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Advances in Technology and Their Implications for Global Pharmaceutical Development

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We are entering one of the most profound periods of human advancement. One that is predicated on the benefits of science and one that can potentially change the nature of human health through direct intervention. Whereas our efforts have previously been to treat illness, our technologies in the near future, by understanding and harnessing human complexity, will also be able to replace and correct what was previously unfixable, and to enhance human performance. Fundamental to these new approaches is the precise knowledge of the molecular causes of human disease, and the ability to engineer chemical, biological, or mechanical solutions to alter these targets. With the advent of high throughput screening approaches, genomics, informatics, combinatorial chemistry, and automation, the speed of biological discovery has increased by thousands to a million fold. This speed of discovery has had a profound impact on the development of precise diagnostic biomarkers, and in developing new drug therapeutics by the pharmaceutical and biotechnology sectors.

The progress in pharmaceutical is well exemplified in the field of cancer. For example, with the introduction of combination chemotherapy in childhood leukemias, and in testicular cancers in young men, the overall mortality from these cancers has fallen by almost 60%. This has been primarily due to intelligent combinations of chemotherapeutic agents. More recently, however, the focus of

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the pharmaceutical industry in cancer therapeutics has been towards therapeutics specifically targeted at defined molecules as compared to the more indiscriminate approach of inducing DNA damage as had been the case for cytotoxic agents of the past. New drugs synthesized to target one class of enzymes, the kinases, are effective treatments for certain cancers. The introduction of Gleevec as a targeted anti-kinase therapeutic for chronic myelogenous leukemia (CML) has significantly reduced mortality from this disease by almost 50%. In all examples given, these were the first reductions in cancer mortality ever documented on a population scale and are reflected in the significant improvement in national health statistics. Though prevention and early diagnosis contributed to these improvements in mortality rates, for cancers such as the leukemias and testicular cancers, they are completely attributable to dramatically improved therapies. Thus, dramatic advances in biology and technology have fundamentally changed medicine and the health care landscape mainly in the last twenty-five years.

In the 21st century, some of the changes that have taken place in science and society will significantly alter how the pharmaceutical business will be conducted. Scientifically, the breakthrough developments are in computational biology, genomics, combinatorial chemistry, and automation. The sequencing of complete genomes including those of humans and important animal models, such as the mouse and the rat, has revolutionized the concept of target identification. In the past, each potential drug target represented by the protein product of a gene was cloned using laborious molecular approaches. The availability of complete genome sequences and full length cDNA (representing the expressed messenger RNA) sequences enables investigators to clone a gene and related molecules with remarkable speed by bypassing physical screening of a genomic library. Advances in combinatorial chemistry provide immense structural diversity for biologists to work with so that millions of unique compounds can be generated and screened rather than only tens of compounds. Structural and computational chemistry has progressed such that any protein target can be virtually assessed for potential chemical inhibitors. Thus, strong candidate drugs can be designed computationally eliminating potentially wasteful wet laboratory experimentation.

The unifying technologies that underlie the genomics and the chemistry are derived from computational advances and from automation. All genomic and pharmaceutical chemistry challenges are being addressed using some form of high capacity computing and employing advanced devices, including robots. The computational advances include electronic communications which allows for scientists and administrators from geographically distant sites to work closely

together. Taken together, the scale of the information and the laboratory research activities has increased by orders of magnitude – thousands to million of times faster and more comprehensive in scope. What research units are pursuing is the reconstruction of all the signal "wiring" of a cell (such as a cancer cell) so that outcomes can be predicted. In many ways, like how aircraft design has progressed, biology and pharmaceutics are emerging from a state where trial and error was standard operating procedure to one where new designs are modeled computationally before a prototype is built.

