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Editorial

Exciting changes

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It has been a hectic year, but the transition is complete. After four years of serving as Managing Editor of the *Journal of Commercial Biotechnology* under the auspices of Palgrave-MacMillan, I have acquired the journal and have incorporated it into thinkBiotech along with my portfolio of books and websites on the business of biotechnology. I would like to personally and publicly thank Neil Henderson at Palgrave-MacMillan for his training and support, and for his assistance throughout the transition process.

With ownership and editorial control I have implemented many changes, and look forward to bringing even more. An exciting line up of special issues, coming out over the next two years, is also in the works.

The first change you may have noticed is the new cover and full-color interior layout of the JCB, but the changes go much deeper than that. I have recruited three associate editors to share the editorial load as I take on more of the publishing responsibilities. They will also be soliciting papers in their areas of expertise, improve the breadth and quality of submissions and published papers.

A new section, *From the Boardroom*, has been added, complementing the *From the Classroom* and *Legal/Regulatory Update* sections in providing practical actionable guidance alongside the *Original Articles*.

The JCB website also has new social functionality — a Twitter stream (@jcommbiotech) and connectivity with LinkedIn and Facebook. Each paper also has an *Add Comment* function, enabling feedback and discussion. The LinkedIn group at http://www.linkedin.com/groups?gid=1241807 is also a great resource to continue the dialogue between JCB issues.

I look forward to continuing to develop the *Journal of Commercial Biotechnology* as an unmatched resource on biotechnology commercialization. I look forward to your thoughts on the new design and ideas for future issues at editor@CommercialBiotechnology.com.

Yali Friedman
Chief Editor and Publisher

Original Article

Bacterial proteins: A new class of cancer therapeutics

Received: August 11 2011

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is a distinguished university professor at the University of Illinois at Chicago. In 1980 Dr. Chakrabarty's genetically modified *Pseudomonas* bacteria became the first genetically-engineered organism to gain a US patent, as a result of the Supreme Court decision in *Diamond vs. Chakrabarty*. He is the co-founder of two companies, CDG Therapeutics Inc. in Chicago and Amrita Therapeutics in India, that are developing protein/peptide anticancer agents from microbial sources.

ABSTRACT

Cancer is a complex disease with a network of multiple metabolic pathways that are interlinked to promote growth and resist immune surveillance. Such a network is efficiently maintained through acquisition of multiple mutations in the human genome that result in the escape from normal cellular growth regulation and formation of lumps of fast growing cells known as tumors. The varied pathways through which cancer cells grow and inhibit their own cell death have made it difficult to develop effective drugs either to prevent the emergence of tumors or to check their rapid growth. Current anticancer drugs are either small molecules or monoclonal antibodies that target and inhibit a key important step in cancer progression pathway, thereby significantly inhibiting their proliferation. No effective drug or vaccine exists to prevent cancer initiation and drug resistance and toxicity are major problems in cancer chemotherapy. This article describes recent attempts to develop bacterial proteins that are used as weapons by certain pathogenic bacteria with long term residence in human bodies to prevent invasion of their habitat by invaders such as cancers, viruses or parasites. In one instance, such a protein, termed azurin, has been shown not only to have entry specificity in cancer cells and prevent cancer cell growth by interfering in multiple pathways by which cancer cells grow, but also to prevent induction of pre-cancerous lesion formation triggered by a potent carcinogen. A 28 amino acid peptide derived from azurin, p28, also shows similar anticancer and cancer preventive activity. In phase I human clinical trials, chemically-synthesized p28 has shown very little toxicity but significant beneficial effects, including partial and sometimes complete regression of metastatic refractory solid tumors in 15 advanced stage (stage IV) cancer patients where no conventional drugs were working. A second such protein, termed ATP-01, very different from azurin and obtained from a different bacterium, has shown similar anticancer and anti-HIV/AIDS activity and a 30 amino acid peptide derived from it has anticancer activity similar to p28. It would be of great interest to test these two proteins, should they prove to be non-toxic and non-immunogenic in humans, and the peptides derived from them, for their efficacy in cancer therapy and prevention. Such efficacies can be tested, singly or in combination, in vulnerable people such as people with predisposition to cancer (women with BRCA1/2 mutations, for example) or in HIV/AIDS patients with Kaposi's sarcoma or other forms of cancer.

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Keywords: anticancer drugs; azurin; bacterial proteins; cancer eradication; cancer prevention; human clinical trials; p28

INTRODUCTION

To be able to eradicate cancer in our life time, an eradicating agent must have at least two properties. It should inhibit the growth and kill any preformed tumor. Secondly, it should inhibit oncogenic transformation of normal cells to cancer cells. Ideally, such an agent should also

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be taken orally rather than through intravenous injection. No such agent exists today, but there might be on the horizon a new class of anticancer agents with both these properties. These agents are bacterial proteins, highly intelligently designed by certain pathogenic bacteria with 3 billion years of evolutionary wisdom, to keep invaders of the human body in check, when such bacteria are resident in the human body for long periods of time. Such intelligently designed proteins are not only effective against cancers but also viruses such as HIV/AIDS. I describe two such proteins, and if proven effective, more such proteins can be isolated, potentially giving rise to an antibiotic-like industry.

CANCER AND ANTICANCER DRUG DEVELOPMENT

Cancer is a complex disease and is often due to introduction of 10 to 100 mutations in the human genome, depending on the nature of the cancer. Consequently, older people accumulating such mutations over the years, are more prone to cancer unless such mutations are inherited from parents or due to environmental exposure. As a result, no single or even combination of drugs, works for all cancers and drugs are normally targeted to specific cancers based on some characteristics called validated targets that are often hyperproduced or hyperactive in cancer cells to allow their unchecked growth. Although some anticancer drugs could be of plant or even mushroom origin, many anticancer chemical drugs, including monoclonal antibodies (mAbs), are developed as inhibitors of such cancer-specific hyperexpressed or hyperactive targets. Such a process is called rational drug design where inhibitors are selected, often by high throughput screening or mAb selection, against a specific validated target in a specific cancer cell line. Successful inhibitors, called hits, are then further screened for efficacy at various concentrations in xenograft animal models, giving rise to lead compounds that can then be taken for pre-clinical or human phase I/II/III clinical trials. The entire process takes years, given the failure of most such compounds, and costs, in the estimate of the pharmaceutical industry, about 1.3 billion dollars to bring a successful drug to the market. Although such a valuation is believed by many economists to be highly inflated, it costs several hundred million dollars to bring a rationally designed anticancer drug to the market, starting from scratch. No effective vaccines exist for cancer.

ACCIDENTAL DISCOVERY OF A POTENTIAL ANTICANCER DRUG: THE STORY OF AZURIN AND P28

If one sets out to develop a new anticancer drug against a targeted cancer, one usually has to follow the costly and time consuming steps outlined above. A unique aspect of basic research is that one never knows where that research will lead to. Let me give an example. I was funded by NIH for 20 years, including a MERIT award for 10 years, to study how a bacterium such as *Pseudomonas aeruginosa* causes chronic infections in the lungs of cystic fibrosis (CF) patients through production of an exopolysaccharide called alginate. I had no interest or expertise in cancer, HIV/AIDS or malaria. *Pseudomonas aeruginosa* normally does not produce alginate except when it infects the lungs of CF patients. It is an opportunistic pathogen that rarely infects healthy people with normal immunity but can infect CF, burn or immuno-compromised patients. Since CF patients have normal immunity and resist infection by other pathogens, my research group reasoned that *P. aeruginosa*, under the highly osmolar environmental conditions of the CF lung, not only turns on the alginate biosynthetic genes but may turn on other genes encoding the production of toxin(s) that can be highly cytotoxic for foot soldiers of the immune system such as macrophages and neutrophils, thereby facilitating infections. To determine if clinical CF isolates of *P. aeruginosa* can produce and secrete toxins capable of killing macrophages, my research group grew such *P. aeruginosa* strains and looked for the presence in their growth medium of cytotoxic agents active against macrophages such as J774 cells. J774 cells are widely used as macrophages because they can be grown in cell culture rather rapidly and behave as macrophages. Indeed, we were thrilled to find out that *P. aeruginosa* secretes in its growth medium a couple of potent cytotoxic factors for J774 cells, which on fractionation and purification turned out to be a redox protein called azurin and its electron transfer partner known as

cytochrome c551. Azurin, in particular, had high cytotoxic activity against J774 cells. Buoyed by such observations that we have found a new macrophage-killing protein, my research team isolated primary macrophages from mouse peritoneum so as to use authentic animal macrophages and not a cell culture macrophage. To our utter dismay, azurin was found not to have any cytotoxicity towards these primary macrophages.

A long shadow of depression hung over our research group for the next couple of weeks. We repeated the experiments several times using various azurin preparations with different batches of J774 and primary macrophages but the results were always the same. With utter confusion and certain amount of panic, I explored the possible differences between J774 macrophages and primary mouse peritoneal macrophages until it dawned on me that J774 cells were tumor-derived and that's why they grow quickly in cell culture — these immortalized cells were not necessarily representative of normal macrophages. I then set up a collaboration to investigate if azurin might specifically attack cancer cells but not normal cells, which turned out to be the case. Indeed, we demonstrated that azurin and a 28 amino acid peptide derived from azurin termed p28 (amino acids 50 to 77 of the 128 amino acid long azurin) had entry specificity in cancer cells but not in normal cells.[1,2] Azurin and p28 both inhibited cancer cell growth but azurin additionally had high cytotoxicity towards viruses such as the AIDS virus HIV-1 and parasites such as the malarial parasite *Plasmodium falciparum* or the toxoplasmosis-causing parasite *Toxoplasma gondii*.[2,3] A unique feature of the anticancer activity of azurin, unlike essentially all rationally-designed anticancer drugs, is its ability to interfere in multiple diverse pathways by which cancer cells grow. Thus azurin was shown to inhibit receptor tyrosine kinase-mediated cell signaling, and because of its entry specificity in cancer cells, inhibited angiogenesis through inhibition of the interaction of vascular endothelial growth factor receptor with its ligand[4] (Table 1). Azurin has also been shown to promote apoptotic cell death in cancer cells through stabilization of the tumor suppressor protein p53 and its enhanced intracellular levels.[5] It should be emphasized that we have studied only these three (inhibition of cell signaling, inhibition of angiogenesis, stabilization of p53) modes of azurin's anticancer action. It is likely that there are many other mechanisms by which azurin can inhibit cancer growth that we have not studied so far. It is thus likely that, unlike the rationally-designed drugs that normally hit a limited number of targets, azurin will be less vulnerable to drug resistance because of its interference in multiple steps in cancer growth progression.

Another unique feature of azurin and p28 is that they not only interfere in cancer cell growth and promote their cell death, but they appear to prevent tumor emergence. Prevention of cancer emergence, in addition to its cancer killing properties, could be potentially exciting to eradicate certain types of cancer. For example, a potent carcinogen such as 7,12-dimethyl-benz-anthracene (DMBA) induces pre-cancerous lesion formation in mouse mammary gland organ cultures (MMOC), when normal mouse mammary cells are grown in presence of certain hormones. Induction of these pre-cancerous lesions by DMBA can potentially lead to tumor induction. When azurin or p28 peptide is included in such assays, either or both can inhibit DMBA-triggered pre-cancerous lesion formation by 70 to 75% in a dose dependent manner[6] (Table 1). Such cancer killing or cancer preventive activities of azurin or p28, along with azurin's ability to inhibit the growth of HIV/AIDS virus or malarial parasite, have been patented by the University of Illinois through issuance of many U.S. (and international) patents, a list of which is shown in Table 1.

POTENTIAL PRACTICAL APPLICATIONS OF AZURIN/P28

It is clear, as we speculated earlier[2] that azurin is a highly intelligently-designed product of bacteria's 3 billion years of evolutionary wisdom. This multi-domain protein is used as a bacterial weapon to keep outside invaders such as cancers, viruses and parasites in check when the bacteria establish a long term residence in the human body. An example would be *P. aeruginosa*'s chronic infections and biofilm formations in the CF lung.[2] Bacterial long term residences in human bodies entail a very slow growth of the biofilm bacteria resulting in minimal damage to the host. Azurin is designed

Table 1: U.S. patents issued to University of Illinois on azurin/p28

Patent Title	Patent No.	Date Issued
Compositions and Methods to Control Angiogenesis with Cupredoxins	7,556,810	7/7/2009
Cytotoxic Factors For Modulating Cell Death	7,491,394	2/17/2009
Methods for Treating HIV Infection with Cupredoxin and Cytochrome C	7,301,010	11/27/2007
Compositions and Methods for Treating HIV Infection with Cupredoxin and Cytochrome C	7,795,410	9/14/2010
Compositions and Methods for Treating HIV Infection with Cupredoxin and Cytochrome C	7,511,117	3/31/2009
Methods for Treating Malaria with Cupredoxin and Cytochrome	7,338,766	3/4/2008
Compositions and Methods for Treating Malaria with Cupredoxin and Cytochrome	7,740,857	6/22/2010
Methods for Treating Conditions Related to Ephrin Signaling with Cupredoxins	7,381,701	6/3/2008
Transport Agents for Crossing the Blood-Brain Barrier and into Brain Cancer Cells, and Methods of Use Thereof	7,807,183	10/5/2010
Cupredoxin Derived Transport Agents and Methods of Use Thereof	7,691,383	4/6/2010
Compositions and Methods to Prevent Cancer with Cupredoxins	7,618,939	11/17/2009
Cytotoxic Factors For Modulating Cell Death	7,084,105	8/1/2006

structurally to look like an immunoglobulin[7] to minimize an immune response when it is released by the bacteria to combat an invader such as a cancer or a virus in the human body. Indeed, we have reported that azurin is released quickly in its growth medium when *P. aeruginosa* cells are exposed to cancer cells[8], demonstrating a bacterial sensing mechanism to detect the presence of its enemy and release its weapon to attack the enemy, making sure that the weapon is insensitive to the host immune action.

Will azurin work as an anticancer agent in human? To address this question, a company I cofounded named CDG Therapeutics Inc. (CDGTI) approached the FDA seeking approval for pre-clinical trial of azurin. The FDA suggested to CDGTI that the company should use p28 which can be chemically synthesized as a drug rather than azurin which must be isolated from bacteria — possibly with cellular contaminants — requiring more stringent regulations. Under a RAID grant from the National Cancer Institute (NCI), p28 showed no immunogenicity or toxicity in animals and had good pharmacokinetic profiling.[9] The CDGTI therefore sponsored a phase I human clinical trial which was completed in mid 2011 with 15 advanced stage cancer patients with metastatic refractory solid tumors. When given in escalating doses, p28 demonstrated no immunogenicity and very little toxicity in these patients with an average life expectancy of less than 6 months. Infusion of p28 not only stabilized the tumors in many patients but several patients had partial and 2 patients had complete regression of the tumors that were refractory to conventional drugs. The life expectancy of some of the patients undergoing partial tumor regression has ranged from 30 to 60 weeks and 6 patients remain alive as of the date of the report (ASCO meeting, Chicago, June 6, 2011; see www.cdgti.com) with 1 patient living disease free for more than 80 weeks.

BACTERIAL PROTEIN/PEPTIDE DRUGS AS OUR NEXT GENERATION CANCER FIGHTING DRUGS?

The fact that p28 elicited partial regression in several and complete regression in 2 patients where no drug was working any longer not only shows its unique mode of action, but raises many interesting questions as well. Do the tumors in the 2 patients that underwent complete regression have genotypic characteristics that make them uniquely vulnerable to p28? Can such attributes be determined, assuming that such attributes are in the tumor genome and not in the patient genome, by

microarray, proteomics or genome scanning analysis, as compared to those that underwent partial regression or only showed stabilization, so that future patients can be recruited based on these attributes? Given that p28 is only a part of azurin, and other domains of azurin such as p26 are known to have anticancer activity through inhibition of receptor tyrosine kinase-mediated cell signaling[10], will azurin be a more potent anticancer drug than p28? Since azurin with 128 amino acids has no glycosylation or other modifications, unlike mammalian proteins, and solid phase peptide synthesis is advancing to allow chemical synthesis of peptides that are 100 to 150 amino acid long, perhaps chemically-synthesized azurin will be the drug of choice. Another important question is if azurin is the only protein weapon produced by bacteria, or are there other protein weapons produced by other bacteria with anticancer and anti-viral activity? Should we look for more such protein/peptide weapons from other bacteria, somewhat similar to antibiotics, since we now know how to look for them? Will that lead to a second antibiotic-like industry?

CANCER THERAPY: FROM DRUGS TO BACTERIAL THERAPY AND MEDICAL DEVICE

The encouraging beneficial effects without any toxicity symptoms, as seen with p28 in the human clinical trials, raised an interesting question: could live bacteria, attenuated in virulence and/or with cloned genes, be effective in cancer therapy? Interestingly, many bacteria have been known for a long time to specifically target solid tumors[8] and fight cancer, as reviewed in a recent book[11] and some viruses are being designed for this purpose.[11] Unfortunately, progress towards using live bacteria to fight cancer has been limited to date, since introduction of such bacteria in the body elicits strong immune response, resulting in toxicity and a lack of significant beneficial effect. It is to be emphasized that p28, derived from azurin, is after all a bacterial product, even though the producer organism, the opportunistic pathogen *P. aeruginosa*, has never been known as a cancer fighting bacterium. Can *P. aeruginosa* fight cancer, as it is also known to produce other anticancer proteins such as arginine deiminase (ADI) from which a truncated derivative, called Pa-CARD, has been obtained with anticancer activity.[2] Anecdotally, some forms of cancer, prostate cancer for example, have been known to be in check from metastatic migration and growth, if there are catheters inserted near the ureterovesicular junction and the catheters got infected with biofilms of *P. aeruginosa*. An Indian company, Amrita Therapeutics, has filed a patent application to use a medical device, a stent containing *P. aeruginosa* biofilms, to fight cancer *in situ* without allowing the bacteria to enter the blood stream to cause toxicity problems. This mode of using a medical device to fight cancer in addition to the use of regular anticancer drugs, taken orally or via intravenous injections, could provide an additional weapon in our arsenal to fight cancer. The same company has also demonstrated the elaboration of another protein, termed ATP-01, from a different bacterium with anticancer and anti-HIV/AIDS activity, similar to azurin. ATP-01 is, of course, a different protein and similar to p28, a chemically-synthesized 30 amino acid peptide, derived from ATP-01 and termed AT-01, has shown anticancer activity against a range of cancers, thus providing important evidence that azurin or p28 is not unique and other bacteria produce similar potential anticancer agents with promiscuity to attack viruses such as HIV-1. An analogy to antibiotics, penicillin, followed by streptomycin, tetracycline and many others, comes to mind and it remains to be seen if bacteria, and particularly their protein products with multi-disease-targeting activity, will lead to an antibiotic-like industry of the future.

