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PHARMACEUTICAL DROUGHT: DO PATIENTS REALLY COUNT?

The evident failure of current strategies for drug discovery has generated widespread concern, and several divergent opinions about the problem and its potential solutions. Paradoxically such failure has followed two monumental events: first, unprecedented scientific conquests in the fields of genomics and proteomics. Second, multi-billion dollars mergers and acquisitions involving giant pharmaceutical companies. The reader may ask why such flood of information combined with enhanced capitals have not been matched by an increased output by giant pharmaceutical companies. A partial answer to this question can be found in some informed opinions, which liken current drug discovery to an intellectually absorbing but meaningless game, divorced from the reality of medicine.

Over the last twenty years most big pharmaceutical companies have experienced what can be described as a radical change in the way they conduct their business. Since its existence the pharmaceutical industry has justly relied on research and discovery to conquest its share of a rapidly expanding market. Having said that, it is surprising to note that current changes in the same industry have identified cuts in discovery research and in particular basic research as one way of saving money. This observation has a number of reasons, which I do not share and therefore I shall use part of this material to support my argument.

The radical changes within the pharmaceutical industry in general and within big pharmaceutical companies in particular have occurred in two distinct phases. The first one started in the Eighties and early Nineties, where big companies tried to be bigger through a series of mergers and acquisitions involving equally big and well established competitors. It is sufficient to remind ourselves that in almost ten years there have been twenty major mergers/acquisitions. The second phase, which started at the early years of this century, went in the opposite direction to the first stage, where big companies have invented various forms of transformation to give the impression that they are working in a similar fashion to

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small biotech companies. I am sorry to say that these marketing changes have been invented and sold to almost all the big pharmaceutical companies by a handful of clever financial consultants who had nothing to do with the world of pharmaceutical research. These consultants have made their names through their work for car manufacturing, banks, insurance companies and other heavy industries but had little or no experience in the world of pharmaceutical research. To put it bluntly these consultants treated car assembly in the same way as discovering an innovative medicine. The main task of these consultants was to present a given pharmaceutical company to the outside world as a slim, efficient and a worth investing entity. The first consequence of efforts by these consultants was the standardization of the methods of practice, including the way research is done in most leading pharmaceutical companies. In other words, they have managed to kill the spirit of healthy competition and individuality, which characterized pharmaceutical research for almost a century. To implement this second phase, which we are currently living, the top managers in many big pharmaceutical companies have conducted a relentless campaign to convince their research scientists that getting smaller is the way forward. In the contest of such campaign you would commonly hear the term "small is beautiful". This term was rigorously implemented in Europe and in North America but not in the emerging markets, such as India and China where most big pharmaceutical companies have competed to open pharmaceutical research centers bigger than those, which the same companies were closing down in the western hemisphere.

In practical terms, the implementation of the phrase "small is beautiful" in the western hemisphere meant closing down research centers, cancelling long years of scientific experience, sending home hundreds and even thousands of highly qualified research scientists, and above all reducing the number of scientists within core research units (the motor of discovery) below a given critical mass required to conduct a serious research.

To understand why many of us can not afford basic health care and the poor performance of giant pharmaceutical companies, the following general considerations may help: first, it is a common knowledge that bringing a new drug to the market requires on average 10-15 years and about 1 billion US $. Despite huge investments in R&D, the development of new drugs is at all time low. The number of new drugs that are approved by the Food and Drugs Administration (FDA) has declined steadily from more than 50 drugs per annum 15 years ago to less than 20 in 2007. This worrying trend has persisted despite mergers and acquisitions and development expenditures exceeding 50 billion US $. Observers have attributed this poor performance to a number of reasons, such as inefficient project managements, an overemphasis on technology-driven research, increased and stricter regulatory requirements, and an unwillingness on the part of the big pharmaceutical companies to pursue products that are not likely to generate annual sales of at least 0.5-1.0 billion US $ [3-5]. In my opinion there are other reasons behind the current disappointing output of the big pharmaceutical companies.

The expensive failure of adopting combinatorial chemistry

Chemistry is one of the pillars of pharmaceutical research. In my opinion excellence in chemistry is the first step if a pharmaceutical company wants to set itself apart from its competitors. Throughout the Nineties big pharmaceutical companies have poured vast amount of money to synthesize as fast and as many new chemical entities. The bulk of these investments were directed to an emerging method of synthesis dubbed "combinatorial chemistry". This method is based on a simple principle, which was first demonstrated by Merrifield in the early Sixties [1]. Based on this pioneering work on solid-phase synthesis, and using a split, couple, recombine approach libraries (collection of compounds) of potentially billions of different chemical entities can be created.

