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**THE FUTURE OF DRUG DISCOVERY
AND
DRUG DEVELOPMENT**

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ABSTRACT

The turn of the century has brought with it some major advances in technology and innovation. This has affected almost all areas of business around the world including drug discovery and development. In the coming years more change is anticipated leading towards globalization of medical treatment and research. Health organizations across the world are striving towards a uniform platform so that fast, effective and inexpensive treatment options can be provided to patients, including the third world countries. In the United States the FDA has already taken several steps to expedite the drug approval process so that pending trials can proceed at a faster pace, without sacrificing the drug safety issue. Many advances in biotechnology have improved detection and diagnosis of several diseases some of which were life threatening in the past. Scientists and clinical researchers are approaching novel and innovative therapies for the cure of deadly cancers in an effort to reduce side effects. The future will bring more innovative partnerships in the areas of pharmacology, chemistry, biology, biotechnology, information technology, medicine and clinical research to make drug discovery a very exciting and challenging field. There is a trend toward globalization of information, technology transfer and outsourcing of various aspects of the drug development process in an effort to cut costs and provide less expensive treatment options in the future.

INTRODUCTION

Drug discovery and development is a wide area that includes the initial idea or discovery of a novel drug usually at the scientist's bench, followed by clinical research on human subjects taken all the way to manufacturing and marketing of the drug. This field used to once be dominated by chemists, biochemists and pharmacists. In the 21st century however, just like all other areas, drug discovery and development can no longer be clearly defined and is now an amalgamation of many different areas of expertise that now includes biotechnology, information technology, law, business etc. Before looking at the future of drug discovery and development let us look at what this actually involves.

Drug discovery

Most pharmaceutical companies are set up with an idea for a new drug that was initiated in a laboratory. This research could be academic research or industry based laboratory setting. Often times an academician with an idea may start his own small biotechnology firm and then grow into a bigger company with time or merge with a preexisting giant.

Drug development

This involves taking the idea from the research bench to actually creating a drug to be used in humans. This involves drug formulations, stability, modifications, and study of effectiveness in cell culture or animal models and possibly studying methods of delivery into humans.

Currently in this century despite the pressure from reforms in the private sector due to growth of managed care, trimming of the budget on Medicare and Medicaid, and the hassles of jumping through all the hoops of FDA regulations, pharmaceutical companies rank as one of the most profitable industry in Fortune 500 Report. Merck, Bristol-Myers Squibb and Abbott laboratories making twice as much profit than expenditure on research and development. In the year 2001 the top 10 Fortune 500 drug companies reported earnings of \$37.2 billion as compared to \$28 billion in 2000. Americans have spent \$154 billion on prescription drugs in 2001 an increase of more than 17 % according to a study by the National Institute for Health Care Management (NIHCM), (The National Institute for Health Care Management (NIHCM), "Prescription Drug Expenditures in 2001: Another Year of Escalating Costs," April 2002.)

Reprinted below is the report from venture Capital which gives an idea of the large investments made towards new drug development in the future.

VENTURE CAPITAL

Portola leads with \$46 million second round.

VENTURE CAPITAL			
COMPANY	AMOUNT/ROUND	LEAD INVESTORS	DESCRIPTION
Portola Pharmaceuticals South San Francisco	\$46 million second round	Advanced Technology Ventures	The money will be used to advance its lead candidate, an oral Factor Xa , into Phase II.
PTC Therapeutics South Plainfield, NJ	\$26.6 million N/A	Credit Suisse First Boston Private Equity and HBM BioVentures	The money will be used to develop PTC124 and advance its preclinical oncology and antiviral programs.
Fovea Pharmaceuticals Paris	\$25 million first round	Sofinnova Partners	The biotech is working on breakthrough treatments of retinal diseases .
Mersana Cambridge, MA	\$21 million undisclosed	Fidelity Biosciences and ProQuest Investments	Mersana is developing cancer therapeutics .
OncoMethylome Sciences Belgium	\$17.5 million second round	Edmond de Rothschild Investment Partners	The company is developing molecular gene methylation tests for early cancer detection.

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www.fiercebiotech.com

ROLE OF THE FDA

The year 2006 marks the centennial year of the US Food and Drug Administration. Over the past hundred years the FDA has played a key role in safeguarding the interests of mankind by stringent monitoring of the drug approval process. However there have been lapses and an effort is being made to bring the FDA abreast with modern technology so that this process can also function smoothly and efficiently. The FDA has often been criticized for being too strict and demanding regarding the requirements for drug approval, making the drug development process long and expensive. However it can be noted that despite these regulations there have been episodes of drug recall Vioxx and Bextra being the most well known lately.