ERADICATING CANCER IN OUR LIFE TIME

Although highly speculative, my goal has been to emphasize a completely new and different approach to cancer therapy and prevention, than is available now, partly because I am a total stranger to the field of cancer and can therefore be frustratingly ignorant and annoyingly naïve. With much trepidation, I can then ask the following two questions. Since p28 has both cancer killing and cancer preventive activities, will it prevent the emergence of cancer in vulnerable people with predisposition

to cancer because of mutations such as BRCA1 and BRCA2? How about older people or people with a recent history of cancer where relapse is always a threat? This can be experimentally tested, given p28's cancer killing ability and lack of toxicity as demonstrated in the phase I trials. Ideally, as new technologies develop, p28, AT-01 or their parent proteins, can by given orally once these protein/peptide drugs are protected from stomach acids and can be made to be absorbed through the intestine to reach the blood stream. Secondly, if *P. aeruginosa* or other bacteria with long term colonization of human tissues have vested interest in protecting their turf (human body), will they produce similar weapons for other deadly diseases or their agents such as diabetes or coronary heart attack? Is it conceivable that *P. aeruginosa* or other bacteria will produce protein weapons that will target nuclear receptors, for example, thyroid receptors or peroxisome proliferator-activated receptor gamma that are involved in such diseases as obesity, diabetes or atherosclerosis? What is important in such efforts is to know how to look for a single protein among 3 to 4 thousand such proteins produced by a bacterium that will have this ability, often expressed in minute amounts in absence of the perceived enemy. Our ability to detect and isolate two such bacterial protein weapons is hopefully an indication that more such protein/peptide weapons can be isolated in the near future, not only for the treatment of cancer but also for viral or parasitic infections such as HIV/AIDS and malaria.[2]

PATENT ISSUES

A major conclusion of this article is that certain bacterial protein weapons can potentially be used as promiscuous drugs not only to treat cancer but hopefully to prevent cancer emergence, contributing to its eradication. It is widely accepted that patenting such drugs is important for bringing them to the bedside and indeed the field of drug design and discovery is replete with court cases involving patent infringement.[12] It is no wonder then that the University of Illinois at Chicago (UIC) filed patent applications (Table 1) to cover and protect its inventions. It is interesting to note that azurin was isolated, purified and studied in great detail for its role in electron transfer, long before we recognized its anticancer potential. The U.S. patents were issued on azurin because of the novelty of our finding and its potential utility as an anticancer drug, two major criteria for patent eligibility. However, a recent court case, Association of Molecular Pathology v. US PTO, involving the patent eligibility of human DNA and genetic mutations, has thrown considerable uncertainty regarding patenting of isolated and purified human DNA and its sequence variations.[13] A judge in the U.S. Court for the Southern District of New York revoked 7 patents licensed to Myriad Genetics that covered two genes BRCA1 and BRCA2 and certain mutations in these genes that predispose women to breast and ovarian cancers.[13] The judge's argument was that such isolated, purified and sequenced DNA is basically the same that occurs in the human body with the same information content and biological activity and hence is unpatentable. An extension of this argument will render all patents issued to antibiotics, and presumably our potential protein/peptide drugs (Table 1), patent ineligible in which case none of them will likely reach the bedside and no more new antibiotics or protein drugs will be looked for. As we argued[13], Myriad Genetics deserves its patents on the genetic mutations because they have great utility for determining susceptibility to breast and ovarian cancers. In contrast, the wild type BRCA1/BRCA2 genes have no particular utility by themselves and these genes should not be patent eligible, leaving other clinicians to work with them and look for other mutations and genetic rearrangements.[13] Recently, however, on July 29, 2011, a 3-judge panel of the Court of Appeals for the Federal Circuit (CAFC) reversed the District Court ruling and held that all isolated DNA claims of the Myriad Genetics patents were valid and patentable inventions because such DNA, covalently linked to neighboring genes, does not occur as such in the genome. The CAFC, however, decided against patent eligibility of diagnostic method claims because such claims were based on analyses and comparisons of various DNA sequences which were thought to be an example of mental exercise and not an inventive step. Further resolution of this decision will depend upon the parties for either an *en banc* review by the CAFC or probably a decision by the U.S. Supreme Court. The negative

impact of the current CAFC decision will mostly be felt in the area of innovations occurring in the field of medical diagnostics and personalized medicine. However, medical devices as outlined in this review that employ stents/catheters with bacterial biofilms should be eligible for patenting because of involvement of machines/transformative processes in potential cancer therapy. Thus much of cancer diagnostic detection, therapy and prevention in the future will depend on patent eligibility considerations by the CAFC, and ultimately by the U.S. Supreme Court, guiding the progress of future scientific research and development in medicine and health in the United States.

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Original Article

Industrial biotechnology — Markets and industry structure

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ABSTRACT

An increasing number of chemicals and materials, like base chemicals and polymers, as well as high value products, such as consumer chemicals and specialty chemicals, are produced using biotechnology in one or more of the process steps. In 2010, the sale volume of biotechnology products was around 92 billion Euro worldwide. Sales are estimated to increase to around 228 billion Euro in 2015 and to around 515 billion Euro in 2020. On a sector level, the largest market potential lies in the production of biopolymers and active pharmaceutical ingredients. As a rule, commercial development is mainly driven by multinational enterprises, whereas small and medium enterprises contribute primarily to the technological development. Especially the latter group faces several challenges during their development. These mainly concern business models and growth strategies as well as financing strategies and resources. Investors have not yet fully identified the area of industrial biotechnology as an attractive investment field but they could become a major capital source as they start to understand more the potential of industrial biotechnology.

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Keywords: Medicare; industrial biotechnology; biochemicals; biobased products; renewable feedstocks; bioeconomy

INTRODUCTION

Consumers see the need for sustainable development and are increasingly conscious about the impacts of their consumption and choosing products that have low negative impact on the environment (e.g. as a way to contribute to a low carbon economy). Industrial biotechnology is the application of biotechnology for the environmentally friendly production and processing of chemicals, pharmaceuticals, materials and bioenergy.[1-3] It uses enzymes and microorganisms to make products in sectors such as chemistry, food and feed, paper and pulp, textiles and energy.[4-6] Industrial biotechnology is widely regarded as the solution to find alternatives for the

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diminishing fossil resources such as oil and natural gas through the increasingly eco-efficient use of renewable resources as industrial raw materials. Raw materials, instead of being derived from fossil fuels, are typically agricultural materials such as starch, and their residues. This enables to maximize the use of agricultural crops, with all obvious benefits. Instead of high temperature, energy intensive processes using chemical catalysts, industrial biotechnology achieves the same or even better results using biological catalysts operating at low temperatures. Industrial biotechnology also provides tools for the development of new products that cannot be made using traditional synthetic methods and processes.

Industrial biotechnology is a key technology for future economic development and offers dynamic growth opportunities both for the chemical industry and related industries.[7-13] Governments recognise the importance of industrial biotechnology and many are increasing their support to take advantage of the potential and remove barriers to growth. Financial incentives given by numerous governmental programmes encourage investments in industrial biotechnology. The notable number of successful implementations of biotechnological processes shows that the chemical industry in Europe and the United States (US) is increasingly using the potential of industrial biotechnology processes to sustain competitiveness especially with regard to Asian challenges.[14]

This article takes a look at industrial biotechnology market segments including market size and growth rates, the industry structure within the companies acting in this area, a special focus on enzyme technology, established as well as emerging business models, growth strategies for industrial biotechnology companies and finally some financing aspects.

MARKET DESCRIPTION

The following market figures derived from a data base regarding industrial biotechnology which has been built up over the last 8 years from 2003 to 2011. Since 2008, this data base uses the structure

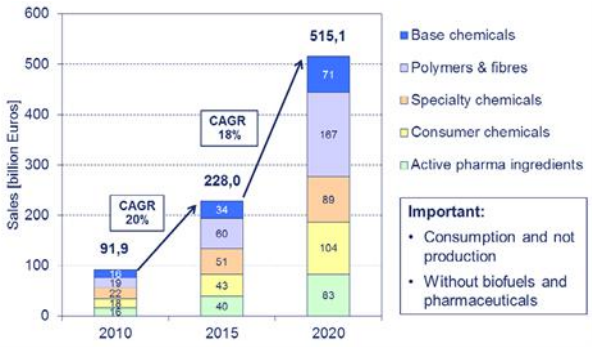


Figure 1: Biotech sales in 2010, 2015 and 2020 (2015 and 2020 data are projections based on 2010 data)

(segments, sub-segments and regions) of the Conseil Européen de l'Industrie Chimique (CEFIC) for global chemical sales: base chemicals (consisting of basic inorganics and petrochemicals), polymers & fibres, specialty chemicals, consumer chemicals and pharmaceuticals.[15] In the pharmaceuticals segment only active pharmaceutical ingredients (APIs) are included and pharmaceutical products are excluded. Biomass derived energy based on biotechnology, including biofuels, is expected to account for an increasing share of energy consumption but is not included in the following numbers. Within the data base, the sales of products made by biotechnological processes were estimated on a sub-segment level (in some cases also on a more detailed product level) as rolling forecast. Subsequently, the sub-segment or product level data for biotechnology sales were aggregated to get the numbers on a segment level. This was done separately for the regions Europe (EU-27 countries and Switzerland), North America (Canada, Mexico and the US), Asia (with China, India, Australia and Japan) and rest of the world (all other countries not covered by the other regions).

Sales of products made by biotechnological processes in 2010 were 91.9 billion Euros representing 6.2% of total chemical sales (Figure 1). Although basic chemicals made up around 60% of global chemical sales in 2010, only 4% of these (16.1 billion Euros) were produced using biotechnological processes. The segment polymers & fibres had 19.2 billion Euros of sales. The segment with the highest absolute biotechnology sales in 2010

was specialty chemicals with 21.9 billion Euros representing 23.8% of total biotechnology sales. Consumer chemicals are, with 18.2 billion Euros, the largest segment. Despite in absolute term with 16.5 billion Euros, APIs is the segment with the highest percentage of biotechnology sales: 28% of the total sales in this segment are based on biotechnological processes.

Looking into the regional level in more detail shows that the strongest region within most of the segments and sub-segments is Asia (Figure 2). In 2010, bio-based polymers & fibres had nearly 6 billion Euros sales in Europe, around 4.5 billion Euros sales in North America and around 7.5 billion Euros sales in Asia. APIs produced with bioprocesses had more than 4 billion Euros sales in Europe, around 4 billion Euros sales in North America and nearly 7 billion Euros sales in Asia. Important subsegments are also organic chemicals, agrochemicals, cosmetics, detergents.

In 2015, sales of products made by biotechnological processes will be around 228 billion Euros representing 12.1% of total chemical sales resulting in a compound annual growth rate (CAGR) from 2010 to 2015 of 20%. In all segments and sub-segments it is expected that by 2015, the percentage of products produced using biotechnological processes will increase. It is estimated that base chemicals will account for 34 billion Euros, polymers & fibres will strongly increase to 60 billion Euros, specialty chemicals will have 51.4 billion Euros, consumer chemicals 42.9 billion Euros and APIs 39.7 billion Euros (Figure 3). In 2015, it is expected that APIs will again be the chemical segment with the highest biotechnology sales percentage with 40.1%. In 2020, around 515 billion Euros representing 21.6% of total chemical sales will be produced by biotechnological processes.

The CAGR from 2015 to 2020 reaches, with 18%, almost the same level as the CAGR from 2010 to 2015. Biotechnology based polymers & fibres will achieve the highest sales figures in total terms in 2020 with 167.4 billion Euros (Figure 4). Consumer chemicals will be the next most important biotechnology segment making up 103.7 billion Euros. By 2020, it is expected that APIs produced using biotechnological process again show the highest biotechnology sales percentage with 53.2% of chemical sales in that segment.

The importance of biotechnology routes within the production of APIs is especially due to the production of complex chiral molecules, such as enantiomerical APIs with chiral centres which can be produced by biotechnology routes.[16] The increasing requirement for chirality results from parallel regulation policies at FDA in the US and EMA in Europe to accommodate the fact that usually only one out of two chemical enantiomers is active and

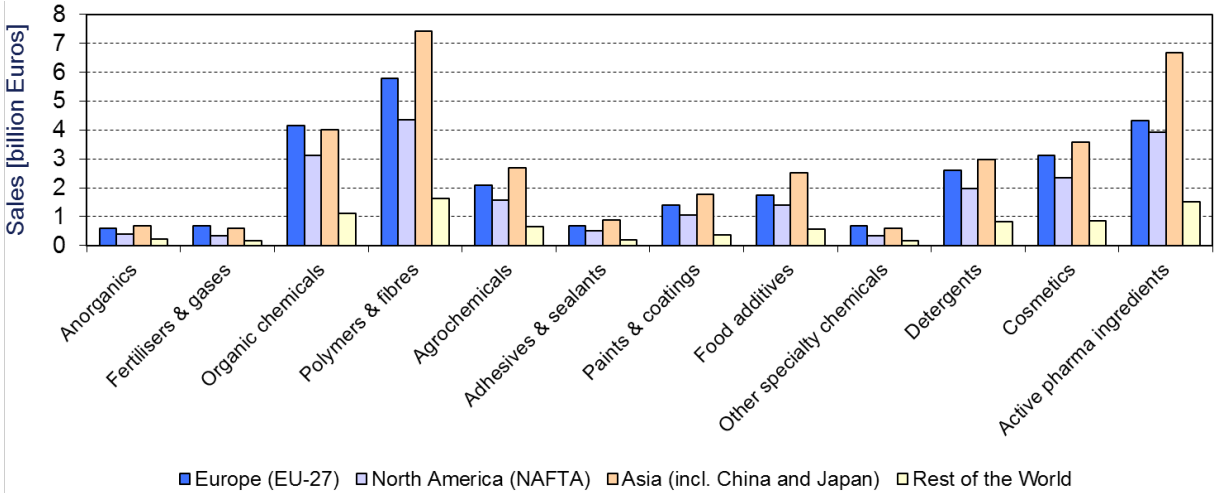


Figure 2: Biotech sales per region in 2010

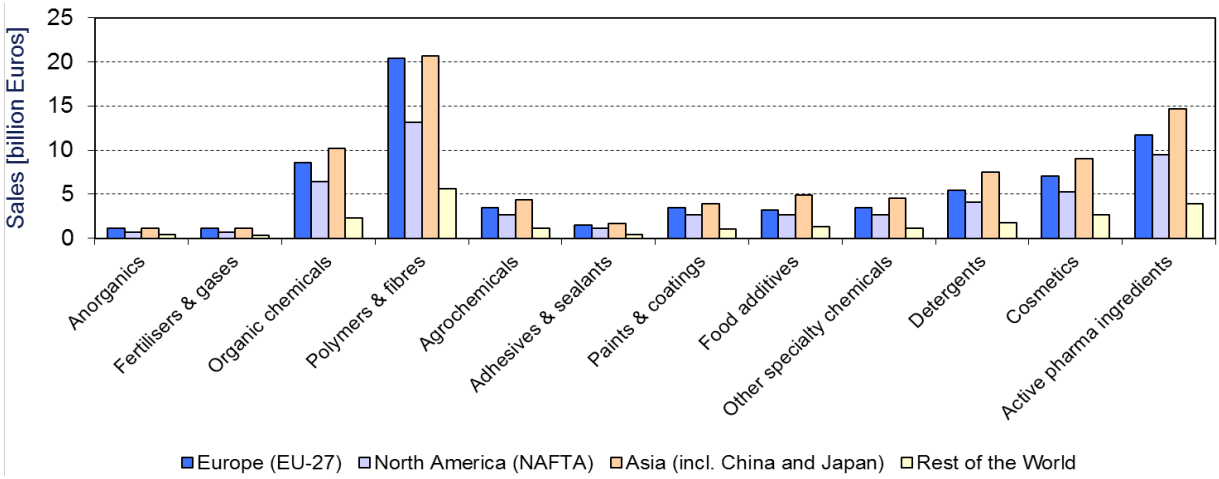


Figure 3: Biotech sales per region in 2015 (2015 data are projections based on 2010 data)

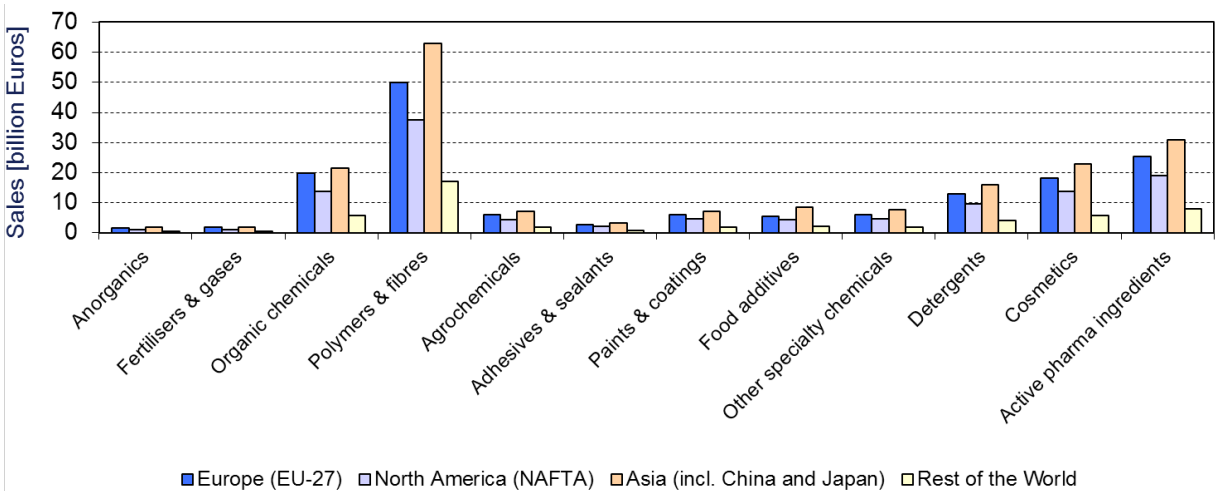


Figure 4: Biotech sales per region in 2020 (2020 data are projections based on 2010 data)

beneficial. The "wrong" enantiomer is regarded either as inactive or even a potential harmful entity which has to be removed. More than 50% of the top 100 drugs are based on enantiomerically pure molecules and such drugs already today exhibit sales exceeding 100 billion US-Dollars. In addition, 60% of the new APIs in drug development phases 2 and 3 are chiral and 90% of the new chiral substances are developed enantiomerically pure.

INDUSTRY STRUCTURE

In the industrial biotechnology area different company types, like multinational enterprises (MNEs), small and medium enterprises (SMEs) as well as start-ups, which are dedicated to industrial biotechnology or diversified over a broader range of areas, can be found. The importance of the different company types for the further development of industrial biotechnology is shown in Figure 5. To obtain a more differentiated picture, the two dimensions, technological and commercial development, are assessed separately.