Briefly, the synthesis is performed in parallel-sequential chemical reactions: the first synthesis step is a batch of millions of microscopic resin beads divided into different reaction vessels and the first building block, e.g., a protected amino acid, is coupled to the resin, the beads are then mixed together and washed extensively, the amino group of the coupled amino acid is deprotected, and the beads are distributed randomly into a second set of reaction vessels and coupled with the next set of building blocks. This process is repeated until a ligand of the desired length is obtained. In simple terms, you start with synthet-

ic beads, few chemical building blocks, and few solvents to end up with potentially millions of compounds.

The reader can easily appreciate that combinatorial chemistry represented an attractive opportunity, which big pharmaceutical companies could not miss. These companies started a race to acquire greater and greater collection of compounds to test in assays, big pharmaceutical companies developed combinatorial synthesis approaches in which drug-like compounds could be produced in short times. The enthusiasm of these companies for the new technology was exemplified by the words of the CEO of Pharmacopeia in 1996 "with their new technology, chemists would boost productivity from tens of novel compounds to nearly 100,000 per year at a fraction of the original cost [2]. These words were music to the ears of CEO's of various big pharmaceutical companies who made a simple calculation, which can be summarized as follow: if two companies have compound stores containing millions and thousands of compounds respectively, the chances of the first to discover new medicines are orders of magnitude higher than the second. As the ability to generate millions of compounds was consolidated, huge investments were made by both small and big drug companies to purchase specialized laboratory equipments for combinatorial synthesis. In my opinion such calculation was naïve to say the least and the following years have demonstrated such naivety. The calculation of these companies were mainly based on a simple numbers game, which did not take into serious account that sizable libraries were often generated as compound mixtures. In other words, researchers were provided with millions of potential drugs, yet when these impressive numbers were screened for biological activities the results were highly disappointing. The frequent failure to identify active single compounds following the de-convolution of mixtures exhibiting biological activity has eventually convinced these companies that high numbers were not sufficient to guarantee quick discovery. After a number of years even the most optimistic CEO realized that these millions of compounds had to go through various phases of purification, analytical, toxicological and biological analyses before they can be sorted out into potentially promising compounds or simple trash. It did not take long on the part of various pharmaceutical companies to realize that fruitful implementation of combinatorial chemistry required two basic elements: more research scientists are needed to interpret and make sense of huge amount of data, and second, more time and resources are needed before benefits can be harvested. Both elements were against the emerging culture in pharmaceutical business. In a very short period of time the glorious combinatorial chemistry has been put on the back burner. Furthermore, the same managers who introduced this technology have made intense efforts to discourage chemists from even using this term, instead terms like high throughput chemistry and parallel synthesis became highly fashionable.

Meta studies

Another unexpected development, which hit big pharmaceutical companies derived from what is known as Meta studies. These studies are generally conducted by highly respected academic institutes and can involve medicines already in the market and used by a large number of patients suffering from various illnesses. Meta studies (analyses) are based on a systemic approach aimed at using statistical analyses of a large collection of results from individual studies for the purpose of integrating the findings. It connotes a rigorous alternative to the casual, narrative discussions of research studies which typify our attempts to make sense of the rapidly expanding research literature. In recent years a number of these Meta studies by highly respected experts in medical sciences have resulted in:

a) additional warnings regarding the side effects of a given medicine. These warnings had the direct effect of frightening both doctors and patients. The first reaction by the doctor is to prescribe an alternative medicine. In certain cases, where the doctor is hesitant to take such action, informed patient would persuade the doctor to do so. There are reported cases involving big pharmaceutical companies, where such warnings have resulted in losses in the range of 5-10% of the total annual sales of the company involved;
b) complete removal of the medicine from the market. In this case as well as the economic losses associated with such removal the company had to face expensive legal battles regarding huge compensations to patients who demonstrated that health damage were caused by the use of the implicated medicine.

Patents of block buster drugs are running out

Many patents protecting a number of important medicines (including block busters) started to run out paving the way to the launch of many generic medicines. These are medicines made by companies that do not own the original patent of such medicines. These medicines were God given gifts to patients who could not afford expensive and patent protected medicines. On the other hand, these generics were big financial blow to giant pharmaceutical companies that had to adjust and manage their shrinking finances to adapt to the new environment.

Fever of Automation and high throughput

Throughout the Nineties till present day the big pharmaceutical industries have invested enormous amount of money in technologies capable of producing tremendous number of new chemical entities and their subsequent identification and testing. I must say that the output in this area of activities can only be described as impressive. The obvious question is why such impressive output was not matched by equally impressive number of new medicines. Part of the answer to this question has been given in the first part of this article; the remaining part of the answer can be gleaned from a number of considerations.