In modern times as the techniques and tools for discovering and manufacturing drugs has been revolutionized. However the methods for testing the safety and efficacy of these drugs are still lagging far behind. In an effort to enhance the Drug Safety Program the FDA has recently awarded four contracts to gain access to pharmacoepidemiologic databases. The contracts allow the FDA access to the data regarding drug exposure and potential adverse side effects in an effort to assess the risks associated with medications that have been approved for marketing. The contract went into effect starting September 2005. (FDA Press release October 2005 <http://www.fda.gov/po>). The databases will be updated from various HMOs, provider networks and state Medicaid programs and may help avoid a repetition of the

Vioxx and Celebrex stories by regular updates on side effects before the drug has been consumed by thousands of people around the world.

The FDA has created the Office of New Drug Quality Assessment as part of internal restructuring in an effort to bring modernization to the drug approval process.

At a recent talk given by the FDA commissioner the following four goals were set for the future.

- Increase access to innovative technology to advance health
- Expand patient protection and empower consumers for better health
- Improve product quality and safety through better manufacturing oversight
- Modernize the FDA infrastructure

(Lester M. Crawford, D.V.M., Ph.D. Commissioner, U.S. Food and Drug Administration – Speech before Drug Discovery Technology and Development August 10, 2005)

Keeping drug safety as foremost in the agenda a Drug Safety Oversight Board has been set up which will be responsible for the managing drug safety issues within the Center for Drug Evaluation and Research (CDER).

DRUG SAFETY

The drug safety issue has been thrown into the spotlight due to recent side effects presented by drugs approved by the FDA after going through the clinical trial process. When examining this information however it should be kept in mind that even when a drug progresses through the Phase II and III of the clinical trial process, it is not until it reaches the masses post approval that side effects such as the ones seen in the case of the Cox-2 drugs become visible.

Celebrex was granted FDA approval in 1998 primarily to be used to treat pain in arthritis. The drug made \$2.3 billion in sales in 2004. However as its use became widespread it came to light that in certain patients the risk of heart attacks, strokes and allergic reactions went up tremendously. A warning has been issued to healthcare providers and the FDA has requested a change in the package insert for this drug including a boxed warning.

Bextra, another Cox-2 inhibitor made by Pfizer is under investigation and Pfizer has voluntarily withdrawn the drug (www.fda.gov 04/07/05). A third drug, Vioxx also faced similar problems and was voluntarily withdrawn by Merck.

Even more recently the prescription birth control patch Ortho Evra has been found to expose women to higher levels of hormone estrogen (upto 60% more) than birth control pills (www.fda.gov 10/11/05). The FDA has since recommended updated labeling for the patch to warn doctors and women.

The drug Iressa, made by AstraZeneca, mentioned above was initially approved by the FDA in May 2003, but considering the fact that it worked in only 10% of the patients treated, the FDA permitted re-labeling of Iressa and allowed use of it under a Iressa Access program allowing its use only in patients that would benefit from it. The drug however is under scrutiny for causing deaths in Japan and for not improving the life expectancy of majority of patients taking it. This is one example of how initial results in the laboratory often do not hold up in clinical trials. The drug was approved under an accelerated approval process and recently a petition has been filed to take it off the market since it endangered the life of patients. However distribution of this drug under a risk management plan allows access to patients who would benefit from it, since the results seen in such patients is dramatic.

If one keeps up with the FDA warnings and alerts it can be seen that despite the very stringent procedures set up before a drug reaches the people, a number of issues arise post marketing. It appears that an availability of accessible information about a drug after it is approved for marketing will help physicians and patients keep up with its progress. Part of the problem stems from the fact that the

modern human population wants quick relief from the slightest of symptoms. Many times doctors are coaxed into prescribing medication and other older, time tested forms of therapies are overlooked in favor of something new and lucrative on the market. This could mainly be the result of misleading advertising by companies in an attempt to boost sales. People should be made aware of resources that they can investigate and make an informed decision before consuming any drug.

Keeping drug safety as foremost in the agenda a Drug Safety Oversight Board has been set up which will be responsible for the managing drug safety issues within the Center for Drug Evaluation and Research (CDER). The FDA is proposing to set up a Drug Watch Web page for new data, risk information as well as information about the agency's decision making process. This website will be public accessible and will bring important information and awareness to everyone so that an informed decision can be made when a drug is made available.