Dedicated start-ups, like Fluxome Sciences, are focused on industrial biotechnology and mainly driven by research and development (R&D). In most cases they develop and commercialise special technologies and their applications. Some of these companies also targeted the red biotechnology area, but with increasing maturity of the companies both businesses were separated (e.g. Direvo Industrial Biotechnology). Dedicated SMEs, like Codexis, focusing on industrial biotechnology

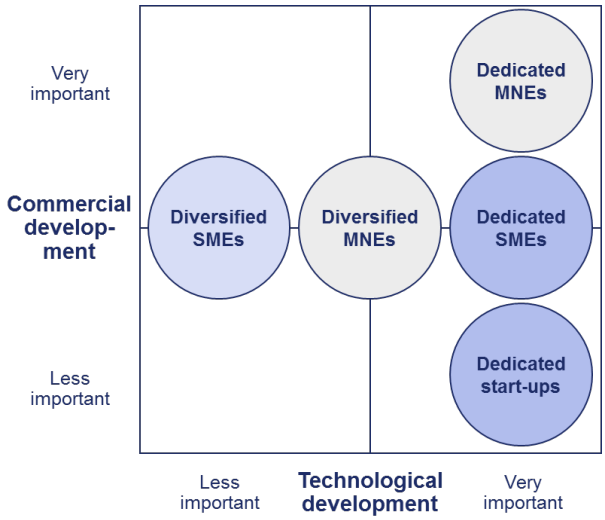


Figure 5: Importance of the different company types

were founded mainly during the last 20 years and are now, after performing intensive R&D during the first years, focused on building up own production facilities and selling their products (e.g. Brain). These companies are the core for the further technological and commercial development of an independent industrial biotech sector. Diversified SMEs, such as Siegfried, are mainly located in established industrial sectors, like the chemical or food industry. Serving already developed markets with highly specialised products, these companies are introducing, step by step, biotechnology processes and products into their markets in order to realise growth opportunities, to reduce costs or to fulfil regulatory aspects. It is expected that they will especially drive the commercial development of industrial biotechnology. Dedicated start-ups and SMEs are expected to contribute significantly to the further technological development of industrial biotechnology.

Dedicated MNEs are dominated by companies that have been active in the area of natural products for decades (e.g. Purac, Lesaffre). Normally, they use over many years optimised biotechnological processes for traditional markets (e.g. starch, yeasts). Industrial biotechnology is one cornerstone in their technology portfolio and increasingly they are moving towards new biotechnology based products and processes. There is also a sub-type of more R&D oriented companies, like Novozymes. It is expected that they will significantly drive the technological and commercial development of industrial biotechnology. Diversified MNEs are mainly established companies from the chemical industry (e.g. DSM), agro industry (e.g. Cargill) or food industry (e.g. Danisco). Their strength is the broad and integrated technology portfolio which complements industrial biotechnology processes (e.g. purification technologies). Dedicated and diversified MNEs are by far the most important groups in terms of biotechnology sales and R&D budgets. They have the technical resources (e.g. engineering) as well as financial resources to commercialise biotech technologies and products worldwide.

Social acceptance of industrial biotechnology is normally high so that industrial biotechnology companies enjoy a fairly liberal attitude for growth and innovation. Nevertheless, in some regions there is still a rather low acceptance of genetically modified organisms.[17] They have attracted negative attention from the media especially regarding their use in food products, but also in other agricultural applications, such as the usage as raw material for industrial biotechnology processes. For industrial biotechnology companies working in the field of genetic engineering there is considerably more bureaucracy and legislation which often inhibits and restricts R&D and jeopardises the growth of these companies. The EU pursues a far stronger set of regulations in this respect than the US or Asia. Another aspect is that growth in industrial biotechnology depends very much on the development of green biotechnology. Cost competitiveness of industrial biotechnology processes are often only achievable with the help of biomass produced by genetically modified plants, so that green biotechnology can make a substantial contribution to the efficient production of biomass raw materials. Green and industrial biotechnology are often combined to an integrated value chain. Therefore, the acceptance problem of green biotechnology, especially in Europe, has a direct impact on industrial biotechnology.

ENZYME TECHNOLOGY

Enzymes are an important product group with diverse applications. Worldwide sales of enzymes are expected to grow, according to Freedonia, on average by 6.3% annually to 7 billion US-Dollars in 2013. The largest part of the enzyme production is attributable to technical enzymes, which are used primarily in the field of detergents (e.g. laundry), and the food industry (e.g. starch processing). Enzymes in detergents improve the washing performance, reduce the waste water load and work at lower temperatures, so that the energy consumption is reduced. In the paper and textile industries, various biotechnological processes in cleaning and bleaching procedures have been established, since the use of tailored enzymes is environmentally friendly and less harmful for the textiles. These markets are dominated by major enzyme producers such as BASF, DSM, Novozymes and DuPont (including Danisco/Genencor). Highly attractive is the market for special biocatalysts with a worldwide market volume of 1.0 billion US-Dollars, which is predicted a significant growth potential especially in the pharmaceutical sector. This is because in the production of intermediate and end products many types of reactions (oxidation, reduction, carbon-carbon bond formation) can be efficiently catalysed by biocatalysts.

Especially enzyme catalysis will be a key technology within industrial biotechnology. The recent technological breakthrough has led to an enormous boost in the number of available enzymatic systems. The genetically engineered modification of microorganisms results in the implementation of new enzymes and reactions, and to new sustainable processes. The increasing knowledge of enzyme reactions in non-aqueous solution will lead to a broadened spectrum of processes and a greater number of substrates. Due to new developments in reactor and process design, the process efficiency will be improved. Thus, both novel enzymatic systems and process optimisation has led to successful applications of biotechnological processes within the chemical industry. Although enzymes have demonstrated their potential in numerous applications, so far only relatively few industrial biotechnological processes have been able to be established. This is due to several factors. First, the purification of enzymes still represents a significant cost factor and secondly, the purified enzymes often exhibit low stabilities, limiting their use in industrial processes. Though it was possible to improve the cost effectiveness of some enzymes by employing different immobilisation techniques, there is still need for improvement, since some enzymes do not tolerate the necessary procedures.

By using new approaches, such as surface display systems, some of these disadvantages can be circumvented. Surface display means a protein expression system in which the enzymes are no longer located inside a cell (e.g. bacteria, yeast), but are displayed on the cell surface e.g. of bacteria such as *Escherichia coli (E. coli*). These surface display systems have several advantages compared to conventional intracellular enzyme production. Displayed enzymes exhibit a higher stability in comparison to the free enzymes and furthermore, the free accessibility of the enzyme for its reaction partner makes purification unnecessary. A further common problem of protein expression in *E. coli*, the formation of "inclusion bodies" (= aggregation of misfolded protein) can also be reduced by using surface display systems.

An example is the autodisplay technology which enables the cell surface display of small peptides as well as large proteins on the surface of *E. coli*. This allows numerous applications in the area of biocatalysis, bioanalytics, screening and separation. In the area of biocatalysis this enables the cost-effective production of biocatalysts and the development of ones. Product purification is still a cost-intensive part in the production of valuable active substances with up to 80% of the total cost. In comparison to the classic intracellular expression, the autodisplay system has significant cost advantages. In the case that an immobilisation of the biocatalyst is not necessary, 65% of the costs can be saved using the autodisplay biocatalysts (Figure 6). Is the immobilisation of a given biocatalyst necessary, 80% of the costs could be saved

using autodisplay biocatalysts. Because of these advantages, the surface display systems are particularly appropriate for the expression of "challenging" (= difficult to express) enzymes which were not or only to a less extent accessible using conventional intracellular expression systems.

Human hyaluronidases are such a class of difficult-to-express proteins. They play an important role in the assembly and degradation of connective tissues and are therefore interesting targets for the cosmetics industry. Up to now human hyaluronidases cannot be produced in sufficient quantities to use them in screening assays for the identification of new active ingredients. Employing autodisplay, human hyaluronidases could be made accessible in sufficient quantities for screening purposes. Moreover, autodisplay does not only allow the display of „simple" enzymes, but also complex enzymes, which are composed of several subunits (e.g. nitrilases), or specific cofactors (e.g. heme groups) can be displayed on the cell surface. The performance of the autodisplay is reflected in the number of displayed molecules, which is in the range of more than 100,000 molecules per cell, without affecting cell stability and viability. Especially when it comes to binding and affinity studies for screening of new lead compounds, cell-surface display systems have significant advantages, because they enable the use of optical assay system which often accelerates the assay time.

A further application field of cell surface display systems is the purification of target molecules. Due to the very complex composition of the reaction media and the presence of impurities, a high selectivity of the used separation material is of utmost importance. A frequently used method is the affinity chromatography. This technique is based on a specific interaction between the target molecule and its binding partner (ligand) enabling an accumulation of the target molecule. The production of such specific ligands is still cost-intensive. Because the outer membrane of the bacterial cells, displaying specific binding proteins for a target molecule, can be isolated and subsequently used for coating separation materials, autodisplay could offer a way to minimise future costs for the production of matrices for affinity chromatography.

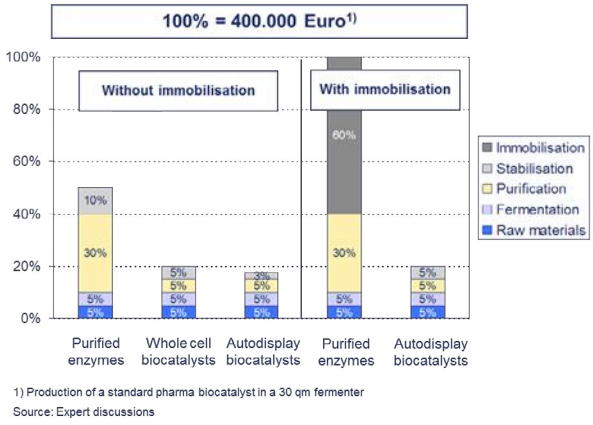


Figure 6: Cost advantage of new biocatalytic systems

BUSINESS MODELS

Established business models in the area of industrial biotechnology are producers and service providers. Producers develop own technologies or buy/license them and are focused on production including the whole supply chain from raw materials to distribution. This business model is realised mainly by diversified SMEs as well as dedicated and diversified MNEs. Most of the service oriented dedicated SMEs are currently in the phase of going into this business model as it offers more growth options. High capital requirements to build-up own production facilities are a disadvantage. The example of biofuel producers (especially biodiesel producers in Europe) showed that there is a significant risk with this model if there is overcapacity in the market after a period of strong investment activities.

For most products, producing chemicals through biochemical routes is considerably more expensive compared to traditional production routes, as the synthesis of existing products by chemical procedures is often so inexpensive, that the development of a biotechnological production process is not cost efficient. Furthermore, existing production facilities for chemical syntheses cannot be changed to biotechnological production without massive new investments. For other products, the technology does not even exist yet (or has not been

commercialised). In some industrial segments, such as the food industry, sometimes higher prices can be achieved for biotechnological products compared to their chemically produced counterparts. But in most cases, there are clear restrictions of biotechnological production processes on the economic side, e.g. operational costs, R&D costs and investments.

Cost differentials between fossil oil derived and bio-based products directly influence the willingness of shifting to industrial biotechnology production processes. However, the last years have shown almost a 1:1 correlation of crude oil and biomass prices, so there have been no cost advantages of bio-based routes. Many industrial biotechnology projects lost competitiveness due to this correlation which had not been anticipated. Also, the hope that biomass shows less cyclicality compared to crude oil prices has not been realised. Furthermore, especially in debates around biofuels, the significantly increased land use has been a controversial issue. Using farmland for producing energy crops (or any bio-based raw materials) competes with other land uses - notably food production, where rising food and feed demand (driven by population growth and increasing prosperity) is a critical driver and significant limitation on the upturn of industrial biotechnology.

Most dedicated industrial biotechnology start-ups and some dedicated SMEs are service providers, offering their particular know-how predominantly as services to support other companies. These companies normally realise primarily organic growth and are profitable, but have sub-critical structures with regard to size and financial strength and are not able to realise growth opportunities due to a lack of financial resources. The disadvantage of this model lies in the fact that intellectual property (IP) normally belongs to the customer and the growth or value creation potential through development and commercialisation of own IP is very limited. The risk is also limited as there are only low capital requirements to realise this business model. In order to realise further growth, the development of own IP is necessary.

There are also some emerging business models, like process developer, focusing on the development of own IP and licensing business. These IP-oriented business models focus on the development of an own portfolio of technologies and products, which are then sold or out-licensed. A suitable network and co-operation strategy has to ensure the successful commercialisation of the IP. The difference between service and solution providers is that solution providers are also taking risks within projects by flexible and result oriented revenue models.

GROWTH STRATEGIES

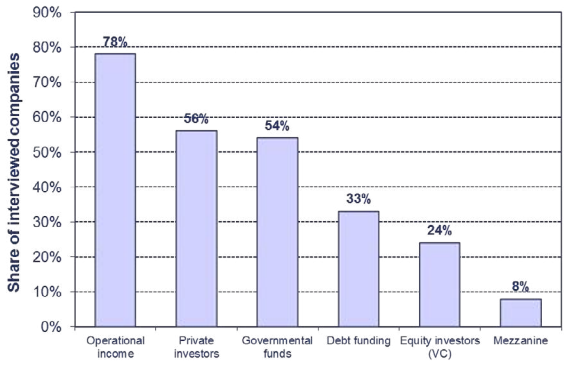
Start-ups, SMEs and MNEs normally have four different growth strategies along the two dimensions established/new markets and established/new technologies. The growth strategies all have their specific advantages and disadvantages, but currently, most industrial biotechnology companies only use a very limited set of these strategies. The preferred strategy is organic growth based on internal R&D for established markets and technologies. Especially start-ups and SMEs use this strategy to move from a service-oriented to an IP-oriented business model. This originates from the fact that start-ups and SMEs maintain very good relationships with universities and research institutions and can therefore rapidly access the latest research results. However, since start-ups and SMEs have to carry the entire costs of R&D activities, the number and size of projects is limited. An option to access new technologies involves R&D co-operations with universities and R&D institutions but also specialised biotechnology start-ups and SMEs. This growth strategy has often been used in the past and nearly all industrial biotechnology companies have such co-operations (e.g. R&D co-operations of BASF, DSM, Henkel and others with Brain as example from the chemical industry and co-operations of Shell with Codexis or Total with Gevo in the area of biofuels). They are of special importance for industrial biotechnology as this ensures the technology transfer of research results from universities and research institutions

to market oriented SMEs and MNEs. In contrast, R&D co-operations between start-ups to realise synergies on the technological as well as the market side are rare, because of strong competition between start-up companies for co-operation projects with SMEs and MNEs.

Joint ventures as the formation of a new company together with another company enable the use of complementary assets, technologies, people or other capabilities. Joint ventures are rather seldom in the area of industrial biotechnology and mainly used to obtain access to emerging markets like China and India. With increasing maturity of the industrial biotechnology sector such partnerships will grow in importance and synergistic risk/reward sharing deal structures will begin to appear. Start-ups and SMEs avoid a time and cost consuming development of new markets, while the market oriented partner is able to incorporate innovative and state-of-the-art technologies into their own product portfolio. Another growth strategy with increasing importance is mergers and acquisitions (M&A) as the acquisition of or merger with another company to create a single new entity. M&A transactions can be found between MNEs and SMEs/start-ups (e.g. the sale of Biopract by DSM) or between SMEs (e.g. acquisition of Jülich Fine Chemicals through Codexis). The first step is often R&D co-operations which give the MNE the opportunity to assess the technology/products of the SME/start-up and incorporate it into the own technology/product portfolio.

FINANCING ASPECTS

Due to the specific characteristics of industrial biotechnology, this sector should be attractive for investors.[18,19] In comparison to red, industrial biotechnology investments often afford lower initial investments and lower risk due to a diversification among applications and industries. Two of the characteristics of industrial biotechnology, to which investors are giving increased attention, are the typically much shorter time span from idea to market (3 to 5 years, compared to 10 to 12 years for a biomedical product) and less regulatory requirements. But, investors still prefer red biotechnology, due to the lack of attention which has been given to industrial biotechnology in the past and that it is still more driven by large chemical corporations. The focus of red biotechnology is on new drugs with a relatively easy to estimate market potential and share, while industrial biotechnology mainly develops new process routes to already known drugs or chemicals. In comparison to red, industrial biotechnology processes or products usually serve a broader range of applications. These characteristics require more knowledge of the industry and often contribute to the lack of investors' attention to industrial biotechnology. Many investors are still not aware of the chances, presumably because of difficulties in reasonably estimating the scope of market potential and market share that could be achieved with a single process or product. Venture capital (VC) is often unaware of the differences between industrial and red biotechnology, which leads to an inappropriate evaluation of the start-up value. Furthermore, they claim that the service oriented business model, to which many industrial biotechnology companies adhere, fails to offer the desired returns. The consequence is that less than a quarter of the start-ups have received funds (Figure 7).



Source: Market Study on Financing Strategies in White Biotechnology of FESTEL CAPITAL from April 2005

Figure 7: Financial sources for industrial biotech start-ups

During the critical growth phase of industrial biotechnology start-ups an equity gap remains in a lot of cases, as the operational income is the most important financing source. Therefore, financial

restrictions are an important limiting factor for further growth within the industrial biotechnology sector. Financial resources offered by private investors are rather small (often not exceeding 0.5 million Euro) and insufficient for further growth. With only small funds provided by the government or private investors, unexpected events can leave the company seriously vulnerable. Funding, especially during the first growth phase, is an important issue in the future. EuropaBio reported that surveys conducted across Europe show that up to 78% of biotechnology SMEs have struggled and failed to find the investment they require to continue important R&D programmes.[20,21] In some cases, government funds can help to overcome funding problems, but unfortunately, these are predominantly allocated to basic research projects rather than product development. Attracting VC will remain a challenge in the short and medium term particularly for industrial biotechnology companies. But, in the current economic situation, VC is faced with a capital sourcing problem for their funds resulting in a capital shortfall and a prioritisation of their investments. VC is currently investing in later stage projects or demanding more equity for their money, which has resulted in the significant fall in VC financing of SMEs. Other financial resources like debt funding and an initial public offering (IPO) are not relevant for industrial biotechnology start-ups, because of the low equity basis of start-ups and the fact that most lack the critical size for an IPO.

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Original Article

Options to change Medicare payment for outpatient prescription drugs and biotechnology products

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ABSTRACT

The debates over the Obama Administration's health care reform law, and, more recently, the federal budget deficit and national debt have focused attention on the growth in costs of the Medicare program. Three approaches to reducing Medicare expenditures command the most attention. Under the first, changes to the Medicare delivery system — such as accountable care organizations (ACOs) and medical homes — are believed to have the potential to reduce the growth in costs in the program over time. Under the second, tinkering with the reimbursement formulae in the Medicare program — pejoratively, government "price fixing" — will reduce the price that Medicare pays for an item or service, thereby reducing the growth in costs. A third approach — converting Medicare to a premium support or defined contribution model — has been passed by the House of Representatives, but has failed in the United States Senate.