These fundamental changes in the conduct of biological investigations have driven concomitant shifts in those management systems and the organizational structures that historically fired the success of the biotechnology and the pharmaceutical industry. For example, biotechnology companies emerged primarily because pharmaceuticals were centered on chemistry and could not readily harness or manage discovery based on molecular biology. As a result, companies rose to provide solutions in discovering targets for diseases. Exelixis, Affymetrix, Celera were all companies based on platform technologies that serviced big pharma. Similarly, other biotechnology companies focused on recombinant engineering in generating biotherapeutics such as therapeutic antibodies and therapeutic proteins. Here Genentech (recombinant insulin) and Amgen (recombinant erythropoietin) were the big names. But now, because of current technologies, discovery and recombinant production are no longer the limiting steps. Genomics enabled easy mining of targets; but validation of these targets as to which one is the most important has become the focus. Recombinant engineering is now a standard technology adopted by all pharmaceuticals. So the new biotechnology companies have become more computational providing structural solutions, and late stage developers of selected compounds that have been abandoned by failed biotech companies or left to languish by big pharma. Technology has changed the focus of biopharmaceuticals.

Equally important, these enabling technologies are also altering the way nations govern, develop, and market their biomedical strategies. Since some of these technologies have become boilerplate, nations have found it lucrative to provide technical services to pharmaceutical and biotechnology companies at a low price. India and China are offering antibody production and generation of recombinant proteins and chemistry to the world; and their governments are supporting this development. Though boilerplate, the processes are complex and require higher technical expertise. The cost differential in salaries for PhDs and engineers in these developing countries make outsourcing to them very competitive. Moreover,

contemporary telecommunications with its wide-bandwidth and improved air travel to these sites allow for outsourcing to not only be cost effective but convenient as well.

So given these developments, where will the pharmaceutical industry be in the 21st century? First, the entire industry will need to bring products to the market much more quickly; these products must be cheaper, and will need to be safer than current drugs are. This trend is not because of market forces, but rather because of demands of social justice. In the past, the United States was the major market for pharmaceutical products in the world. Though Europe and Japan has risen in the post-war era to be major pharma markets, the US still dominates the market. This is primarily due to a health financing system of subsidized free enterprise which has allowed for unchecked rises in health care costs. In 2002, health care consumed 15% of the US G.D.P. and is projected to be 18% in 2012, as compared to about 9% for Europe, Japan, and Canada, and 3% in Singapore. Health care costs for pensioners have become a major financial burden that jeopardizes the competitiveness and viability of US companies. Moreover, as the population ages, the burden onto Medicare will further exacerbate an already problematic Social Security system. Thus, this rise in health care costs in the US is untenable and cannot be supported in the future. Drug costs will be progressively controlled either directly by governments (even in the US), or indirectly because of political demands. This, in turn, puts pressure on the pharmaceutical industry to be more efficient in developing drugs to maintain profit margins and shareholder value.

Paradoxically, despite these financial and social demands, the trends in the pharmaceutical industry have been in the opposite direction. The pipeline of many companies has been of concern sparking a wave of mergers; the time to market has increased significantly, and the costs for development have skyrocketed. There will progressively be greater pressure on the pharmaceuticals by shareholders and by governments to provide cheaper drugs which means faster development and lower development costs. Simultaneously, the sophistication of many drug markets, including the emerging markets in China and India, places increasing regulatory demands for safety in these countries. The question therefore, is how to provide more drugs that are better, safer and less expensive? The answer, found in other industries from financial services to airline construction, is in technology and in globalization.

Certainly, as mentioned before, complex but modular tasks in the drug development path such as chemistry, toxicology, and clinical trials can now be outsourced to lower-cost regions on a global scale without a concomitant loss of

quality. Therefore Eastern Europe, Ireland, China, India, Taiwan, and Singapore have all have benefited from this outsourcing trend in pharmaceuticals; so much so, that most of these countries have specific governmental plans to develop pharmaceuticals as a means to diversify their economies. Unlike standard manufacturing, pharmaceutical development has more stringent quality control requirements and, therefore, successful entrants have had a strong focus on higher education. Because the modularity makes it easy for multinational pharmaceuticals to shift sites quickly, there is intense competition amongst the entrants to maintain a competitive edge.