Apart from the FDA the government also is proposing some changes so that the drug safety issue is managed better. Legislators have proposed a mandatory public registry of all U.S. drugs at the time of their introduction along with listing eligibility requirements for participants, funding sources, results including those not published in journals. This will give public access to a lot of information that had so far been treated as business secrets in company sponsored trials. Some pharmaceutical companies have agreed to set up such registries and companies like Eli Lilly and Pfizer have pledged to release more trial information and data (Couzin, J 2004).

An example of increasing transparency is the recent announcement by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) the launch of its new IFPMA Clinical Trials Portal. Created in collaboration with information technology leader IBM, it is the first internet search engine constructed specifically to provide on-line information about clinical trials worldwide. The IFPMA Clinical Trial Portal, which represents more than 7 months work by pharmaceutical industry technical and regulatory experts, as well as IBM consultants, currently contains more that 250,000 links. The Portal URL is: www.ifpma.org/clinicaltrials. Geneva, 9/21/2005.

All in all a serious attempt is being made to provide healthcare providers and patients easier and faster access to safe, effective and predictable drugs along with the information necessary so that an educated decision can be made regarding treatment options.

FUTURE OF BIOTECHNOLOGY AND PHARMACEUTICALS

We live in the post-genomics era. The human genome sequence project has unveiled hidden treasure chest of information regarding the human body that were never accessed before. Having available all this information the new age drugs will try to target more specifically the diseased cells causing fewer side effects. Also the information will allow for the development of more tailor made drugs and the patient's genetic profile will help a physician determine the mode of treatment.

Micro fluidics and nanotechnology have enabled an increase in output and require only small amount of samples to aid in diagnosis at a much faster rate. This has taken scientific research to the next level and analytical technologies have vastly improved. The applications of such micro-technology include cancer detection and monitoring, screening for infectious diseases, sexually transmitted disease screening and blood typing (Gwynne, P 2004).

Recently small biotech companies have experienced funding shortages due to lack of investors. It has become more and more common to find mergers between biotech firms and pharmaceutical companies. Biotech companies often lack the funding and infrastructure to take a drug through the clinical trial process to marketing and business development. The pharmaceutical company gains technical knowledge without having to build this expertise in-house. Biotech companies with new and innovative drugs in early (pre-clinical) stages of the development process are targeted by pharmaceutical companies looking to boost their productivity by having more drugs in the pipeline. Oncology is the sector most favorable for alliances and accounts for 28% of all alliances in this year. Among them is AstraZeneca-Astex a deal worth \$275 million and Genentech-Curis for \$140 million. Overall, among the multinational firms, GlaxoSmithKline leads with majority of collaborations and is followed by Boehringer Mannheim, Merck and Novartis. Areas in other fields of biology are also lucrative and a few examples of recent deals are AstraZeneca's monoclonal antibody alliance with Cambridge Antibody Technology, and Pfizer's \$480-million collaboration with Medarex (Clifford and Jones 2005). Alliances like these not only lead to a

business merger with an opportunity for growth, but also to an exchange and merger of innovative ideas and will speed up the drug development process.

Major mergers across Europe and United states have lead to globalization of industry standards and increased the importance of patenting and trademark registration.

In modern times big pharmaceuticals are reaping profits by pushing forward drugs called “blockbuster drugs” because they have brought in profits of greater than \$1 billion in a year. Among these big drugs are Lipitor (\$4.5 billion), Zoloft, Norvasc and Neurotonin all made by Pfizer. (Public Citizen’s April 17, 2002 Congress Watch 1).

INNOVATIVE THERAPIES

Researchers have been able to uncover the pathway for chronic pain and have new targets for developing new pain killing drugs. Soon physicians will be able to design a treatment protocol for an individual specific for his/her type of pain. The compound Capsaicin that makes chilli peppers hot exerts its effects through a receptor TRPV1 (Marx, J. 2004).

The analgesic acetaminophen (Tylenol/paracetamol) has been used clinically to treat pain and reduce fever for over a century. However the exact mechanism of its action was unknown until very recently. It has been found to be metabolized to make *N*-acyl phenolamine AM404, an activator of the ion channel, TRPV₁. Am404 also has stimulatory influence on a Cannabinoid receptor called CB₁. Both TRPV₁ and CB₁ receptors are part of pain and thermoregulatory pathways (Hogestatt, E. 2005). These two new molecules are now seen as potential targets of new line of drugs for the treatment of pain and inflammation.