This article addresses the effect of these various approaches on Medicare payment for outpatient prescription drugs and biotechnology products. It begins by analyzing the Administration's ACO regulation and the effect that this regulation may have on reimbursement for outpatient prescription drugs and biotechnology products. It then addresses legislative proposals to alter the Medicare reimbursement formulae for these products. It concludes by speculating on how the Medicare reform legislation passed by the House of Representatives might affect reimbursement for outpatient prescription drugs and biotechnology products.

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Keywords: Medicare; ACO; prescription drugs; healthcare reform

INTRODUCTION

The underlying concept behind the Centers for Medicare & Medicaid Services (CMS) Accountable Care Organizations (ACO) program — the Medicare Shared Savings Program or "MSSP" — is to encourage teams of physicians, hospitals, and others involved in patient care to achieve what CMS describes as the three-part aim: (1) providing better quality of care for Medicare beneficiaries; (2) that results in better health for patient populations; and (3) lowers growth in expenditures. Congress described the MSSP in six brief pages of the federal health reform law, tasking the program with "promot[ing] account-

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ability for a patient population and coordinat[ing] items and services under parts A and B, and encourag[ing] investment in infrastructure and redesigned care processes for high quality and efficient service delivery."[1] The statute provides that acute care hospitals, eligible professionals (which include physicians, nurse practitioners, and physicians' assistants), and other providers of services and suppliers, as the Secretary deems appropriate, may participate in ACOs.

In the months prior to issuance of the proposed regulations, interest grew and discussions in health policy circles centered around whether ACOs might be the answer to achieving coordinated care to improve beneficiaries' health while at the same time reducing inefficiencies and unnecessary costs in the health care system, beginning with Medicare. While the initial excitement and rallying around the ACO concept prior to the proposed rule is not completely gone, stakeholders asked for numerous changes to the ACO proposed rule, described in more detail below.

CMS released the much anticipated ACO proposed rule on March 31, 2011. 76 Fed. Reg. 19528 et. seq. (Apr. 7, 2011). As soon as the regulations were issued (including regulations and guidance issued by the HHS Office of Inspector General, Internal Revenue Service, Department of Justice, and Federal Trade Commission, not addressed in this article), providers, payors and other stakeholders anxiously delved into the text to understand the proposed framework within which ACOs would be formed, measured for success, and rewarded or held accountable for the care provided and costs expended. What has emerged over the past three and a half months is concern that the effort and risk required of potential ACO professionals and hospitals to participate in the program outweigh the potential reward that the participants could expect to gain, given the way the proposed rule is written.

Moreover, there is growing concern that while the ACO goals are admirable, there may be unintended financial incentives for providers in the program to inappropriately shift patients from Part B drugs to Part D drugs where clinically sound reasons for doing so do not exist.[2] This is of particular concern to pharmaceutical and biologic companies, as well as patient advocates. We discuss this issue further below after providing an overview of the ACO proposed rule.

In the proposed rule, CMS proposed to require ACOs to create a separate legal structure in order to receive and distribute shared savings to the professionals and hospitals participating in the ACO. In addition, in accordance with the quality goals of the MSSP, CMS proposed that ACOs that meet the minimum savings requirement will only share in savings if they also meet the required quality standards for that year. CMS proposed to measure ACO performance based on 65 quality standards that span five quality domains, including patient/caregiver experience, care coordination, patient safety, preventive health, and at-risk population/frail elderly. The 65 listed quality measures relied heavily on existing quality measures used in the Physician Quality Reporting System and the Hospital Inpatient Quality Reporting Program.

Pursuant to the governing statute and details proposed in the ACO regulations, CMS is required to develop a benchmark for each ACO based on estimated expenditures for the ACO's beneficiaries. (An ACO is required by statute to have at least 5,000 beneficiaries assigned to it). CMS will use the benchmark to measure the ACO's actual expenditures and to determine whether the ACO is eligible for shared savings for that year. Once an ACO is determined to be eligible, the amount of shared savings—or accountability for losses—depends on further constraints specified in the regulations. In the proposed rule, CMS described two "tracks" that an ACO would be able to choose from in modeling its shared savings and risk. Un-

1 Social Security Act § 1899(a)(1), 42 U.S.C. § 1395(a)(1), as added by the Affordable Care Act (ACA), § 3022.

2 In the section that follows, we more fully describe the pathway to coverage of drugs under Part B vs. Part D.

der the proposed Track One, an ACO would share in savings in years one and two of the ACO contract, and then automatically be at risk for losses in year three. ACOs that choose this track would have the advantage of being under a bonus-only model for the first two years, but would be eligible to share in a smaller percentage of the savings, 50%, than ACOs under Track Two. The proposed Track Two was designed for more sophisticated entities. ACOs on this track would be eligible for up to 60% of the shared savings in each year, but would also be at risk for losses during all three years of the ACO's contract.

It is important to note that both the statute and CMS regulations make clear that reimbursement for MSSP participants remains under the Medicare fee-for-service (FFS) model.[3] Further, ACOs are held accountable for items and services under Medicare Parts A and B, but not under Part D.

CMS received approximately 1,150 comments to its ACO proposed rule during the public comment period that closed on June 6, 2011.[4] One of the issues that stakeholders raised, as noted above, is that the MSSP may create unintended incentives for providers to switch their patients from Part B drugs to Part D drugs. Since Part D drugs are not taken into account in the calculation of expenditures for purposes of the MSSP, an ACO professional may find that shifting their patients from drugs and therapies under Part B to those available under Part D allows them to realize more "cost-savings," and thus, additional financial reward. Further, concerns were raised that the MSSP does not have adequate safeguards against such inappropriate and potentially dangerous practices. Some commenters suggested that CMS should monitor ACOs with respect to Part B versus Part D utilization and should create consequences for ACOs that are found to be inappropriately shifting patients from Part B to Part D therapies.

In addition, CMS received comments on its proposal to accept applications on a "rolling" basis and to potentially use multiple start dates for the first year of the program, allowing some ACOs to start the program on January 1, 2012 and others to start on July 1, 2012.[5]

On November 2, 2011, the final ACO rule was published in the Federal Register.[6] In the final rule, CMS responded to the criticisms of the proposed rule that the structure was too unwieldy to meaningfully transform the health care delivery system. In response to those criticisms, CMS made several changes to the proposed rule including the following:

- Two-sided risk has been remov-ed from the Track One model (i.e. Track One will be bonus-only; Track Two will be two-sided with bonus and risk. The higher sharing rate for Track Two remains);
- Assignment of beneficiaries to an ACO will be made prospectively;
- Fewer quality measures (33) across fewer domains (4) required for reporting and performance;
- Savings will be shared on the first dollar of savings in both Track One and Track Two, once the minimum savings rate has been achieved;
- Additional entities may qualify to participate as ACOs, including community health centers;
- "Meaningful use" of health information technology will not be required, although it will be a quality measure used for scoring purposes; and
- First round of applications will be due in early 2012 with the first ACO agreements to start April 1, 2012, and July 1, 2012.

3 See Social Security Act § 1899(d)(1)(A), 42 U.S.C. § 1395(d)(1)(A), as added by ACA § 3022; 76 Fed. Reg. at 19602.

4 See CMS-1345-P, Docket ID: CMS-2010-0259, at regulations.gov (accessed July 27, 2011).

5 See 76 Fed. Reg. at 19553.

6 See 76 Fed. Reg. at 67802 (Nov. 2, 2011).

The Agency made these changes to the MSSP in the final rule in order to attract more potential participants to the program. While concerns with the program remain, including those described above, potential applicants welcomed many of CMS' revisions, including, for example, the reduction of required quality measures, shared savings available on the first dollar, and the availability of a track without any down-side risk. Whether or not CMS will receive the volume of applicants it is seeking to attract is yet to be seen. CMS has stated that it will establish the MSSP by the statutory deadline of January 1, 2012.

ALTERING FFS REIMBURSEMENT

Prior to 2006, the Medicare program had very limited coverage of outpatient prescription drugs and biologics. These drugs are covered as "medical and other health services" under section 1832(a)(1) of the Social Security Act. That term, defined in section 1861(s) of the Act, specifically names the following classes of outpatient prescription drugs and biotechnology products as covered items:

- Drugs and biologicals not usually self-administered that are administered incident to a physician's service (§ 1861(s)(2)(A)). These drugs are usually either oncology drugs or drugs used to treat rheumatoid arthritis.
- Blood clotting factors for hemophilia patients (§ 1861(s)(2)(I)).
- Immunosuppressive agents to avoid organ rejection (§ 1861(s)(2)(J)).
- Erythropoiesis stimulating agents used to manage anemia in patients with end-stage renal disease (§ 1861(s)(2)(O)).
- Oral chemotherapy drugs (§ 1861(s)(2)(Q)).
- Oral anti-emetic agents used as a full replacement for anti-emetic therapy that would otherwise be administered intravenously (§ 1861(s)(2)(T)).
- CMS also takes the position that a drug that is necessary for the effective use of durable medical equipment can also be covered under Part B (CMS, Medicare Benefit Policy Manual, Ch. 15, at § 110.3).

On December 8, 2003, former President George W. Bush signed the Medicare Prescription Drug, Improvement and Modernization Act (also called the Medicare Modernization Act, or MMA) into law. Title I of the MMA added a new Part D to the Medicare program under which Medicare would cover all outpatient drugs not otherwise covered under Part B.[7] As a result of the enactment of the MMA, then, virtually any FDA-approved drug or biological has coverage under Medicare subject only to the program's overarching requirement that the drug or biological must be "reasonable and necessary for the diagnosis or treatment of illness or injury."[8]

Whether a drug is covered under Part B or Part D has implications for both patients and manufacturers given the different benefit design of each program. From the perspective of Medicare enrollees, Part B of Medicare requires that enrollees pay an annual deductible, and then 20% coinsurance once the deductible is satisfied. Social Security Act § 1833(a)(1); (b). Most Medicare beneficiaries purchase supplemental insurance so that their financial exposure is limited under Part B. Under

7 Section 1860D-2(e)(1) of the Social Security Act defines a covered Part D drug as a drug or a biological product that can only be dispensed pursuant to a prescription and that is approved by the Food and Drug Administration (FDA). In addition, in order for coverage for a drug or biological to be available under Part D for a particular Medicare beneficiary, coverage for the drug or biological must not be available for that beneficiary under Part B. See id. at § 1860D-2(e)(2)(B).

8 Id. at § 1862(a)(1)(A). This medical necessity requirement also applies in Part D; see id. at § 1860D-2(e)(3).

the standard Part D benefit design, Medicare beneficiaries pay an annual deductible and then either 25% coinsurance or a flat dollar co-payment for costs up to $2,930 in 2012. [9] Beneficiaries must then incur $4,700 in true out-of-pocket spending before catastrophic coverage begins.[10] Supplemental insurance cannot provide coverage for Part D cost sharing. Social Security Act § 1860D-2(b)(4)(C)(ii). Thus, Part B is a better program, from the perspective of beneficiaries with high prescription drug costs, than Part D, although that benefit will narrow over time as the coverage gap is phased down. Conversely, most Part D plans offer more generous benefits to beneficiaries who do not fall into the coverage gap.

From the perspective of manufacturers, program reimbursement is also dramatically different. For Part B drugs, the program reimburses the purchasers of those drugs or biologicals (typically the physicians who administer the drugs or biologicals, but also, in some cases, a retail pharmacy) at the average sales price of the drug, plus 6% (or 5%, for Part B drugs used in the hospital outpatient setting). Social Security Act § 1847A(b)(1)(B). "Average sales price," or ASP, for a calendar quarter is defined by the statute as the manufacturer's sales to all purchasers of the Part B product in the United States (at the National Drug Code level) for the quarter, divided by the total number of units of the drug or biological sold during the quarter. Some sales — such as those at a nominal price and those to certain socially-favored organizations — are not included in the calculation.

Program reimbursement under Part D is completely devoid of these rate-setting models. Rather than devising a rate-setting model, Part D relies solely on private Part D plans to deliver the benefit. Government involvement is limited to making subsidy payments to the plans. It was anticipated by the sponsors of the MMA that the marketplace — acting through pharmacy benefit managers — would determine the price that a pharmacy would be reimbursed by a Part D plan for a Part D drug. Indeed, the government may not "interfere with" negotiations between Part D plans, manufacturers and pharmacies.[11]

Thus, instead of government price-setting, reimbursement amounts for Part D drugs and biologics is determined by negotiations between manufacturers, Part D plans (represented by pharmacy benefit managers), and pharmacies. Prices for Part D drugs and biologics must also take into account rebate payments made by manufacturers. In this sense, Part D resembles a defined contribution model than a defined benefit model, because CMS cannot prescribe a plan benefit design nor reimbursement policies and procedures.

With this by way of background, we turn now to proposals to change the structure of Part B and Part D that have been discussed by policymakers.

REDUCE ASP PERCENTAGE ADD-ON

Under this approach, Congress would simply direct CMS to continue to use the ASP model for reimbursing Part B drugs and biologics, but reduce the percentage add on from 6% to some lower number. This would produce immediately calculable savings that would accrue to the benefit of the Medicare program. It would also produce savings for beneficiaries because their cost sharing would decline (i.e., it would be 20% of a lower number). There are reports that this proposal was considered by Congressional negotiators on the budget deficit.

This crude tool of achieving Medicare savings will be objected to by the physicians who administer Part B drugs and biologics, especially those in

9 These amounts are indexed for inflation each year.

10 Because of revisions to Part D made as part of the health reform law, manufacturers must provide a discount equal to 50% of the negotiated price of Part D drugs to beneficiaries when they are in the coverage gap. Social Security Act §§ 1860D-14A(b)(1)(A); 1860D-43(a)(1). The 50% discount counts as true out-of-pocket spending for Part D enrollees. Id. at § 1860D-2(b)(4)(E). Of the remaining 50% coinsurance, the government will increase its subsidy and pay half of the remainder by 2020. Id. at § 1860D-2(b)(2)(D)(ii).

11 Social Security Act § 1860D-11(i)(1).

rural areas. They will argue that they are not always able to purchase drugs or biologics at the "average" sales price for the drug and need the 6% margin to compensate for their relative lack of bargaining power. Other physicians will argue that the Medicare physician fee schedule under-compensates them for their office and professional work expense, and use the margin to compensate for the shortfall in the fee schedule. Some physicians may simply refuse to administer drugs in their office, shifting the expense to hospital outpatient departments and ambulatory surgical centers. To the extent that Medicare's pricing model affects drug choice and therefore demand, manufacturers will object to the policy as well.

There has been less discussion of altering the framework ASP model itself, although this issue has been suggested by some parties. For example, the HHS Office of Inspector General (OIG) is required to compare ASP to the average manufacturer's price for Part B drugs. Social Security Act § 1847A(d)(2)(B). In November of 2010, the OIG identified 13 drugs for which the average manufacturer's price exceeded the ASP by at least 5%.[12] This could imply that ASP reporting is lagging what is actually happening in the marketplace.

CONVERT SOME PART B DRUGS TO PART D

Since the very early days of Part D, there had been some interest in switching all drug coverage to the Part D model. A recent study has examined the feasibility of this switch.[13] The study found that there would be savings for Medicare if Part B drugs were moved to Part D; savings for moving three classes of Part B drugs to Part D (anti-cancer, pump-administered insulin, and nebulizer inhalants) could be as high as $150 million per year. However, the switch would not be as advantageous for beneficiaries, given the Part D coverage gap.[14] Because of the relatively small amount of federal savings, and the effect on beneficiaries, it does not seem likely that Congress will adopt it as part of any budgetary negotiations.

REBATES FOR DUAL-ELIGIBLE ENROLLEES

Prior to the enactment of the MMA, individuals who were dually eligible for Medicare and Medicaid had their outpatient prescription drugs paid for through the Medicaid program. This was far from ideal for beneficiaries or for states. From the perspective of Medicare beneficiaries, each state Medicaid plan is different. Some states capped the number of prescriptions per month that a beneficiary could fill. Others had restrictive coverage policies. From the perspective of states, drug costs were growing well beyond the rate of inflation, and states had few tools at their disposal to manage prescription drug costs. With the onset of the Part D benefit in 2006, the Medicare program assumed the burden of outpatient prescription drug costs for dual-eligible beneficiaries. Social Security Act § 1935(c). [15]

One of the few tools that states did have to manage prescription drug costs was the payment of rebates from pharmaceutical manufacturers. A manufacturer of covered outpatient drugs must, as a condition of coverage of those drugs under a state Medicaid program, pay a rebate to the state for the drug.[16] From the perspective of states, once

12 See OIG, "Memorandum Report, Comparison of First-Quarter 2010 Average Sales Prices and Average Manufacturer Prices" (Nov. 1, 2010).

13 See Grecia M. Marrufo *et al.*, "Estimating the Effects of Consolidating Drugs Under Part D or Part D", available at http://www.cms.gov/Reports/Downloads/Acumen_PartBtoDBase_Final_2010.pdf (August, 2010).

14 As noted, supra note 8, the coverage gap is going away, however. As a result, over time, it may be that Part B to Part D consolidation becomes beneficial to both the government and enrollees.

15 States are required to pay for the federal government's largesse; the statute provides for a phase-down of a state's Medicaid payment equal to a percentage of the state's expenditures on outpatient prescription drugs in the base year (2003). Social Security Act § 1935(c)(1)(A); (c)(5).

16 The rebate was recently increased, in the Affordable Care Act, to at least 23.1% of the average manufacturer's price of the drug. Social Security Act § 1927(c)(1)(A)(ii)(II).

the federal government took over coverage of prescription drugs for dual-eligible beneficiaries, the rebates went away as well.

Some proposals in Congress would re-impose the Medicaid rebate on outpatient prescription drugs and biologics covered under Part D and provided to dual-eligible beneficiaries.[17] As is the case with changes to Part B drugs, there have been reports that this proposal is being considered as part of the negotiations over the budget deficit.[18] It is estimated that the proposal would raise $122 billion over 10 years.[19]

Such a proposal would be particularly harmful and, arguably, unfair to manufacturers of pharmaceutical products and biologics. While it is true that states lost a revenue stream when the Medicaid rebates went away after assumption of Part D drug costs for dual-eligible enrollees by the federal government, the obligation of manufacturers to pay rebates did not go away. This is because manufacturers still pay rebates to Part D plans for formulary placement.[20] Thus, the Congressional proposal to require rebates to the federal government for dual-eligible beneficiaries would result in manufacturers paying double rebates for the same patients. This would drive up the cost of prescription drugs and biologics at a time when most policymakers believe that drug costs are too high. The higher costs to manufacturers could also be expected to hinder innovation, as more manufacturer dollars are funneled away to non-innovative uses.

