www.allos.com>); Kosan Biosciences (<http://www.kosan.com>); Nasdaq (<http://www.nasdaq.com>). Market cap = market capitalization.

As a case in point, it should be mentioned that the small group of biotech companies that went public in 2001, and have since succeeded in increasing their market value against general market trends, belong to this group of ‘smart little pharmaceutical companies’ as one could call them (Table 1). These companies have been successful in using the traditional space of pharmaceutical enterprises. However, they do this in specific ways: they discover novel products by applying current knowledge about the interaction of small molecules with proteins in systematic and efficient ways; they find new and sometimes surprising ways, in which known compounds can be used to treat rare diseases; some even specialize on novel methods of drug delivery. They can all show success by having brought compounds into intermediate or late stages of development.

Of course, new biotech companies will emerge as new technologies become known and applicable. Compared to the 1980s and early 1990s, biotech companies that appear on the scene today appear to be more geared to the improvement and optimization of existing technologies than to the achievement of any breakthroughs of their own. The technological case that they can make for themselves is generally weaker than that of their predecessors. At the moment, future Genentechs, Biogens or Milleniums are not visible. Instead, there are companies that are applying whatever technology is available to the identification of potential

new products, which they will hardly be able to develop on their own. For the time being, the esprit and the innovative drive of earlier years appear to be superseded by more pedestrian approaches and more sobriety in the setting of goals.

Biological science and perhaps science in general do not always proceed at the same speed. There are times of rapid changes and times in which new paradigms are tested and exploited more broadly [24]. The same fluctuations seem to occur in the application of biological (and chemical) science to drug therapy. This, however, is not a reason to be pessimistic. The old system of drug innovation in which the big pharma companies played the central role is giving way to a polycentric system. In this new system, the big pharma companies will be responsible for the worldwide development and marketing of widely used drugs that represent first-line therapy.

## Conclusions

The first tier of biotech companies is likely to become the most effective segment of the drug industry. At present, this group combines considerable innovative potential with a high degree of professionalism. Like no other segment of the drug industry, the first tier of biotechnology has provided drugs that made a difference to patients, not only in convenience or in minor details but also in quality years added to lives. To name but a few examples should illustrate the point: the interferons have made important inroads into the treatment of several diseases; the combination of pegylated interferons and Ribavirin has made a significant contribution to the treatment of patients with chronic hepatitis B or hepatitis C [12]; antithrombotic enzymes like tissue plasminogen activator (tPA) are today indispensable in dealing with acute myocardial infarctions and ischemic strokes; colony-stimulating factors like erythropoietin and G-CSF have opened up new paths in the treatment of kidney disease and in oncology. Most importantly perhaps, monoclonal antibodies and their derivatives are coming to the forefront of treating malignancies and of interfering with autoimmune and inflammatory processes. Herceptin, Rituxan, Zenapax and Enbrel (a hybrid between receptor and antibody) are only a few examples. In fact, the evolution of therapeutic antibodies has been so vigorous that some insiders expect these agents