First, high number of newly synthesized molecules does not on its own guarantee the discovery of new medicines. Synthesis is one component of a fairly complex process, where not only each component has to be optimized but also the combination of these components has equally to be optimized. The same pharmaceutical companies have also invested intensively in technologies associated with the emerging fields of genetic and proteomic research. Unfortunately the impressive investments in chemical synthesis on one hand and in genetic/proteomic research on the other were treated as separate investments. In other words, these companies were doing well in each individual area of research but were doing badly in creating the right working environment to facilitate early communications between the different components of the discovery machinery. This meant that progress and successes in the area of small organic molecules were not rationally combined with successes in the area of large bio molecules (e.g. proteins, genes).

Furthermore, metabolic studies and pharmacokinetics were treated by the same companies as separate component of research, which has to be kept away from chemical synthesis, genetic and proteomic findings. The failure to coordinate and integrate these powerful achievements in the areas of small and large bio-molecules produced an effect easily comparable to the absence of findings in both camps. To put it in simple terms, the fever of high throughput and automation generated an impressive amount of data, which the pharmaceutical companies failed to reap from it the expected benefits.

Second, substantial cuts in human resources by big pharmaceutical companies meant shortage in experienced scientists who were desperately needed to sort out these mountains of data. This had the direct result of spending equal efforts on both highly promising molecules as well as on molecules, which should have been excluded at a much earlier stage. In other words, the absence of clear scientific guidelines resulted in bottle necks which not only slowed down the discovery process but also buried highly promising molecules under many layers of other molecules, which should not have been there in the first place.

Third, with stricter guidelines by the various control agencies in particular the FDA, the pharmaceutical industries suffered a substantial depletion in their pipelines. Many future decisions by these companies were based on the number of molecules in these pipelines. These molecules were treated as future medicines, many of which were quickly disappearing because they did not meet certain criterion by the FDA. Strangely enough many of these companies had enough data in their hands to allow them to make a realistic assessment of the rate of success of the molecules within their pipelines. The last few years have demonstrated that such assessment was widely different from that of the regulatory agencies. Such difference in assessment can be tentatively attributed to two reasons: the first is fairly obvious and related to stricter guidelines by the regulatory agencies, which took the pharmaceutical industry by surprise. The second and less obvious reason (at least for the reader) can be in part attributed to various big pharmaceutical companies. These companies have in some way given the impression of possessing rich pipelines, which resulted in short-term advantages. The reader can appreciate that presenting rich pipelines by a given company can have a positive response from investors and at the same time give the outside world the hope that research is going well and new medicines will be delivered to the market by this company. At this point I want to be generous with such pharmaceutical companies and suggest that presenting rich pipelines was not deliberate but has more subtle reasons behind it. For example, if the scientific data regarding a pipeline candidate are not comprehensive or in some cases are not accurate enough then a decision taken in a good faith can contribute to an increasing numbers within such pipeline but certainly not their quality, which is in my opinion the determining factor in the destiny of such candidate. Anyone who worked in the pharmaceutical industry knows that numbers are central to the way of thinking within such industry. However, the same industry has failed to grasp the fact that to discover and market innovative medicines, numbers on their own are not sufficient.

The recent years have registered an exceptionally high rate of failure in the applications to the FDA for the progression of molecules derived from the pipeline of various pharmaceutical companies. This high rate of failure has substantially depleted the reserves of what these big companies have been considering the financial guarantee for years to come.

In summary, huge investments in automation and high throughput technology have filled the pharmaceutical stores with newly synthesized molecules but very low percentage of these molecules have progressed to a stage where they can be considered as potential medicines. It can be said that the impressive output of the high throughput techniques was accompanied by an equally impressive rate of attrition, which shattered the dream of a class of managers who were determined to impress their company and the outside world by presenting impressive number of molecules in the pipeline of their respective companies.

Small is beautiful

Following the poor results inherited from the first phase of big mergers/acquisitions the big pharmaceutical companies found themselves in a blind allay with an increasing pressure from investors and markets to change course. This change was easier said than done; these companies could not retreat back and at the same time did not have a clear vision how to move forward, it is the classical case of the cat biting its tale. In their desperation to get out of this situation, the big pharmaceutical companies turned to the famous handful of consultants. The advice of these consultants came loud and clear: cut down the number of employees including experienced research scientists, close down research centers in the western hemisphere, and look for new centers in emerging countries, where the costs are much less. In simple words, big and well established research centers in the west should be either shut down or reduced in size to give the impression