It is unlikely that there will be significant changes to reimbursement for Medicare-covered drugs this year. Negotiations over the budget deficit ultimately fell apart in November and it is likely that Congress will adjourn for 2011 without addressing the deficit and debt in a comprehensive way. Nevertheless, these proposals are worth monitoring by manufacturers of pharmaceutical products and biologics.

RYAN PROPOSAL

The proposal by Representative Paul Ryan (R-WI) to fundamentally re-shape the Medicare defined benefit model could also have an effect on pharmaceutical and biologics pricing and reimbursement, but in an entirely different manner. Under the Ryan proposal, as passed by the House of Representatives, individuals in Medicare who were born after 1957 would be given a defined contribution to purchase a private health insurance plan in a tightly-regulated market.[21]

In this sense, then, the Ryan proposal would operate similarly to Part D. Beneficiaries would have a choice of plans, and plans would have multiple benefit designs. Under Part D, there is a standard benefit design, but the vast majority of enrollees choose the plan design that best meets their needs. The Ryan plan would follow the same model.

Under the current original Medicare program (other than Part D), the federal government calculates the reimbursement amounts payable for virtually all items and services that Medicare covers, often using extremely precise formulae that are spelled out in the statute or regulations. As indicated above, in Part D, the government cannot interfere in pricing negotiations in the Part D

17 See "House Democratic Leaders Introduce Legislation to Save More Than $100 Billion in Medicare Drug Costs" (hereafter, Democratic press release), available at http://democrats.energycommerce.house.gov/index.php?q=news/house-democratic-leaders-introduce-legislation-to-save-more-than-100-billion-in-medicare-drug-c (June 16, 2011).

18 See Matt Dobias, "Eric Cantor, PhRMA fight drug discounts in debt deal," Politico (July 14, 2011).

19 See Democratic Press Release, quoting Congressional Budget Office.

20 Manufacturers do have a bit more leverage in formulary negotiation when it comes to "six protected class" drugs, given CMS' requirements that all drugs in these classes must be included in Part D plan formularies. See supra note 9.

21 The market would be tightly regulated in the sense that the selection of private health plans from which Medicare beneficiaries would select would be guaranteed issue; in addition, plans could not exclude someone from coverage for a pre-existing condition.

program and so, unlike the rest of Medicare, the government stays out of Part D pricing decisions.

It seems likely that this is the way the Part D model would continue to work under the Ryan plan. Certainly, nothing would change in Part D. But it is also likely that under the Ryan legislation, Part B drug prices would also be moved away from an ASP-plus methodology to one where they would be negotiated between the private plans that the Ryan model envisions and the manufacturers. The result would likely be rebates for Part B drugs administered to Medicare patients paid by manufacturers to private health plans.

CONCLUSION

Assuming that political leaders are serious about tackling entitlement spending and the budget deficit, it seems possible that changes in reimbursement for pharmaceutical products and biologics dispensed to Medicare beneficiaries will occur over the next few years. These could include more precise government price-tinkering, along the lines of the Part B model, or a more private market approach, along the lines of the Part D model.

What is certain to occur is the gradual move to integrated delivery models such as ACOs. There, too, decisions about drug utilization and pricing will not be solely made by the government, but by the ACO itself. All of these changes have serious implications for manufacturers that should not be ignored.

Original Article

The emergence of bio-clusters in Egypt and South Africa

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ABSTRACT

There is a wide body of literature on biotechnology clusters. However, most of the works has been focused on the description of the clusters as well as the development of biotechnology clusters in USA, Europe and other developed countries. Much less attention has been paid to the development of biotechnology clusters in developing countries. The aim of this paper is to gain a better understanding of the emergence of biotechnology clusters in Egypt and South Africa.

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INTRODUCTION

OECD (the Organization for Economic Co-operation and Development)[1] defines biotechnology as "the application of science and technology to living organisms as well as parts, products and models thereof, to alter living or non-living materials for the production of knowledge, goods and services." According to Audretsch[2] biotechnology is defined as "a group of techniques and technologies that apply the principles of genetics, immunology and molecular, cellular and structural biology to the discovery and development of novel products." Early biotechnology includes traditional animal and plant breeding techniques, and the use of yeast in making bread, beer, wine and cheese whereas modern biotechnology focuses on the industrial use of recombinant DNA, cell fusion, novel bio-processing techniques, and bioremediation.[3,4]

Biotechnology is not seen only as an industry by itself but also a set of specific activities and technologies such as biomaterials, DNA markers, genetic engineering, and recombinant DNA. These technologies not only have the potential to produce new products but also new processes for existing products, and new organisms for environmental cleaning, medical applications or human consumption.[5]

Many countries have recognized the importance of biotechnology in the growth of their economies[6] and it has increasingly become a key source of scientific innovation.[7,8] This emerging industry has great potential to improve the quality of life and business efficiency in regions and nations.[9, 10]

The industry has the ability to provide crucial leads in areas of human health and agriculture. Biotechnology has a strong research and development thrust, and is increasingly being viewed as a solution provider to diseases such as cancer and

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AIDS. It is also an instrument used to enhance agricultural productivity and the promotion of sustainable development through the use of biofuels.[11]

It is generally accepted that from the inception of the biotechnology industry in the late 1970s and early 1980s, the USA followed by Europe have been the forerunners in the world.[12, 13] The biotechnology industry is, however, no longer the exclusive domain of the USA and Western economies. It is reported that Australia, Israel, China and India have the 5th, 8th, 9th and 11th largest biotechnology sectors, respectively, in the world. Other countries like Japan, Taiwan and Cuba have nurtured biotechnology for a long time and continue to mature in it while some emerging economies like Singapore, South Korea, Brazil, Chile and South Africa are hoping to kick-start their biotechnology industries.[13]

There is a wide body of literature on clustering in biotechnology.[3,4,7-9,14-19] Biotechnology companies are concentrated at a geographical level, forming clusters. Most of the studies have focused on the description of the clusters and the development of biotechnology clusters in USA, Europe and other developed countries. Much less attention has been paid to the development of biotechnology clusters in developing countries. The aim of this research is to investigate the development of bio-clusters in Africa continent and especially identifies the key mechanisms that favour the development of biocluster in Egypt and South Africa.

The remainder of this paper is structured into four sections. In the next section a brief survey of the literature on clusters is presented. We then focus on the emergence of bio-clusters in Egypt and South Africa. In the final section the main discussions are highlighted and recommendations regarding policy are made.

THE IMPORTANCE OF CLUSTERS

Clusters consist of both high-tech concentrations of firms such as life sciences, biotechnology, nanotechnology, Information and Communication Technology (ICT), semiconductors as well as those based in more traditional industries such as food, wine, furniture, textile, shoes. Porter[20] identifies a cluster as "a geographic concentration of interconnected companies and institutions in a particular field." Another definition stated by Zhu and Tann[21] indicates that "clusters can be characterized as being economic networks of strongly interdependent firms (including suppliers), knowledge producing agents (universities, research institutes, engineering companies), bridging institutions (brokers, consultants) and customers, linked to each other in a value-adding production chain."

Clusters have been increasingly regarded as potential drivers of economic development[16] and have become an important source of competitive advantage through increased productivity, innovation, creation of new businesses and access to new knowledge in the global economy.[19,21] Clusters of emerging science-based industries (i.e. biotechnology, medical biosciences, nanotechnology) are critical factors in shaping the economic growth in 21st century.[16] With increasing global competition, governments around the world have sought to develop mechanisms to identify actual and potential clusters in order to create national or regional advantage through their formation and operation.[21] By ensuring both national and regional policies do not unintentionally place barriers to cluster development, governments can create the conditions which encourage the formation and growth of clusters; thereby catalyzing the formation of collaborations within a cluster, and ensuring research and innovation support programmes build on existing strengths.[9] According to Singh[22] government perform the following functions to encourage cluster development:

- playing a role as 'broker', 'facilitator', 'initiator', 'participant' and 'listener' to engage partners in a productive dialogue and create a sense of urgency to cause action
- conducting ongoing cluster assessments to determine their

viability and relative strength to ensure global competitiveness
- institutionalizing cluster upgrading (e.g. restructuring government programmes and services, diffusing new knowledge, and collecting and disseminating data/information by clusters)
- directly investing in and providing investment incentives for technical, physical and knowledge infrastructure
- sponsoring cluster conferences and forums to promote 'social capital' opportunities for participants

Clustering can bring benefits to both business and the wider economy.[15] Some of the benefits of clusters include raise innovation and productivity, knowledge-sharing about best practices, cost-reduction by jointly sourcing services and suppliers, interactions facilitate formal and informal knowledge transfer that encourage collaboration between institutions.[23] According to Galliano[15] key benefits of cluster development include: 1) increased levels of expertise; 2) the ability to draw on complementary skills; 3) the potential for economies of scale; 4) improved information flows within a cluster and 5) the development of an infrastructure of professional, legal, financial and other specialist services.

The development of the biotechnology industry has been characterised by a high concentration of firms at a geographical level.[4,7,18] Development of clusters has been one of the critical factors in the success of many countries that have achieved the highest level of innovativeness in the field of biotechnology. These clusters, which are mostly region specific, essentially provide a platform for effective communication, resources, infrastructure, expertise and sharing of experiences among science agencies, state governments, research institutions, universities, and industries thereby facilitating the creation of a knowledge-based hub.[11]

Many studies have yielded similar conclusions on critical factors needed to develop the biotechnology sector. They emphasize the role of strong science base, skilled workforce, supportive infrastructure and the availability of services, financing and policy support.[4,24] The factors for successful biotechnology clusters were also identified as follows: 1) Strong science base 2) Entrepreneurial culture 3) Growing company base 4) Ability to attract key staff 5) Premises and infrastructure 6) Availability of finance 7) Business support services and large companies 8) Skilled workforce 9) Effective networking 10) Supportive policy environment.[4,9,15]

EMERGING BIO-CLUSTERS IN AFRICA

In this section we show the development of biotechnology in two leading African countries; Egypt and South Africa.

Egypt: Mubarak City For Scientific Research and Technology Applications

Egypt is in the early stages of establishing a successful health biotechnology sector. Promoting clusters in health biotechnology has become a standard policy in Egypt but sector is not yet geographically clustered. Pharmaceutical firms are located in several cities and industrial zones, and research centres are found all over the country.[25] The country's first science park, Mubarak City for Scientific Research and Technology Applications (MuCSAT) is located at New Borg El Arab City, west of Alexandria, was inaugurated in 2000.

MuCSAT was established as a centre of research excellence in advanced biotechnology. The goal of the institution is to introduce valuable biotechnology products and services to the market through R&D and technology transfer. Of the 12 institutes to be created within MuCSAT, four have already completed, including the Genetic Engineering and Biotechnology Research Institute.[25] The institute is aiming to carry out biotechnology research to serve in different fields such as medical, environmental, industrial and pharmaceutical

areas. MuCSAT possesses state-of-the-art facilities, equipment, and highly qualified researchers and encourage international cooperation.

South Africa: South African Technology Innovation Agency

In South Africa, government introduced a key policy driver to build a biotechnology hub in South Africa was the National Biotechnology Strategy (NBS) in 2001. The government allocated R450 million (around US$58 million) in public funding for biotechnology development for the years 2004-2007.[26,27] The aim of this strategy was to stimulate the development of biotechnology skills, capacities and tools in South Africa.[28]

The NBS pointed out some conclusions from a review of management of biotechnology activities of other countries which are:[29]

- A dedicated agency was needed to champion biotechnology and manage relevant activities to ensure coherence between programs
- Strong science & technology capabilities must build, targeting human resource development
- Investment must focus on the commercial products and processes locally and internationally

As an important result of the NBS strategy was the creation of the Biotechnology Regional Innovation Centres (BRICs) which aimed to develop and commercialize the biotechnology industry and strategically develop bio-clusters.[30,31]

According to National Biotechnology Audit[32], there are 78 biotechnology active companies and of which 38 companies are core biotechnology companies. A "core" biotechnology company is one that is using at least one biotechnology related technique and whose major economic activity is biotechnology whereas an "active" company is one that either performs R&D in biotechnology or produces and sells biotechnology products. Total number of employees in the biotechnology active firms exceeded 72,800 whereas core companies only employ 765 people. The revenues of active firms reached R767.6 million during 2006 (R624.4 million during 2004). The profits of core firms were R520 million in 2006 (see table 1).

One of the BRICS is the Cape Biotech Initiative (CBI)[1] was launched in 2002/2003 which had a R150 million (approximately USA$ 20 million) to establish incubators in terms of the National Biotechnology Strategy. The CBI represents the interests of all stakeholders in the region, including industry, academia, government, finance, the public and all other role players in the field of biotechnology.

Through a regionally focused projects, the CBI acts as a centre for the development of a range of businesses and new product offerings, as well as have the capacity to support these with the aim of contributing to the development of world-class skills, economic development and job creation in the region.[33] CBI has three major roles; industry stimulation through capacity creation, management of government funds by investing in promising projects and co-ordination of business support networks. Its functions include investment, networking, bio-economy intelligence, marketing and capacity development.[34] CBI focuses on five areas; diagnostics, vaccines, drug delivery, bio-prospecting and nutraceuticals.

Based on the number of biotechnology companies based in Gauteng and Cape Town, we propose that these are emerging bio-clusters in these regions. These regions also have leading universities, a critical mass of researchers, and growing number of qualified skilled scientific researchers with better IP policies that incentivizes commercialisation.

1. Cape Biotech Initiative no longer exists and is now a component of the centralized Technology Innovation Agency (TIA). The Department of Science and Technology (DST) is recently established a new public institution, the TIA, which is a single public agency that was formed from a merger of seven DST-funded organisations, namely, Tshumisano, Lifelab, Biopad, Plantbio, Cape biotech, Innovation fund and Amts (Advanced Manufacturing Technology Strategy).

Table 1: Core and Biotechnology Active Companies in South Africa

Characteristics	Core Biotechnology Companies	Active Biotechnology Companies
Number of companies	38	78
Location	Gauteng 43%, Western Cape 30%, KwaZulu-Natal 19%, Rest of SA 8%	Gauteng 43% Western Cape 26%, KwaZulu-Natal 12%, Rest of SA 19%
Spin-off companies	16 (44% from universities, 31% from government)	25 (28% from universities, 36% from government)
Foreign owned companies	5	12
No of employees (2006)	765	72,844
Profits (2006)	R 520 million	R 767.6 million
R&D expenditure	R 76 million	-
Fund raised (2003-2006)	R 216 million	-
Major funding sources	BRICS 36% IF 19%	-

Note: BRICS: Biotechnology Regional Innovation Centres, IF: Innovation Fund
Source: DST[32], 2008

DISCUSSION

Developed countries have shown that successful biotechnology clusters have some of the following attributes: 1) Strong science base 2) Entrepreneurial culture 3) Growing company base 4) Ability to attract key staff 5) Premises and infrastructure 6) Availability of finance 7) Business support services and large companies 8) Skilled workforce 9) Effective networking 10) Supportive policy environment.

Egypt has taken steps to create infrastructures by developing their first science park, MuCSAT. This provides opportunity for effective networking, creation of a strong science base and the employment of a skilled workforce.

In South Africa there is evidence of emerging clusters in the Gauteng and Western Cape regions, based on the number of companies concentrated within the regions. These regions have leading universities, a critical mass of researchers, and growing number of qualified skilled scientific researchers and better IP policies that incentivizes commercialization.

Despite this, there is a lack of public and private financing; confidence in African governments which affects foreign investments; an entrepreneurial culture and a low tendency among academics to commercialize research. The available public funding is also not easily accessible due to the lack of biotechnology expertise by regional government funders.

We recommend that the South African government can support and facilitate cluster development in a variety ways. They can continue to play a crucial role to create the conditions that encourage the formation and growth of biotechnology clusters through supporting policies. More effective mechanisms, such as faster application processing for finance, setting up companies and laboratories should be implemented to facilitate a supportive policy environment. Foreign investment can possibly be attracted through government funding that matches foreign venture capitals that exploit South Africa's rich biodiversity and African traditional knowledge that may have potential benefits in health care.

Collaborations between industry and academia are also key to cluster development and should be encouraged in the South African setting. Stakeholders in the sector should also be encouraged to have a shared aspiration to form clusters through effective networking, social interactions and by promoting role models and recognition of entrepreneurs.

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Original Article

Patent litigation in India and interim injunctions — An evolving jurisprudence

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ABSTRACT

This paper attempts to summarize and analyze the judicial trend towards granting or denying interim injunctive relief in patent litigation arena.

The content of this paper is intended to only provide a general guide to the subject matter. The views expressed in this paper are purely personal of the authors.

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INTRODUCTION

With the advent of pharmaceutical patent regime in 2005, it was expected that patent litigation in India would be an evolving area. Often, what has been seen is that the outcome of applications for interim injunction is determinative of the outcome of the litigation as a whole. However, the approach of courts in deciding on interim injunctions in patent cases has not been consistent. As a result, there has always been felt a need for the unswerving standards to be followed by the courts while deciding on interim injunctions in patent cases. The exercise of sound judicial wisdom by the court while deciding on interim injunction becomes even more important in view of the fact that a patent matter often involves complex technologies and huge amounts at stake.

The commentary on patent law, *Patent Law*, states that "What constitutes infringement of a patent is not defined in the Patents Act, 1970. One has, therefore, to gather the meaning of infringement from the scope of the monopoly rights conferred on the patentee; for infringement is the violation of those rights."[1]

Section 48 of the Patents Act, 1970 confers monopoly rights on the patentee. Infringement of a patent can be termed as the unauthorized making, using, offering for sale, selling of any patented

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1 P. Narayanan, (*Patent Law*), 4th Edn, 2006, Eastern Law House, Page-498

invention within a jurisdiction, or importing into that jurisdiction of any patented invention during the term of that patent. The Patents Act, 1970, provides under Chapter XVIII provisions pertaining to "Suits Concerning Infringement of Patents". These provisions are covered under section 104 to section 115 of the act.

The above said commentary also states that "In deciding whether what the alleged infringer is doing amounts to an infringement of a particular patent three questions are involved: (1) the extent of monopoly right conferred by the patent which has to be ascertained by a construction of the specification; (2) whether the alleged acts amount to making, using, exercising, selling or distributing a product; or using or exercising a method or process in the case of a process patent; and (3) whether what the alleged infringer is doing amounts to an infringement of the monopoly conferred by the patent grant."[2]

This commentary also states that "To infringe a patent it must be shown that the invention as claimed in the relevant claim, has been infringed in all essential respects — essential that is to say, upon the true construction of the claims."[3]

The determination of patent infringement requires that the infringing product or process falls within one or more claims of the patent. The test of infringement involves reading a claim onto the technology of interest. A claim is said to read on the technology, if all of its elements are found in that technology.