RNA interference (RNAi)

The discovery of RNAi was made during experimentation using antisense RNA to knock out a particular gene function in animal models like fruit flies, nematodes and mammalian cells. In this technique double stranded RNA complementary to known RNA are introduced into the cell to specifically destroy that RNA hence blocking the function of a particular gene (www.ambion.com). This technique is thus used as a gene-silencing method and used to understand the function of the gene in the absence of its normal expression. Lately, it has been realized that this capacity to down-regulate the function of a gene holds tremendous therapeutic potential and this technology is being exploited to design new drugs to target various disorders. Currently RNAi screens are being carried out to identify key elements of cancer pathways to identify new targets for oncology drugs. In the near future this research tool will become a therapeutic tool. Pre-clinical studies are planned for treatment for asthma, cancer, diabetes, HIV, hepatitis C and Huntington’s disease. There are companies working solely on developing therapeutics using the RNAi technology. Sirna therapeutics already has in clinical trials a therapy for macular degeneration using this technology and is pioneering systemic delivery of the siRNA in the cells (<http://wsw.com>).

Targeted therapies for cancer

DNA micro arrays have been used to determine gene expression profiles for the understanding of the many pathways that cause cancer in human cells. The understanding of several oncogenic pathways allows for mapping out patterns of deregulation in these different pathways. Thus each type of cancer can have its own signature of pathway deregulation. This can also help in predicting the sensitivity of a particular type of tumor to therapeutic agents. Hence patients will be classified according to the genetic profile of their tumor and customized therapy can be given based on the sensitivity of their cancer to the drugs (Bild et al. 2005) (Wells and Nevins, 2004).

Based on similar lines a DNA test has been developed to identify non-small cell lung cancer patients who may be helped by the drug Iressa. This test is designed to look for mutations in the EGF receptor (EGFR) gene. The drug Iressa targets the protein made by this gene. Researchers have found that only EGFR-dependant tumors respond to this drug. Identifying these patients became possible by the efforts of scientists at Mass general Hospital and Dana–Farber Cancer Institute. This team reported that Iressa responding tumors have specific mutations in the EGFR gene, and that these mutations can be screened for in patients (Couzin, J 2004). This test is not commercially available but having something like this can save patients and families alike the agony of going through a therapy that promised to give life but fails.

There are available now some genetic screening methods like Mammoprint developed by Agendia (Amsterdam) that screens for 71 genes to identify the risk of recurrence of breast cancer. Another called Oncotype DX by Genomic Health Inc. (Redwood City, CA) looks at 21 genes to predict response to chemotherapy or hormonal therapy (www.hmnews.org Oct 2005)

Immunotherapy for cancer

If our body is capable of fighting of bacterial and common viral infections, then why does it fall short of blocking tumor growth? Advances in cellular and molecular immunology are helping answer this question and a new wave of cancer therapies will emerge that harness the body's own capacity to fight infection and use it as to act against tumors. This line of therapy includes increasing the immunogenicity of tumors by expression of molecules like the tumor necrosis factor at the tumor site making the tumor more visible to the body's immune system. Other ways include injecting monoclonal antibodies into patients. Rituximab an antibody that binds CD20 used in the treatment of B cell lymphomas has shown success in inducing remission. Two monoclonal antibodies approved for clinical use in breast cancer act on the Her-2/Neu receptor (Blattman, J and Greenberg, P. 2004).

Therapeutic vaccines

Prophylactic or preventative vaccines were first introduced when Edward Jenner in 1796 was able to prevent smallpox. Since then these vaccines have come a long way and now are routinely used to prevent infections such as chickenpox, smallpox, polio. Louis Pasteur for the first time demonstrated a therapeutic vaccine as a cure for rabies after exposure to the pathogen. This still remains the only cure for this disease. However many years later therapeutic vaccines have not developed much and many have failed the clinical trial process. Vaccines currently being developed include those for HPV, HBV, and HIV (Autran *et al*, 2004). These vaccines aim at preventing severe complications after an infection has occurred when conventional drugs alone are not sufficient. Clinical trials need to be more closely monitored and with all the new information available regarding the biological and clinical aspects of these viruses, there is hope for a therapeutic vaccine in the future. Although no therapeutic vaccines are FDA approved yet, there are several that are being studied in clinical trials. DNA and protein based vaccines as well as vaccines aimed at boosting the immune response to cancer are the next wave in development.