The second trend in pharmaceuticals will be to exploit complexity. Biologists have always known living systems to be very complex, but until recently, have not been able to precisely identify the components and their working relationships. The computational advances have provided solutions to many of these challenges. At the same time, chemistry is now very precise in targeting specific molecules. This combination of the detailed mapping of complex systems and precisely targeted chemical inhibitors has opened the possibility of using combinations to tailor treatments. This realm of combinatorics, whereby combinations of different drugs at different doses tailored for the unique physiologic composition of an individual patient, is progressively a reality. Pharmaceutical companies, previously focused on pushing single chemical entities, will need to develop combinations very early in the developmental cycle. Since combinations of drugs exponentially increase the possibilities of therapeutic interventions, the demand for quickly completing clinical trials will be great. Moving these trials from North America and Europe will not only be cost-effective but essential, given the number of patients needed. Again, globalization of the development process is the solution.

Finally, all these new research and business models spawned by advanced technologies in a global field will need to be managed to maximize output. Financial markets have readily adopted communication technologies to their advantage. The transactional nature of their business, where massive bits of information need to be transferred securely, is well suited for the technologies available. By contrast, the business of creation, which is the fundamental of research and discovery in biomedicine, is more ephemeral and requires different forms of management. But there are distinct trends.

Outsourcing research in the form of contract research in a creation intensive environment is not optimal. Pharmaceutical companies instead have used a strategy of establishing multiple research sites that span many continents, each

playing distinctive and important roles in the creation process. IBM has pursued this in their many centers of excellence, each with an area of focus. Eli Lilly has a number of research units in Europe and Singapore to amplify their capabilities in Indianapolis. Often, the research units are a product of an acquisition, but more frequently these will be part of a larger strategy to exploit specific concentrations of expertise, or simply to globally distribute sensors of new thinking. This last reason tacitly acknowledges that no single center is the sole well-spring of creative potential, and that a company is wise to "harvest" new ideas and concepts from thought leaders anywhere in the world. This is best done not by traveling programme directors, but by forming research roots in regional research communities.

If structured appropriately, these distributed sensors can also advise the corporate leaders on opportunities based on leveraging differences in social and health care preferences of different regions. A simple example has been the shifting of animal-based research from UK sites where animal rights activists are disruptive to regions where animal experimentation is more accepted, such as the United States. Similarly, more companies focusing on stem cells are relocating from the US with its restrictive regulations against stem cell research to other jurisdictions more favorably inclined, such as Europe and Singapore. A more complex situation, however, might be to explore the following: Asian patients pay out of pocket for diagnostic tests – technologies used in diagnostics can be manufactured more cheaply in Asia where regulations around diagnostics are less restrictive, and investors appear to be more willing to fund biomarker companies in Asia than in the West. Therefore, it may be advantageous to manufacture and market new diagnostics first in Asia. Later, at a favorable time, the same diagnostic may be introduced in the US and EU. This form of "social arbitrage" takes advantage of differentials in social preferences to advance therapies for human disease. This strategy should not be interpreted as supporting unethical testing in regulatory lax jurisdictions, which cannot be condoned. However, it is clear that for historical and social reasons, different societies are more or less enthusiastic or cautious about certain practices and place greater regulatory constraints (e.g. stem cell research in the US, recombinant engineering in Germany, animal experimentation in the UK). These differences can be used to optimize pharmaceutical development.

Taken together, advanced technologies have already dramatically changed the landscape of drug discovery. It has accelerated discovery by orders of magnitude and carries a promise of bringing better and safer drugs to the market. Technology

also has facilitated globalization, which in turn will help develop safe drugs faster. Without this increase in efficiency and throughput, the pharmaceutical industry will face a challenge of survival. Finally, globalization, if harnessed correctly, can bring the economic and social benefits of biomedicine to a much wider audience and at significantly lower costs.

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