Injunction is as an equitable remedy in the form of a court order, whereby a party is required to do, or to refrain from doing, certain acts. An injunction may be preliminary or permanent which are provided under Order XXXIX, Rule 1 & 2 of Indian Code of Civil Procedure (CPC), 1908.

Interim injunction being a remedy that prevents the violation of rights pending the trial of the suit; it requires sound judicial wisdom to be exercised by the courts while deciding upon an application for the grant of interim injunction.

2 Ibid, Page-499

3 Ibid, Page-526

In view of a number of legal pronouncements leading to a set of formal standards, there has evolved criteria in terms of three basic factors that a court should weigh while granting interim injunctions. These factors are: (i) *Prima facie* case, (ii) Irreparable damage and (iii) Balance of convenience.

The above mentioned first factor i.e. *prima facie* case that has led to different interpretations is a substantial question which requires the plaintiff to show that he has a good chance of success at a *prima facie* level. It also requires him to establish a *prima facie* case of validity of the patent in question apart from establishing a *prima facie* case of infringement of that patent. The second factor i.e. irreparable damage requires the plaintiff to show that irreparable injury would be caused to him in the event the interim injunction is denied by the court. The third and final factor i.e. balance of convenience requires the plaintiff to show that comparative hardship of inconvenience which is likely to ensue in the event the interim injunction is not granted will be greater than that would be likely to arise if the interim injunction is granted.

The origin of these factors may be sourced to 'celebrated' English decision in the case of *American Cyanamid Co. vs. Ethicon Ltd.*, 1975 AC 396.

In this leading case, the House of Lords contemplated and laid down some principles on how the court's discretion to grant interim injunctions should be exercised. These principles consider:

- Whether there is a serious question to be tried on the substantive claim;
- Whether damages would be an adequate remedy for the claimant;
- Balance of convenience of each of the parties in the event an order is granted and
- Any special factors.

The House of Lords, while proposing a new standard of "triable issue" envisaged a flexible standard of prima facie assessment.

Although, the court is always expected to mull over all these factors before deciding on interim injunction, pending the suit, the *sine qua non* of interim injunctive relief is that the plaintiff must establish that the failure to grant an injunction would result in the likelihood of irreparable harm to his interests.

A number of judgments suggest that the factor of *prima facie* case is considered since there is an absence of presumptive validity of a patent as provided under section 13 (4)[4] of the Patents Act, 1970. We, however, observe that this particular section does not completely bar a presumption of validity and merely suggests that there is no warranty as to the validity of the patent. A close analysis of the section reveals that its application is confined to examination and investigations required under section 12 and 13 only and does not affect a patent which has been subjected to opposition proceedings.

Another principle evolved by way of caution that has often been considered by the courts while deciding on interim injunctions is the controversial "six year rule"[5]. It states that if a patent is more than six years old and there has been undisturbed possession and enjoyment over it for such time, a stronger presumption of validity must be attached to it. This particular rule first applied in India in the case of *Manicka Thevar vs. Star Plough Works*, AIR 1965 MAD 327, has lost its significance over the years for lack of any basis for its application.

4 Section 13(4) reads as: The examination and investigations required under section 12 (Examination of application) and this section shall not be deemed in any way to warrant the validity of any patent, and no liability shall be incurred by the Central Government or any officer thereof by reason of, or in connection with, any such examination or investigation or any report or other proceedings consequent thereon.

5 English commentary — Terrell on the Law of Patents, Ninth Edition is considered to be the authority for the origin of the "six year rule".

SOME LANDMARK PATENT LITIGATION CASES: VARIED APPROACH OF JUDICIARY IN DECIDING ON INTERIM INJUNCTIONS

A representative chart of significant patent infringement cases in India where interim injunction was decided is presented in Table 1.

In recent years, of a number of cases, the high profile case of *Bajaj Auto Ltd. vs. TVS Motor Company Ltd.* was most significant as the Supreme Court concurred with the observations made in *Shree Vardhman Rice & Gen Mills vs. Amar Singh Chawalwala* that matters relating to trademarks, copyrights and patents should be finally decided very expeditiously by the trial court instead of merely granting or refusing to grant injunction.

The Supreme Court held that in matters relating to trademarks, copyright and patents the proviso to Order XVII Rule 1(2) C.P.C.[6] should be strictly complied with by all the courts, and the hearing of the suit in such matters should proceed on day to day basis and the final judgment should be given normally within four months from the date of the filing of the suit. The court also directed that these directions be carried out by all courts and tribunals in this country punctually and faithfully.

Practically, the proposition laid down by Supreme Court seems a bit unfeasible and unrealistic in view of the existing framework. Nonetheless, these guidelines certainly have a wider significance for the speedy trial of high stake IP cases. However, in order to make speedy trial of such cases a meaningful reality, the implementation of these guidelines would be equally important.

PATENT AND PUBLIC INTEREST: A TUG OF WAR

The most talked about decision having far reaching ramifications in the pharmaceutical patent arena in India has been the decision of Delhi High Court in *F. Hoffmann-La Roche Ltd. and Anr. vs. Cipla Limited.* [2008 (37) PTC 71 (Del.)]. In this case, the plaintiffs filed a suit praying for permanent injunction restraining defendant from infringing its patent in respect of anti-cancer drug "*Tarceva*".

6 Order XVII Rule 1(2) CPC: Costs of adjournment

Table 1: Landmark patent cases

S. No.	Case Details	Patented Invention	Decision
1.	*National Research Development Corporation of India, New Delhi vs. The Delhi Cloth and General Mills Co. Ltd. & Ors.* AIR 1980 DEL132 (Delhi High Court)	IN138571 (Titanium substrate insoluble anodef assembly for diaphragm type chloral kali cells)	• If the patent in question is sufficiently old and has been worked, the court would presume the patent to be valid for the purpose of temporary injunction • *Ex-parte* interim injunction confirmed
2.	*Surendra Lal Mahendra, New Delhi vs. M/s. Jain Glazers New Delhi & Ors.* ILR 1981 Delhi 257 (Delhi High Court)	IN143964 (Laminating apparatus)	• Invention does not involve novelty/inventive step • *Ex-parte* ad-Interim injunction granted earlier vacated • Status Quo to be maintained
3.	*Jimmy Sorab Canteenwala & Anr. vs. Shellco* – AG 1996 IPLR 357 (Guj.) (Ahmedabad High Court)	Sealing device	• Ad-interim injunction granted by trial court allowed to continue
4.	*Franz Xaver Huemer vs. New Yash Engineers* 1996 (25) ARBLR 522 Delhi (Delhi High Court)	IN161520, IN162589, IN162369, IN163591, IN163095 (Mechanical devices)	• Trial court's order vacating interim injunction confirmed • Injunction refused, in equity, for non use of the patent
5.	*Hindustan Lever Limited. vs. Godrej Soaps Limited. And Others* AIR 1996 Cal 367 (Calcutta High Court)	IN170171 (Detergent bars suitable for personal bathing or fabric washing)	• Patented invention merely a rearrangement of known devices and therefore not an invention under the Act • Interim injunction denied
6.	*Standipack Private Limited & Anr. vs. Oswal Trading Co. Ltd. & Castrol India Ltd.* AIR 2000 Delhi 23 (Delhi High Court)	Pouch for storage and dispensing of a liquid	• Plaintiff failed to act with clean hands rather suppressed material facts • Provisions of the Patents Act, 1970 and Rules framed therein violated by post-dating patent • Interim Injunction granted by District Court vacated
7.	*Cadila Pharmaceuticals vs. Instacare Laboratories Pvt. Ltd.* 2001 (21) PTC 472 (Guj.) (Ahmedabad High Court)	IN183097 (Novel drug delivery process for a combination medicine)	• Prima facie, the process evolved by Cadila not patentable • Defence to infringement action is always available to defendant regardless of his not availing the opportunity of filing pre-grant opposition or revocation petition • Trial Court's order vacating the *ex-parte* ad-interim injunction (granted to Cadila) affirmed
8.	*Telemecanique & Controls (I) Ltd. vs. Schneider Electric Industries* SA 94 (2001) DLT 865 (Delhi High Court)	Product range of electric contractors and accessories	• Once a violation is established in case of a registered patent, subject of course, to the patent being used, it will not be permissible to contend that the said patentee is not entitled to an injunction • Balance term of patent in question matters • Working of patents requirements (Section 83) met by the sale of the product in the country (though not manufactured but imported) • Order of single judge granting interim injunction confirmed

S. No.	Case Details	Patented Invention	Decision
9.	*Dhanpat Seth and Ors. vs. Nil Kamal Plastic Crates Ltd.* 2006 (33) PTC 330 (HP) (Himachal Pradesh High Court)	IN195917 (Device of manually hauling of agriculture produce)	• The single judge held that the statutory law prevailing in India is contrary to the rules laid down in the American Cyanamid case, on *prima facie* presumption of validity of patent, in view of the section 13(4) of the Patents Act, 1970 • Single judge's order denying temporary injunction confirmed in appeal before division bench • Division bench held that the device developed by the plaintiffs is in fact the result of traditional knowledge and aggregation/duplication of known products
10.	*Bilcare Ltd vs. Amartara Pvt. Ltd.* (2007) (34) PTC 419 (Del) (Delhi High Court)	IN197823 (Metallized packaging films)	• Interim injunction (granted by district court) obtained by not disclosing complete facts • In infringement suits, non disclosure, concealment of facts or improper disclosure would result in denial of the equitable relief of injunction • District court's order granting *ex-parte* ad-interim injunction vacated
11.	*K Ramu vs. Adayar Ananda Bhavan and Muthulakshmi Bhavan* 2007 (34) PTC 689 (Madras High Court)	IN200285; IN193899 (Low glycemic sweets; Process for preparation of low glycemic sweets)	• The object of the interlocutory injunction is to protect the plaintiff against injury by violation of his right for which he could not be adequately compensated in damages recoverable in the action if the uncertainty were resolved in his favor at the trial • Ad-Interim injunction granted

12.	*FDC limited & Ors. vs. Sanjeev Khanderwal & Ors.* 2007 (35) PTC 436 (Mad) (Madras High Court)	IN197822 (A synergistic antibacterial formulation and a method of making the same)	• The *ex-parte* injunction can be granted only after proper judicial scrutiny and appreciation of elaborate oral and documentary evidence adduced by both sides
			• Guidelines formulated on *ex-parte* injunctions:
			  • Whether the plaintiff and the primary defendant are residing outside the State and their identity, addresses etc., are easily known;
			  • Whether sales of the offending products are not on a commercial scale;
			  • If the grant of interim injunction is going to result in closure of operations/business of the defendant. If the *ex-parte* injunction has a nationwide operation and is not just within the State;
			  • Where the dispute involves patent/trade mark issues, the trial court should carefully peruse the certificates, offending marks etc;
			  • An *ex-parte* injunction should not be granted in cases where no evidence of proof of infringement has been filed by the plaintiff; and
			  • In patent cases, the trial court has to carefully note the distinction between a product patent and a process patent. If the plaintiff alleges violation of a process patent, then the *ex-parte* injunction should not be granted unless the plaintiff has adduced the evidence of an independent scientist/other technical expert who has tested the plaintiff's and defendant's product and arrived at an independent finding as to the identity of the processes used. In process patent cases, opportunity must be given to the defendant to explain how their process does not constitute infringement within the meaning of Section 104-A of the Patents Act, 1970
			• *Ex-parte* ad-interim injunction granted by the trial court suspended

S. No.	Case Details	Patented Invention	Decision
13.	*Acme Tele Power Limited vs. Lamda Eastern Telecommunication Ltd.* 2008 (38) PTC 628 (Utt) (Uttrakhand High Court)	IN197086; IN197108 (Cubodial shaped green shelter and compact power interface)	• Interim injunction granted by district court confirmed
14.	*Bajaj Auto Ltd. vs. TVS Motor Company Ltd.* 2008 (36) PTC 417 (Mad) (Madras High Court)	IN195904 (An improved internal combustion engine working on a four stroke principle)	• Classic test for granting interim injunction satisfied • Bajaj has already come up in the world market by sale of its product; TVS has not even marketed its alleged product • The quantum of damages which the plaintiff may suffer in not granting injunction cannot be ascertained in monetary sense • Six year rule used to ascertain the validity of a patent affirmed • At the interim stage, it is sufficient for the plaintiff to show that the patent has prima facie novelty • The question of whether the patented invention is "obvious" will have to be decided in an appropriate manner in a full fledged trial • Interim injunction granted to Bajaj • Order of single judge set aside in appeal • Appeal preferred before Supreme Court • Supreme Court held that TVS shall be entitled to sell its product but it shall maintain accurate records/accounts of its all India and export sales
15.	*J. Mitra & Co. Pvt. Ltd. vs. Kesar Medicaments* 2008 (36) PTC 568 Del (Delhi High Court)	IN194638 (A device for detection of antibodies to hepatitis virus in human serum and plasma)	• The use of patent in question being limited (the early detection of HCV was stated to be critical as no vaccine for the same present), the factors of irretrievable prejudice and balance of convenience lie in favor of the plaintiff • Temporary injunction granted
16.	*Mariappan vs. A.R.Safiullah* 2008 (38) PTC 341 (Mad) (Madras High Court)	IN198079 (Food-grade laminated paper, method and apparatus for manufacturing the laminated paper)	• The artificial banana leaf (food-grade laminated paper) prima facie appears to be of not an invention but can be termed only as an innovation • In terms of Section 13(4) of the Patents Act, the grant of patent itself cannot be deemed to be *prima facie* case on the side of the patentee • The controversial six year rule disregarded for it has lost its significance in view of the latest development in the field of science and technology • Single judge's order of denial of ad-interim injunction confirmed
17.	*Strix Limited vs. Maharaja Appliances Limited* MANU/ DE/2174/2009 (Delhi High Court)	IN192511 (Liquid heating vessels)	• In order to raise a credible challenge to the validity of a patent, even at an interlocutory stage, the defendant will have to place on record some acceptable scientific material, supported or explained by the evidence of an expert, that the plaintiff's patent is *prima facie* vulnerable to revocation • The burden on the defendant to show that it has put forward a creditable challenge will be greater if there was no opposition (pre-grant or post-grant) filed to the patent • Interim injunction granted

The case acquired significance for the very reason that it was the first case in which the court considered the aspect of "pricing" of the drug in deciding on the interim injunction. This case was also important as it diluted the six year rule.

This case was yet another instance reflecting the sheer inability of judiciary to effectively handle patent matters involving a number of complex issues. In this case, public interest factor was one of the predominant factors that the court took into account while denying Roche the interim injunction.

The single judge of the high court laid down several crucial principles as follows:

i. In patent infringement actions, the courts should follow the approach indicated in American Cyanamid case, by applying all factors;
ii. The courts should follow a rule of caution, and not always presume that patents are valid, especially if the defendant challenges it and
iii. The standard applicable for a defendant challenging the patent is whether it is a genuine one, as opposed to a vexatious defense. Only in the case of the former will the court hold that the defendant has an arguable case.

The court, taking a *prima facie* view on the situation on hand, opined that Roche's case though arguable and disclosing *prima facie* merit, it has to answer a credible challenge to the patent raised by the defendant Cipla. The court opined that in such a situation the question of balance of convenience will have to be decided. The court was of the view that while deciding the issue of balance of convenience; it has to consider the following factors:

- The extent to which disadvantages to each party would be incapable of being compensated in damages in the event of his succeeding at the trial;
- The nature of the product and its use;
- The timing of the action and
- If the balance is approximately equal, the court may consider the relative strength of each party's case only where it is apparent by undisputed evidence that the strength of one party's case is disproportionate to that of the other party.

The court was of the opinion that as between the two competing public interests, i.e. the public interest in granting an injunction to the patentee, as opposed to the public interest in access to a life saving drug for the people, the balance has to be tilted in favor of the latter. The court also opined that the patients in India can ill-afford high priced imported versions of the drug like "*Tarceva*".[7]

Aggrieved by the ruling of the single judge, Roche went in appeal. However, the Division Bench dismissed the appeal imposing heavy costs quantified at Rs. 5 Lakhs to be paid by Roche to Cipla. The court however, restrained Cipla from exporting its drug to countries where Roche had a patent during the pendency of the appeal.

The contention of Cipla was that the X-ray diffraction data of Roche's patented drug "*Tarceva*" showed that it corresponded to polymorph B for which Roche did not have a patent as the patent in suit pertained to polymorph A+B only. Cipla contended that Roche was seeking an interim injunction in respect of a drug corresponding to polymorph B which was not covered under a patent as a separate application for polymorph B[8] was pending consideration before the patent office.

The division bench held that Roche failed to establish a *prima facie* case in its favor in view of the fact that a serious challenge to the validity of the patent in suit was raised. It was also held that Roche failed to make a full disclosure of the facts

7 The court while hearing the case noted that the plaintiff's capsule costs ~USD 97.58 (INR. 4, 800/-) and the equivalent tablet of the defendant costs ~USD 32.53 (INR. 1, 600/-).

8 The application for polymorph B (IN/PCT/2002/507/DEL) was ultimately allowed with process claims only.

pertaining to the patent in suit including the fact that there was another patent application pending in respect of Polymorph B in which Roche had stated that "polymorph B is claimed to be thermodynamically more stable and it helps in providing improved oral dosage in solid form". It was also held that Roche ought to have filed X-ray diffraction data of "*Tarceva*" and "*Erlocip*" along with the plaint.

The division bench held that to the extent that Cipla has raised a serious doubt whether Roche in fact holds a patent for the product sold in the tablet form as "*Tarceva*", Roche must be held not to have been able to cross the first hurdle of showing that it has a *prima facie* case in its favor.

Moreover, the division bench concurred with the single judge on the public interest factor. However, it laid emphasis on greater availability of a life saving drug by stating that even if the price of Cipla's drug "*Erlocip*" at ~USD 32.53 (INR 1600) per tablet does not make it inexpensive, the question of greater availability of such drug in the market assumes significance.

While dismissing the appeal, the court getting overtly optimistic formulated the following principle which may have its own implications in a pharmaceutical patent litigation:

> *"In an application seeking ad interim injunction in a suit for infringement of patent, it would be incumbent on the plaintiffs to make a full disclosure of the complete specification of the product whose patent is claimed to have been infringed. The plaintiffs will also have to disclose to court the x-ray diffraction data of the product, particularly if it is a pharmaceutical drug. The plaintiffs have to make an unequivocal disclosure that the patent they hold covers the drug in question; whether there are any other pending applications seeking the grant of patent in respect of any derivatives or forms of the product for which they already hold a patent and the effect of such applications on the suit patent."*

The decision in this high profile case has drawn mixed reactions in India. The decision of the single judge was particularly unappreciated for some very apparent reasons. It was observed that the public interest factor discussed in the decision permeated all other relevant factors thereby leaving a too little scope for a balanced approach required from the court in deciding on interim injunction in such a complex matter. It was also observed that the court was not expected to transgress into the domain of the executive for trading into the area of pricing of drugs as it would be violative of Doctrine of Separation of Power[9]. There has also been fear that infringers may misuse this over-emphasized principle of public interest to serve their private interests.