that they are working in a fashion similar to successful biotech companies. It is not very demanding on the part of the reader to realize that such advice is a typical remedy of desperation. And as all desperate measures it needed a miracle for its success. As an ex research scientist in one of the big pharmaceutical company I can say with some confidence that this stage was one of the most confusing transitions from very big to small that I ever witnessed. Entire research departments/units were cancelled overnight, other were split in ever decreasing dimension. It was common to see units, which were composed of 20 persons split into five smaller units with five heads of newly formed units. The irony is that these smaller units were asked to perform the same type of research which was done by a single unit from which these smaller units were formed. Such moves entailed a highly damaging fragmentation of the discovery process and the loss of valuable and well established communication lines between the various components of the same process. Superficially such small units looked slim and efficient, yet the loss of experienced scientists in the process of reducing costs coupled with a fragmented and badly organized research structure have plunged these pharmaceutical companies into deeper waters. The rush to open research centers in emerging countries and the fever of outsourcing are among the steps taken by big pharmaceutical companies to get out of their current crisis. Whether such desperate steps are sufficient to guarantee the survival of these companies will be to the coming years to decide.

Marketing is the motor of discovery

In recent years most big pharmaceutical companies have adopted strategies that aim primarily at profitability. Within such strategies marketing occupies a prominent place. The marketing departments tend to articulate their needs on the basis of their relative positions in different world markets. Currently, marketing determines the areas in which a company invests, the markets in which it wants to be strong, even the compounds that admitted to development. The reader can appreciate that such strategies rendered the heads of marketing and finance as the most influential figures in today's pharmaceutical industry. The unprecedented race by most big pharmaceutical companies to increase their presence (including R&D centers in China and other emerging countries) is the result of ever increasing power of marketing managers. It is worth noting that two decades or so ago heads of R&D were the influential figures in the same industry. The emerging role of marketing and finance meant distancing of big pharmaceutical companies from open and unrestricted scientific investigations, which are perquisites of invention and creation.

From my own experience I can state that it is almost impossible to convince a marketing specialist of the utility of basic research in the process of innovative discovery. This is because marketing people have a time scale, which is in full contrast to that perceived by a research scientist. To put it bluntly, marketing did not care about long-term research, including basic research, which for marketing became a luxury that pharmaceutical companies could not afford.

Some readers may think that I have an unfair opinion towards the pharmaceutical research in which I have spent over 20 years of my professional career. To defend my opinion against such probable criticism I shall cite a relatively obvious aspect, which tends to be ignored by the pharmaceutical industry.

Any pharmaceutical industry regardless of its size cannot survive without selling their medicines. In any civilized society such medicines are paid for either by the central governments and/or by private health insurance policies. In either case the money are derived from taxes/contributions of most individuals within such society. What I am trying to say that the ordinary person (healthy or otherwise) has the right to question the output of entities, which receive part of his/her income. The denial of such right may justify the opinion of some informed observers such as that cited by Horribon [6]. The author compares modern biomedical and pharmaceutical research with the "glass bead game". In his article, Horribon points out that a metaphor of much modern medical and pharmaceutical research can be found in a book entitled "The Glass Bead Game by Herman Hesse". In his story, Hesse [7] describes how the leaders of a real world brings together the brightest scholars to create a magical state within a state, the isolated world of Castalia. These recruits are persuaded that the highest achievement of the human mind is to play a complicated and subtle "glass bead game", an intellectual Olympics which challenges and stretches the most talented. The world of the game is beautifully refined and internally self-consistent. However, this wonderful world is fully isolated from the real world, and that playing the game makes no contribution to real world issues.

Based on my own experience in the pharmaceutical world, I fully agree with Horribon when he says "When I look at the world of medical and pharmaceutical research it seems to me that we are well on the way to creating a Castalia which is entirely acceptable to the majority of scientist-priests. They receive funding from the real world and are inducted into a complex organization which, for those who know how to play the game, creates an ever expanding universe of intellectual and social possibilities". Fortunately there is a big difference between Castalia's world and the world we are living today. The castalians were confident of the absence of any need to justify their game, on the other hand, today's world expect the pharmaceutical and biomedical research to provide a pay off. The sequencing of the human genome combined with an increase in genetic and proteomic data in the late 1990s fueled the idea that once all of the disease targets were characterized, drugs for each target would eventually follow suit. However, many pharmaceutical companies did not take into serious consideration that target validation was still lagging behind the enhanced access to potential targets. In effect the new scenario of increased therapeutic targets has increased the chances of failure. It is hard to understand why such extraordinary scientific achievements had the opposite effect on the productivity of the pharmaceutical sector. I am sorry to say that such paralysis in the pharmaceutical research is likely to continue for years to come. This apparent pessimism is derived from the knowledge that some well established and well financed pharmaceutical research centers have over the last twenty years failed to produce a single molecule worth of marketing. I hope that the managers of such centers realize that such negligible productivity is stretching the patience of both the taxpayer and the patient.

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