**Table 2. Some mid-size public and private company merger and acquisition transactions (2001–2003)**

Date announced	Target name	Acquiror name	Transaction value (in US\$1000)	Target business description
16 Jan 2003	3 Dimensional Pharmaceuticals	Johnson and Johnson	88,000	3 Dimensional Pharmaceuticals is a drug company that has developed a technology that provides an accelerated methodology for small molecule discovery.
4 Dec 2002	Triangle Pharmaceutical	Gilead Sciences	406,900	Triangle Pharmaceuticals develops new drug candidates primarily in the antiviral area.
30 Nov 2002	Baxter Healthcare	Epic Therapeutics	100,000	Developer of proprietary drug delivery technology for the development and commercialization of extended-release human therapeutics.
27 Mar 2002	Martek Biosciences	Omega Tech	50,000	Developer of natural bioactive compounds (NBCs) that have nutritional and pharmaceutical applications. NBCs are molecules found in nature that provide preventive and/or therapeutic health benefits to both humans and animals.
18 Jul 2002	Genomic Solutions	Harvard Bioscience	25,854	Genomic Solutions designs, develops, manufactures, markets, and sells genomic and proteomic instrumentation, software, consumables, and services.
8 Jan 2002	MediChem Life Sciences	deCode Genetics	83,628	MediChem Life Sciences, a drug discovery technology and services company, offers a variety of integrated chemistry research and development capabilities to pharmaceutical and biotechnology companies. The company focuses on the study of protein structure and function.
7 Jan 2002	Matrix Pharmaceutical,	Chiron Corp.	58,995	Matrix Pharmaceuticals develops novel drug candidates for cancer. The company's product candidates are designed to improve the delivery of cancer drugs for more effective local treatment for solid tumors.
12 Jul 2001	Lexicon Genetics	Coelacanth	34,090	Developer of proprietary high-performance chemistry platform enabling the supply of novel drug-discovery compounds in the form of combinatorial chemistry libraries. The company's research focuses on enhancing drug discovery and pre-clinical development through the use of proprietary chemistry and filtering platforms which are used to create libraries of orally active NCEs.
13 Jun 2001	AXYS Pharmaceuticals	Celera Genomics Corp.	166,077	AXYS Pharmaceuticals integrates life science technologies with a focus on transforming gene discoveries into drugs. The company conducts a broad and diversified pipeline of research and development programs partnered with pharmaceutical companies.
Spring 2003	EOS Pharmaceuticals	Protein Design Laboratories	37,500	EOS has a focused genomics approach to identify abundant protein targets in cancer. Two antibodies at IND stage.

All monetary figures are in thousands. The list is not complete but representative of the fact that important mergers and acquisitions are presently shaping the biotechnology industry. 3 D Pharmaceuticals (<http://www.3dp.com>); Johnson & Johnson (<http://www.jnj.com>); Triangle Pharmaceutical (<http://www.trianglelabs.com>); Gilead Sciences (<http://www.gilead.com>); Baxter Healthcare (<http://www.baxter.com>); Epic Therapeutics (<http://www.epictherapeutics.com>); Martek Biosciences (<http://www.martekbio.com>); Omega Tech (<http://www.omega-technical.com>); Genomic Solutions (<http://www.genomicsolutions.com>); Harvard Bioscience (<http://www.harvardbioscience.com>); MediChem Life Sciences (<http://www.medicchem.com>); deCode Genetics (<http://www.decode.com>); Matrix Pharmaceutical (<http://www.matx.com>); Chiron Corporation (<http://www.chiron.com>); Lexicon Genetics (<http://www.lexgen.com>); Axy's Pharmaceuticals (<http://www.axyspharm.com>); Celera Genomics (<http://www.celera.com>); Protein Design Labs (<http://www.pdl.com>).

to account, within ten years, for at least half of novel compounds entering the markets annually [25].

Like no other group in the industry, large biotechnology firms will define the cutting edge of scientifically based drug therapy. Groups of more mature companies are likely to emerge: developers specialized in particular disease areas, 'smart little pharma companies' and companies that offer novel and comprehensive technologies like pharmacogenomics. If eventually accepted, pharmacogenomics will permeate all of drug therapy and will secure considerable leverage for their providers.

Mergers and acquisitions will be an indispensable strategic tool in creating more order and functionality in the biotechnology world. A list of recent examples (Table 2) shows that, despite defensive financial markets, the consolidation process within the biotechnology industry, and also between pharmaceutical and biotechnology companies, continues.

We are, at present, living in an era of transition. Less than 30 years ago, the industry appeared rather homogeneous despite the differences between individual pharmaceutical companies. Today, the picture has changed completely. The contours of tomorrow's industry are barely becoming visible. Ironically, the powerful forces that enforce more consolidation have also led to, and will continue to generate, greater complexity.

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