The court failed to appreciate that the issue of "affordability" of the drugs is altogether irrelevant as enough safeguards are already present in the substantive law i.e. Patents Act, 1970 to protect the "public interest" requirement. It may be noted that one of the established executive agency National Pharmaceutical Pricing Authority, a part of the Ministry of Chemicals and Fertilizers under the Drug Price Control Order has adequate power to monitor the price of drugs. The court also failed to appreciate that patented drug "*Tarceva*" was not the unique anti-cancer drug to treat lung and pancreatic cancer as several other cancer drugs were also available in the market.

Moreover, the division bench failed to appreciate that a patent infringement case involves claim construction/interpretation as perhaps it did not analyze the independent claim of the patent in suit. Awarding whopping costs of ~USD 10,165.63 (INR 5 Lakhs) could also never be justified in view of the fact that (i) it was the stage of interim injunction only when the ruling came and (ii) this case involved several contentious issues yet to be decided by the court requiring a full fledged trial.

The outcome of the judgment in this case has really been alarming since it opened floodgates to

9 The doctrine of separation of powers refers to the separation of the legislature, the executive and the judiciary.

more and more infringers to infringe the patent in suit in question. It has compelled Roche to file nine more lawsuits[10] against different infringers till date in respect of the same patent in question out of which seven suits (except *Roche vs. Matrix Lab* and *Roche vs. Intas Biopharmaceuticals*) are pending before the Delhi High Court. It has also been seen that the judgment in this particular case has had a substantial impact on Roche's other cases also which are pending before the Delhi High Court. Importantly, in one of these suits i.e. *F.Hoffmann-La Roche Ltd.* and *Anr. vs. Natco Pharma* [CS (OS) 2465/2009] almost six months have elapsed since the high court reserved its order on the interim injunction application filed by Roche.

Roche, however, was able to get an interim injunction from the Madras High Court in another suit [CS (OS) 801/2010] filed in respect of the same patent. The court granted interim injunction after taking a note of elaborate laboratory research involved behind the patented invention of Roche.

PATENT LINKAGE

In *Bristol-Myers Squibb Company & Ors. vs. Dr. B. P. S. Reddy & Ors.* [Suit no. CS (OS) 2680/2008], a suit filed for the permanent injunction restraining the defendant from infringing the patent IN203937 in respect of the drug "*Dasatinib*", the Delhi High Court granted an *ex-parte* ad-interim injunction[11] in favor of the plaintiffs restraining the defendants from manufacturing, selling, distributing, advertising, exporting, offering for sale or in any manner dealing directly or indirectly in any infringing product.

The court, in an unusual event, directed the Drug Controller General of India (DCGI) to not allow any party to infringe any laws. The court also directed the DCGI not to grant the approval of the alleged drug to the defendants, if the drug is in breach of the patent of the plaintiffs. Moreover, the plaintiffs were asked to make a representation to DCGI making out a case for the alleged drug being in breach/violation of the patent of the plaintiffs.

There was a similar decision[12] of the Delhi High Court in another patent infringement suit *Bristol-Myers Squibb Company & Ors. vs. Mr. J. D. Joshi & Anr.* [CS (OS) 2303/2009] filed by BMS in respect of the same patent IN203937.

There was a significant backlash against the decision as it contemplated to provide for "patent linkage" even though there is no provision under the Drugs and Cosmetics Act, 1940 and Rules 1945 for the same. The controversy surrounding patent linkage finally ended in *Bayer Corporation & Anr. vs. UOI & Ors.* case where the Supreme Court dismissed the Special Leave Petition [SLP(c) No. 6540/2010] filed by Bayer arising out of Bayer's case before the Delhi High Court seeking a direction from the Court to restrain the DCGI from granting marketing approval to the alleged generic drug "*Soranib*" of Cipla which would infringe Bayer's patent.

RE-EMERGENCE OF PUBLIC INTEREST FACTOR

In *Bristol-Myers Squibb Company & Anr. vs. Ramesh Adige & Anr.* [Suit no. CS (OS) 534/2010], a suit filed for the permanent injunction restraining the defendant from infringing the patent IN213457 in respect of the drug "*Baraclude*", the Delhi High Court refused to grant the interim injunction to Bristol-Myers Squibb (BMS) on the ground that patent in suit is a product by process patent and not a pure product patent. It was also held that since BMS failed to bring out the necessary comparative efficacy data in respect of the claimed low dose of "*Entecavir*" (API of *Baraclude*) to meet the requirements of section 3(d) of the Patents Act, 1970, the patent in suit should not have been granted and becomes vulnerable. It was held that the defendants, by raising a credible challenge to

10 The names of defendants in nine other patent infringement lawsuits filed by Roche are as follows: (i) Natco Pharma Limited; (ii) Reddy's Laboratories Ltd.; (iii) Glenmark Pharmaceuticals Ltd.; (iv) Matrix Laboratories; (v) Intas Biopharmaceuticals; (vi) Innova Life Sciences Pvt. Ltd., (vii) Accura Care Pharmaceuticals Pvt. Ltd., (viii) Oncare Life Sciences and (ix) Aureate Healthcare Pvt. Ltd..

11 This is an unreported decision.

12 This is an unreported decision.

the patent in suit, have tentatively shown that the patent has been rendered vulnerable.

The court relied on the judgment passed in *Novartis AG and Anr. vs. Mehar Pharma and Anr.,* 2005(30) PTC 160 Bom, in which the Bombay High Court, while denying the plaintiff interim injunction expressed its concerns for public health.

The Delhi High Court held that since hepatitis B is a chronic infection and its prevalence in India is not in dispute, its medication ought to be easily available and accessible to the patients across the country. It was held that plaintiffs (BMS) are not entitled to interim injunction in view of the fact that plaintiffs import the patented drug "*Baraclude*" and do not manufacture it locally and the price of this drug is almost three times higher than the defendants' product.

Aggrieved by the ruling of the single judge, BMS went in appeal before the division bench. The division bench, however, disposed off the appeal by directing the expedited trial of the suit.

The decision of the single bench holding the patent in suit as a product by process patent was not appreciated as being fundamentally incorrect on account of the fact that the claims of the patent in suit show that it is a product patent, and not a product by process one.

NEED TO ELIMINATE INTERIM INJUNCTIONS

Another worth discussing decision is seen in the case of *Bayer Corporation & Anr. vs. Cipla Ltd.*, [CS (OS) 523/2010] pending before the Delhi High Court. Bayer filed the suit for permanent injunction restraining Cipla from infringing its patent IN215758 in respect of the anti-cancer drug "*Nexavar*" (Sorafenib). This drug was also the subject of controversial patent linkage case *Bayer Corporation & Anr. vs. UOI & Ors.*

The present suit is being seen as a trend setter in Indian patent litigation arena in view of the fact that the Delhi High Court, which is increasingly being recognized as most IP-savvy Indian court, in a significant departure from the standard practice in Indian patent trials had ordered that instead of disposing off the interim injunction application, the present suit be expedited directly to trial and to that effect, also appointed two scientific advisors under section 115 of the Patents Act, 1970, to give their opinion on terms of reference settled with the consent of both Bayer and Cipla. The appointed scientific advisors will be subject to cross-examination by either party. These scientific advisors who specialize in chemistry and life-science have submitted their reports before the court.

The judicial innovation of directing the matter straightaway to trial surfaced perhaps because normally it takes more than six months for the court to decide on the interim injunction application filed by the plaintiffs. It is expected that a rapidly scheduled full trial will be far better and productive in resolving the issues between both parties.

However, the overall progress in this matter does not seem to reap the benefits of not having the interim injunction application disposed off first as the matter is yet to witness some typical procedures followed in a trial like admission/denial, recording of evidence etc.

In an interesting development there is one more patent infringement lawsuit [No. CS(OS) 1090/2011] pending before a different judge of the Delhi High Court between *Bayer Corporation and Natco Pharma Ltd.* in respect of the same patent. In this case the high court has adjourned the hearing on Bayer's application for interim injunction against Natco until the controller of patents renders a decision on the application for compulsory license filed by Natco on the subject patent before the patent office.

This is yet another instance where more than one patent infringement suit in respect of the same patent is pending before two different judges of the same high court. In view of these two pending patent cases, it becomes apparent that there is also a need to have a congruous and consistent patent litigation system in place so as to avoid the potential ramifications of having contradictory findings from two different judges of the same court on the validity of the same patent.

IMPLICATIONS FOR THE MARKET

Interim injunctions being important instruments if decided incorrectly cause enormous losses to both competitors and consumers. Although the Indian legal framework has improved yet the Intellectual Property enforcement in India is quite weak. Following some recent patent cases like *Roche vs. Cipla* where interim injunction was denied, there is a perceptible sense of fright among the global pharmaceutical companies towards the enforceability of their patent rights in India.

The annual report for the year 2009-10 published by controller general of patents, designs & trademarks mentions that the trend of filing of patent applications during 2009-10 witnessed a 6.8% decrease as compared to previous year possibly due to global economic crisis. However, some of the leading patent practitioners observe that there appears to be emerging a correlation between frightening IP ecosystem and a sharp decrease in the trend of filing patent applications in India.

The total number of applications for patents filed in 2009-10 was 34,287 as compared to 36,812 applications filed in 2008-09. This decrease was primarily attributed to a sharp fall in filing from foreign applicants who have been the major filers in previous years.

It cannot be denied that unless the rights of the patentees, acting in good faith, are respected in India, it will go on to hamper the attractiveness of India as a potential market and R&D destination.

PROBLEMS

As discussed hereinabove, patent disputes require both technical as well as legal expertise on part of the adjudicatory body like the courts. Very often it has been seen that patent matters take a very long time to be finally decided by the over-burdened higher courts. Another possible associated reason for this is an un-streamlined procedural system for frequent change in roster of sitting of judges of high courts thereby disrupting the momentum of hearing in a particular patent dispute. Considering the fact that the patent litigation is generally expensive, uncertain and risky affair, the slow pace of the law[13] and court's jitteryness while dealing with patent disputes, may not be conducive for the progress of the technology involved behind the patent.

SUGGESTIONS

Some of the suggestions for restructuring policy to overcome the problems discussed hereinbefore are highlighted as below:

- Eliminate the relief of temporary injunction and let the matter move directly to the trial stage, where the case involves a complicated and evenly poised patent dispute;
- Expedite the trials with minimal adjournment requests allowed;
- Provide a practical framework of procedural law with less technicalities and necessary flexibility;
- Ensure a congruous and consistent patent litigation system to avoid duplication and contradiction of events;
- Establish specialized intellectual property courts with specialized judges equipped with technical expertise and/or reinforce the legal competence of the intellectual property appellate board;
- Avoid the possibility of conflicting decisions by postponing the trial until any post grant opposition and/or revocation proceedings against the subject patent are concluded and
- Appropriately make use of the services of the scientific advisors empanelled under section 115 of the Patents Act, 1970.

13 There is a well known legal principle that "law should take its own course".

CONCLUSION

The landscape of judicial decisions unequivocally tends to prove that interim injunctions are granted very rarely and often tend to delay the speedy progress of the patent infringement lawsuit. As a result there has been felt a need for dispensing with the interim injunction phase and moving to the trial stage directly in view of the fact that the Indian Courts are relatively inexperienced in handling complex patent disputes.

Very often it has been seen that unless the patent in suit is an unscathed one; the patentee will find it extremely hard to get an interim injunction against the infringers. Another crucial factor that has an impact on the possibility of granting interim injunction is whether the infringing product has yet to be launched. The landscape of patent litigation also suggests that there is a need to recognize the importance of quality of patents that reflects the enforceability of patents in a litigation proceeding.

It is by and large expected that the coming few years will be vital as the Indian patent litigation arena has yet to see a reflection of the judicial application of the tenets governing the grant of an interim injunction.

From the Boardroom

Digital health investment opportunities abound, but standouts deliver disruptive change

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I HAVE AN UNUSUAL case for my iPhone. It looks like an ordinary case, but on its back are two electrodes. If I hold the device in my hands or to my chest, the phone is transformed into an electrocardiograph, displaying and capturing in real-time the electrical changes of my heart wherever I may use it.

The device, developed by Oklahoma City-based AliveCor is not commercially available yet and it still must win 510(k) clearance from the U.S. Food and Drug Administration before it can be sold in the United States. Burrill & Company recently led a series A venture round for the company along with Qualcomm Ventures and the Oklahoma Life Science Fund.

AliveCor is an example of the emerging world of digital health that is transforming the way healthcare is accessed and delivered. The term digital health means different things to different people. Alternatively, the terms eHealth and mhealth have been used to encompass everything from electronic health records to iPhone apps that help people count calories.

The convergence of ubiquitous smartphones, wireless Internet, and low-cost monitoring devices, is driving the emergence of this new world of digital health. At the same time, cost pressures on healthcare are creating demand for new ways to not just improve the way patients receive information and care and the way doctors provide it, but fundamentally change the way they interact with each other.

There's much excitement around digital health today because it is seen as a way to address some of the big drivers of healthcare cost, by helping change people's behavior, address the burden of chronic disease, allow for early intervention before health problems become costly to treat, and monitor and treat patients, when possible, without keeping them in a hospital.

For instance, consider Vitality, the developer of GlowCaps, a wireless device that's used to improve patient compliance with drug regimens. The device, which serves as the cover for a vial of medication, flashes when it is time for a patient to take his or her medicine. If the patient fails to do so, it sends a reminder to the patient's cell phone. If the patient still fails to take the needed medication, notification is sent to the prescribing physician and a designated family member. Patrick Soon-Shiong thought it was a pretty good idea. The surgeon and entrepreneur, flush with cash after selling his company Abraxis Bioscience to Celgene for $2.9 billion, announced in February that he was buying Vitality for an undisclosed amount. Vitality said the price represented a 10-fold return on investment to its shareholders.

General Electric and Intel have teamed up to launch a new company called Care Innovations to develop digital health technology to enable independent living for seniors. The venture became operational at the start of 2011. The jointly owned company's focus is to help address some of the

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largest issues facing society today, including the aging population, the growing number of people with chronic conditions, and increasing healthcare costs. The market segments for telehealth and home health monitoring are predicted to grow to an estimated $7.7 billion by 2012.

Then there is WellDoc, which is integrating clinical, behavioral, and motivational applications with the Internet and cell phones, to engage patients and healthcare providers in ways that improve outcomes and reduce healthcare costs. WellDoc's system combines a patient coach, with decision support tools and an expert system. Users can enter their blood glucose readings, medication information, and other lifestyle information into WellDoc's DiabetesManager, which through the use of a clinical analytics engine provides automated, real-time feedback on the patient's specific data. It also shares the information with the user's doctor.

Though there are many issues we consider when evaluating an investment, here are three I think are critical when considering venture investments within the area of digital health. In thinking about these issues, consider Burrill & Company's investment in AliveCor.

The first thing we look for are companies that are driving disruptive change. That means not just making incremental improvements that allow something to be done cheaper, faster, or better, but instead allows something to be possible that wasn't possible before. Under today's reimbursement environment, CMS will only reimburse patients for a two-week study or about $800. Though AliveCor hasn't yet set pricing, we expect it to be at $100 or below. What that means is that a patient can be followed for six months and provide that information to a doctor without worrying about reimbursement.

We want to invest in developers who begin their work with a blank sheet of paper. If someone sets out to build a device with the current reimbursement system in mind — something that addresses a market for an $800 study — they would fail to develop the disruptive change we seek. AliveCor designed its ECG with a consumer electronics philosophy and mindset. The question wasn't, "How complex a device could we build?" Rather AliveCor asked, "How affordable can we make this and still get clinical performance? Can we build something that is reliable and useful and sells for less than $100?" By doing so, it is able to solve a problem everyone agrees exists, but can't solve today.

The second thing to consider is whether the digital health company is leveraging a platform. In the case of AliveCor it is making use of iPhones and Android phones. That means it is getting computing, display, storage, mobile connectivity, and power for free. Building a stand-alone device would be too expensive and time consuming and make the product cost-prohibitive.

That may sound obvious, but consider EPI Life, an ECG phone designed by Singapore company Ephone International that is available in Singapore, Malaysia, and Hong Kong for around $400. It requires an additional monthly subscription for the health concierge service. According to reports, the basic $77 plan limits users to 10 ECGs per month compared with an unlimited upload version at $233.75 bundled with a free handset. AliveCor gets about 90 percent of what it needs by using existing components and at the same time doesn't have to worry if the device is any good as a phone.

The third thing we look for is a disruptive business model. In the case of AliveCor, the company sought to build a device that could sell at a price point that consumers would be willing and able to pay. Rather than worry about how to navigate the reimbursement system, it avoids the need to go through CMS entirely.

There is, of course, another attraction for life science investors. We completed the Series A round for AliveCor in August. We expect a product launch within 12 months of that investment. Unlike traditional biotechnology which is typically involved with drugs, biologics, and diagnostics, often with high development costs and difficult regulatory pathways, digital health represents a confluence of technologies coming together to improve outcomes at substantially lower cost. That is quite compelling.

From the Boardroom

Strategies for collaboration agreements focusing on innovation

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INTRODUCTION

Collaborations focusing on innovation are often born with the conception of a technology, typically as a result of one side's research effort. Collaborations for innovation can also be made through a deliberate process of identifying strategic synergies that should, with appropriate incentives, lead to jointly created technology in the selected area of interest.

The predominant factors motivating the parties to collaborate will heavily influence the agreement structure selected to support the collaboration. If a specific technology was "born" prior to the collaboration, the parties will most likely memorialize their collaboration in an agreement specific to the joint development and commercialization for that technology. In contrast, when the parties are entering the collaboration to stimulate innovation, the agreement is often structured as a master agreement.

Regardless of the agreement structure, there are two keys to a successful collaboration for innovation: (1) effective communication; and (2) balancing incentives.

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1. COMMUNICATION

During the initial stages of the collaboration communication is commonly facilitated by internal champions on each side. These champions believe in the collaboration, drive the process of the negotiation and research, and handle the most important aspects of communication so long as they remain with their organizations. However, personnel and organizational priorities change, so the agreement structure may become critical to effective communication as the collaboration progresses.

The following are several concepts to include in your collaboration agreement to foster communication and mitigate the effect of changing circumstances:

- Require external working groups with business, technical and legal representation. A joint management committee should oversee these groups and issue written progress reports. These efforts are most effective when coupled with internal meetings with key stakeholders.
- The joint management committee may also be a voting entity to allow for gated development via separate project agreements. The benefit of this approach is that it allows for

re-evaluation when more facts are available before commencing the next step of the collaboration.