INFORMATION TECHNOLOGY IN DRUG DISCOVERY AND DEVELOPMENT

An increasingly vast amount of data is made available every day, making it almost impossible to keep up with this fast pace of scientific research. This definitely has led to an increase in collaboration of three important fields: Biology, Chemistry and Computer science (Information technology). Without the amalgamation of these areas it would be impossible to handle all the information that is being churned out from laboratories across the world, in academia as well as pharmaceutical industry. This has led to the rise of a new and upcoming area of bioinformatics. No longer can one visualize any of these fields as separate areas of science and the border between them has definitely blurred.

The assimilation of information technology into drug research has allowed scientists easy access to new information, thus allowing for exchange of ideas and data faster than ever imagined. Scientific publications in leading journals are accessible even before they come out in print. The internet has become a laboratory in a sense and is a tool that no researcher can do without.

Tools such as FlexiDock, (Tripos) allow scientists to look virtually for receptor-ligand interactions. Before something like this existed, scientists had to manually set up experiments to look for such receptor-ligand interactions. Now a large scale screening of compounds can be done virtually and then probable candidates tested in the laboratory. This has cut down the time spent at bench research tremendously.

Intranet technology is becoming a key technology for information exchange in pharmaceutical environments. Companies like Tripos (St Louis) are busy developing new technology for analysis of combinatorial libraries.

OUTSOURCING DRUG DEVELOPMENT

Rising drug costs and expensive manufacturing has led to an increase the tendency to look for cheaper and more economical means to achieve the target. Outsourcing to countries that have the availability of highly skilled technical force as well as an advanced technology network are being looked upon as an alternative to drug development in US and Europe. Many large pharmaceuticals already have established bases in Asia. Contract Research Organizations (CROs) offer companies the drug sponsors the opportunity to monitor and manage clinical trials in countries like Russia, China and India. These companies observe all the ICH/GCP rules and SOP standards.

It apparently is easier to conduct trials in countries like India and China with a large patient population, where paper work required is less compared to the US and Europe and the whole process is less expensive.

Outsourcing of clinical trials is not something new and has been done for a long time since the 1970s. However in the mid 90s this activity increased and since then not only the clinical trial aspect but the entire drug development process which includes preclinical evaluation, study design, clinical trial management, data collection and statistical analysis etc have been outsourced on a large scale. In the 90's only 4% of the processes were committed to outsourcing as compared to the year 2004 when almost 42 % was outsourced. In 2005 about \$2 billion of drug research process has been outsourced by companies across the world to US companies like Pfizer, Merck, Novartis and Eli Lilly (www.forbes.com. The drug Research War 2005).

In the coming years Asia is poised at becoming a major contender in this war. In the next 7-10 years it is estimated that \$800 million worth of processes will be outsourced to India and China. To keep up with this activity these countries will have to change a lot of internal policies like patenting processes and keeping up with International GMP practices.

Companies are outsourcing not only the clinical trial process, but have downsized even the R&D and manufacturing process and moved a large portion of this to the above mentioned countries. It is estimated that a US trained Ph.D. would get paid \$8000-\$10,000 in China as compared to four times as much in the US.

CONCLUSION

Considering the investments made in the past year and the future profits anticipated by pharmaceutical companies, it is very obvious that the future is good for drug discovery and development. As new technology comes into the market it will bring more information and ideas for drug discovery. The new-age drugs seem to be heading towards customized drugs to meet patient needs. This may seem expensive now but as more and more companies gear towards this methodology, it may prove cost effective in the long run. Also educated and informed consumers may actually prefer this line of treatment to avoid taking unnecessary medications. Outsourcing of many sectors of drug development not only cuts down on cost of manufacture in countries like the United States, but also provides economic growth to the less developed countries in Asia, where technical skills are available in abundance. One of the major challenges in these countries currently is the AIDS pandemic. Hence these countries too are investing in new drugs and vaccines in an attempt to cure and stop the spread of this deadly disease. This is going to require an organized attempt globally and organizations such as WHO have already taken steps to provide therapy on a large scale to underdeveloped countries. Together with all the information generated by the human genome sequencing program, and the amazing capabilities of new technology in piecing all this information together, we can expect to see fascinating changes in the drug discovery and development process.

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