- Benchmarks and/or staged payments can be structured into the agreement to prompt mandatory discussion points during the collaboration to re-evaluate risks and the level of commitment of the parties.
- While a negotiated point, an assignment and change of control provision that requires prior consultation with the collaborator, and an option to terminate when the new entity or owner is an inappropriate substitute for the original collaborator, protects against the uncertainty of a new entity thereby allowing the parties to invest in the collaboration.
- Effective exit strategies that are not administratively burdensome or financially painful can provide added comfort to the parties if communication falters. The goal should be to have early triggers for discussing the winding-down of the collaboration at least six months prior to the need for termination. For example, termination at-will with the ability to license project intellectual property on appropriate terms (perhaps including background rights where necessary to practice) will provide a path forward if collaboration becomes undesirable. A template license could be attached to the agreement to minimize the number of issues to negotiate thereby decreasing the barrier to executing the license when the communication fails and increasing the likelihood of a judge having specific terms to enable enforcement.

2. BALANCING INCENTIVES

Balancing incentives in the collaboration is easier when the specific facts and scope of the collaboration are known. When a master agreement is used, the parties must dedicate more time in the negotiation to soliciting areas of common interest and aligning interests with obligations and rewards upon completion.

Do not avoid areas of potential conflict. For example, ownership of intellectual property is almost always a negotiation point in a collaboration agreement. With a specific and disclosed portfolio of intellectual property, it may be appropriate to designate the assignee for categories of intellectual property rights arising in the collaboration, especially knowing each collaborator's background intellectual property. In contrast, in a master agreement where the intellectual property is not known, there may be inflexibility on assigning project intellectual property to any party other than an inventor's employer. When that is the case, the parties may negotiate an allocation of rights through licenses: where ownership follows inventorship as determined under U.S. patent law, and each side grants exclusive licenses in the respective field of interest of the parties. Keep in mind that a nonprofit institution often has less flexibility when negotiating ownership of intellectual property due to legal prohibitions against assignment and other statutory or policy requirements.

Allocating the risks and rewards in an agreeable manner increases the likelihood that each side will continue to be able to justify its commitment to the collaboration and supporting the relationship between the collaborators. When the relationship fails, the collaboration often cannot be saved. Forcing the parties to collaborate usually proves ineffective, so appropriate dispute resolution may be the only way to keep a bad situation from becoming worse. There are numerous forms of dispute resolution which should be chosen based on the subject matter of the collaboration and size of the collaborator/collaboration. Mediation or arbitration with the AAA, ICC or JAMS may be specified in the agreement and subject-specific experts are often required.

You increase the likelihood of success in your collaboration by keeping the relationship a focused priority in structuring the collaboration to balance incentives and including terms in the agreement that require the parties to behave in a manner that maintains a high degree of communication throughout the collaboration.

From the Boardroom

Biomarketing strategy and tactics 101: Part I of III

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ABSTRACT

The American Marketing Association defines marketing as the activity, set of institutions, and processes for creating, communicating, delivering, and exchanging offerings that have value for customers, clients, partners, and society at large.[1] According to the Pharmaceutical Research and Manufacturers of America appropriate marketing of medicines ensures that patients have access to the products they need and that the products are used correctly for maximum patient benefit.[2] The most important promotional tools for biopharmaceutical firms are 1) personal selling, 2) advertising, 3) public relations and publicity, and 4) web promotion. Part I of this three-part article focuses on the nature of the biopharmaceutical marketing's four P's, the importance of marketing strategy, the conduct of environmental analysis, and maket segmentation. Part II delves into the processes of targeting and positioning, marketing planning, as well as biopharmaceutical branding. Part III completes the series by focusing on the push and pull promotional strategies, advertising, selling, and biopharmaceutical web and social marketing.

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Keywords: biopharmaceutical; marketing; targeting; positioning; branding; advertising

INTRODUCTION

Professors Neil Borden and Jerome McMarthy identified in the mid '60s a set of company actions influencing the consumer decision to buy a company's goods or services.[3] This set of actions was coined "marketing mix", and was comprised of the now famous four P's, namely product, place, price, and promotion.

Products in the healthcare biotechnology industry are defined as mass-produced goods (or tangible object), in the form of a biopharmaceutical therapeutic medicine (e.g. a pill, capsule, granules, spray, or injection), or a biosynthetic preventive vaccine (usually an injection), or a biotechnological diagnostic test (e.g. home pregnancy tests), that is sold to the public. Price is the amount of money a customer pays when buying a product. However, due to the universally precious nature of people's health and the role nations play in preserving their citizens' health, the price of biopharmaceutical medicines, vaccines, or diagnostics is often supplemented by state / private health coverage, or is so-called "reimbursed" by the states at various percentages of their original selling price. Place is the location where these biotechnology products can be purchased by the customer (at retail locations) or a patient can have them administered (at an out-patient clinic, a hospital, etc.) under medical supervision.

Promotion in the healthcare biotechnology industry is every means of communication used by the biotechnology industry in making its products known to the public, either the physicians who prescribe them, or the patients who use them, or

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even patients and families considering their use. The promotional activities used by biotechnology companies are usually advertising, public relations, word-of-mouth, web activities, and personal selling. Figure 1 depicts the four P's of a biopharmaceutical product.

MARKETING STRATEGY

Biopharma vision, mission and core values

A company's vision is the ideal future state of the company, as desired by the company's top management. In the healthcare biotechnology industry, a company's vision may take the form of any of these examples below:

- We strive to become the top biotechnology company in the world
- We wish to be among the top 10 largest pharmaceutical companies in the world by global sales
- We want to be the world-wide leaders in neurological biotherapeutics

The company's vision needs to be powerful, visionary, and challenging. In doing so, it seeks to motivate its employees, entice its customers, thrill its stakeholders, and align all its resources behind a common goal. Its time horizon is more than ten years ahead, so that it does not re-align too often, and it gives ample time to all employees to focus all their energy and dedication to the achievement of this audacious long-term goal. Figure 2 outlines the components of a company's vision statement. Having set the long-term goal, the company's employees then proceed in a top-down approach in setting functional, divisional, therapeutic area, and territory plans that cover every single company function, from the world-wide to a regional, country, and finally local territory scale. As the table indicates, the company's vision is gradually transformed to an overall strategic plan, and then respective business plans, therapeutic area strategic plans, global and local marketing plans.

A company's mission is a set of business objectives and goals that attempt to bring the company closer to its desired vision. The company's mission has thus been also called its reason for existence, credo, or creed. A typical biopharmaceutical mis-

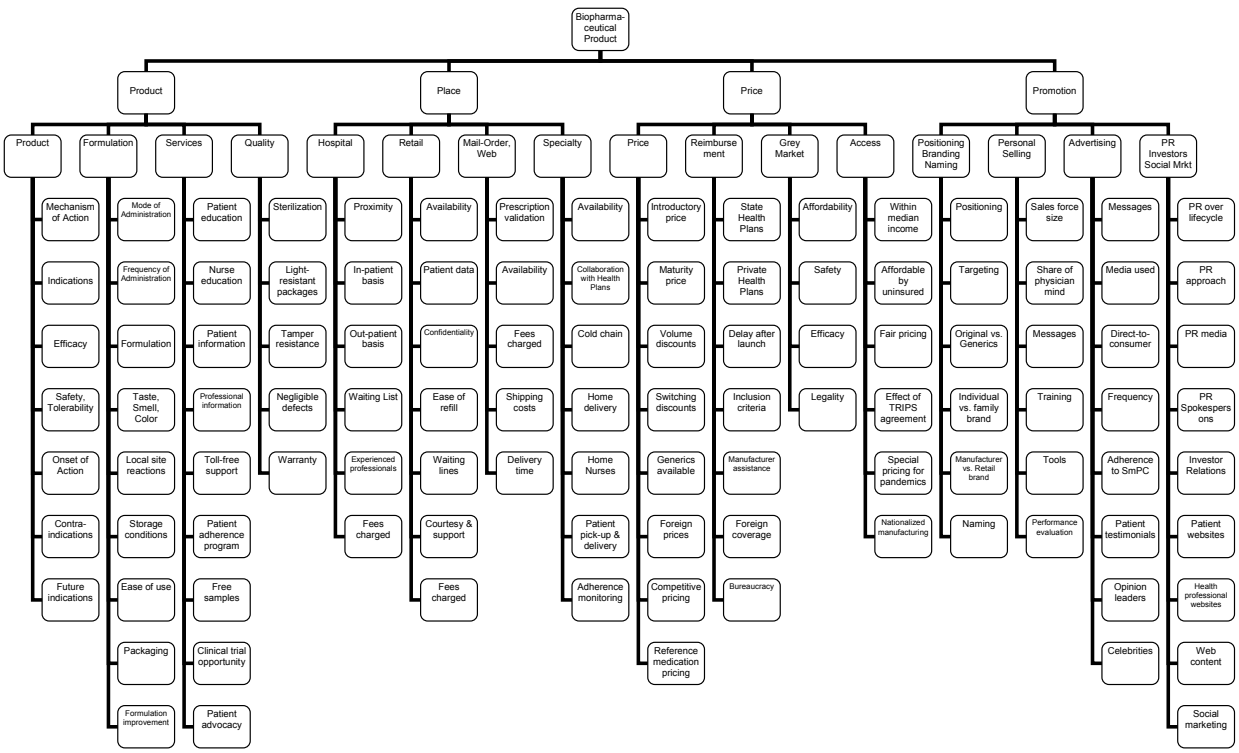

Figure 1: The four P's of a biopharmaceutical product

sion statement would be the following statement: "we wish to become a market leader in human immunology therapeutics, growing our global volume sales by 10%, by the year 2015, harnessing biotechnology in the fields of rheumatoid arthritis, ulcerative colitis, and psoriasis, in order to provide our prescribers and their patients the best in anti-TNF therapies, and thus becoming their partner-of-choice." Figure 3 indicates how a biopharmaceutical company can come up with its mission statement.

We have just mentioned how a company's mission statement is progressively transformed into functional, global and local plans. The whole strategy cascade is further assisted by declaring the company's guiding values, a valuable tool-set of ethical principles, business orientations and aspirations that help guide the whole organization in its everyday performance.

Box 1: Actelion's strategy[4]

Actelion's four Strategic Principles describe the fundamental priorities required to reach its long-term business objective – to become one of the top biopharmaceutical companies in the world:

1. Follow innovation where it leads: Pursue top quality science, internally and externally, balanced with medical need and commercial potential.
2. Retain the value of innovation: Develop projects ourselves and seek partners when necessary to maximize value.
3. Excel in sales and marketing: Expand innovative commercial capabilities to new customers and regions. Manage alliances, putting the product first.
4. Drive core values together: Culture of Innovation, Trust & Teamwork, Open Communication, and Results Driven.

Box 2: Amgen's mission and values[6]

Amgen strives to serve patients by transforming the promise of science and biotechnology into therapies that have the power to restore health or even save lives. In everything we do, we aim to fulfill our mission to serve patients. And every step of the way, we are guided by the values that define us.

Our Mission: To Serve Patients

Our Values: Be Science-Based; Compete Intensely and Win; Create Value for Patients, Staff and Stockholders; Be Ethical; Trust and Respect Each Other; Ensure Quality; Work in Teams; Collaborate, Communicate and Be Accountable.

Strategy Level	Responsibility	Time frame	Objectives	Example
Vision				Top 5 global companies
Strategic plan				CNS and cardiovascular leader in US, Europe, Asia
Business plan				Sales and R&D investments equally in 3 therapeutic areas
Therapeutic area strategy plan				Product X the leading anti-asthma choice by respiratory Drs
Global marketing plan				Intensive distribution, premium pricing, heavy advertising
Local Marketing plan				Detailed marketing mix activity plan for product X in market Y

Figure 2: Biopharmaceutical strategy framework

Alternative names	Role	Example
Mission	Set the starting points	To become market leader in …
Corporate objectives	Give directions	By yearly growing by …
Reason for existence	Unite the people	by the year …
Credo	Define product mix	Harnessing biotechnology …

Figure 3: Developing a biopharma mission statement[5]

ENVIRONMENTAL ANALYSIS

A biopharma's strategic planning process includes four grand steps, namely: 1) environmental analysis (external and internal), 2) market segmentation, targeting and positioning, 3) choosing a segment strategy, and 4) marketing planning and budgeting.

The macroenvironment

The macroenvironment comprises of all societal forces that may affect the company's operations today or into the future. Biopharmaceutical marketers often focus on five or six major societal forces, namely demography, politics, economy, natural forces, technology and culture.

Demography is the study of human population characteristics, for example, size, location, density, age, gender, race, and occupation. These important parameters are closely monitored in the developed world, and one of the most useful monitoring tools is the periodic conduct of a population-wide census. A census attempts to account for every single person in a given country, and may record numerous population parameters, such as birth rate, fertility rate, death rate, life expectancy, education, language, nationality, religion, ethnicity, marital status, and employment. The study of demographic parameters is significant for biopharmaceutical marketing for two critical reasons. First, they give an estimate of market segment size for the products to be marketed. Second, they describe important characteristics of each segment identified that are inter-related to the product characteristics, and thus give an indication of the importance of each segment on the product's marketing. For example, a common demographic segmentation of the population is groups of people born over certain periods of time, such as the baby boomers, or people born en masse following the Second World War between the years 1946 and 1964. This generation will be turning into senior citizens following 2010, a very significant statistic for biopharmas active in neurological diseases often manifesting among seniors.

The political environment is of paramount importance to the biopharmaceutical industry. This includes the national, federal, state, city, and municipal authorities who set all health-related laws, regulations, and decrees, and thus influence almost every aspect of biopharmaceutical marketing. For example the political environment is critical in approving a patent, a clinical trial, a product to be commercially launched, the on-going pharmacovigilance process, the product's pricing, reimbursement, inclusion into formularies, etc.

The economic environment plays another important role for the biopharma industry. First, the relative strengths of national economies play a direct role in stock market valuations and financings, a make-or-break process important for biopharmaceutical research and development. Second, national currency fluctuations play a role in imports and exports, as well as global profitability of biopharmaceutical multinational corporations. Third, the economic power of national governments dictates their healthcare policies, including the pricing of new treatments, the reimbursement of hospital treatments, medicines and diagnostics, as well as the life-long insurance coverage and pension schemes of their countries' citizens. Fourth, the economic power (purchasing power) of a country's citizens plays a significant role in seeking diagnosis and treatment, paying for new medicines, or covering the required co-payment for healthcare products and services they receive.

As far as the natural environment is concerned, a biopharmaceutical company is dependent on the availability of natural resources, such as raw ma-

Box 3: Abbott financial review 2010[7]

In 2010, the U.S. government passed health care reform legislation which included an increase in Medicaid rebate rates and the extension of the rebate to drugs provided through Medicaid managed care organizations beginning in 2010. The legislation also imposes annual fees to be paid by pharmaceutical manufacturers and medical device companies beginning in 2011 and 2013, respectively, as well as additional rebates related to the Medicare Part D "donut hole" beginning in 2011. In addition to a one-time charge of approximately $60 million to reduce deferred tax assets associated with retiree health care liabilities related to the Medicare Part D retiree drug subsidy, the legislation negatively impacted Abbott's performance by more than $200 million in 2010 and that is expected to increase to more than $400 million in 2011.

terials, water, air, energy, and more. In addition, it requires protection and safety from natural disasters, such as hurricanes, floods, earthquakes, tsunamis, etc. Furthermore, it needs to abide to strict regulation concerning the natural environment, for example air pollution, sewage management, crop contamination, accidental cross-breeding from transgenic species, etc.

The technological environment refers to a biopharmaceutical company's access to high-technology academic institutions, highly educated personnel, technology incubators and incentives, IP protection, available IP, new ideas, tools, devices, platforms, and technologies, venture capital and mature stock markets, and more. The biopharmaceutical industry is especially technology-hungry due to the very nature of genetic manipulations needed to produce new therapeutics, vaccines, or diagnostics. It is an explained phenomenon, therefore, that countries possessing highly-advanced technological environments have been the effective beacons for biotechnology advancement, and are also associated with biotechnology IP production and commercialization.

Another aspect of the macroenvironment is the cultural environment, not so much related with fine arts and humanities, but instead the one referring to the common attitudes, values, beliefs, and behavior that defines a country's existence. For example, the attitudes and beliefs toward age and gender, and health and disease, are some of the important factors defining a country's attitudes versus the life-saving products and services of a biopharmaceutical company. Furthermore, the citizens' beliefs on genetic manipulation of the DNA, monoclonal antibodies, diagnostic DNA testing, stem cell research, and transgenic organisms also play a critical role in defining their responses toward healthcare biotechnology. A biopharmaceutical company's future, therefore, is inextricably related to each market's culture, and huge and continuous efforts need to be allocated toward public education, public relations, and web communications for the company's messages to become known and accepted.

Porter's five forces model

A very practical, and by now famous, external analysis tool is based on the five forces' model, originally proposed by Michael Porter of Harvard Business School in 1979.[8] According to this model, the five forces affecting the industry are: 1) industry competitors, 2) new entrants, 3) suppliers, 4) buyers, and 5) substitutes. Let's analyze them one by one.

Industry competitors: This force is described by the number of existing competitors, their respective products, their competitive advantages (product differentiation or lower cost), their market shares, the total market and competitor growth, the maturity of the market and the competitors, the competitor strategies, their alliances, etc. It is also associated with reduced competition (due to competitors falling into bankruptcy or diversifying into other markets), as well as the barriers to exit (for example stock market conditions, government limitations, or patient outcry) when a competitor wishes to exit the marketplace.

New entrants: This force refers to the number of competitors who are attempting to enter the specific market. For a biopharmaceutical company with commercialized products fighting Alzheimer's disease, new entrants could become potential competitors in Alzheimer's per se, or in the greater therapeutic area of neurology. The rate and number of new entrants is related to the existing "barriers to entry". These barriers are existing either due to governmental regulations, or specific market conditions, or characteristics and strengths of the

Box 4: Amgen's marketed products[9]

We market our principal products, Aranesp, EPOGEN, Neulasta, NEUPOGEN and ENBREL in supportive cancer care, nephrology and inflammation. Certain of our marketed products face, and our product candidates, if approved, are also expected to face, substantial competition, including from products marketed by large pharmaceutical corporations, which may have greater clinical, research, regulatory, manufacturing, marketing, financial and human resources than we do. Our products' competitive position among other biological and pharmaceutical products may be based on, among other things, safety, efficacy, reliability, availability, patient convenience/delivery devices, price, reimbursement and patent position and expirations.

incumbents themselves. For example, governmental regulations impose clinical trial, marketing approval, pharmacovigilance, pricing, reimbursement, formulary, and custom duties and taxation barriers. Industry incumbents impose economies of scale, lower cost base, preferential relationships with regulators, prescribers and the media, access to distribution channels, competitive advantages, intellectual property, internal know-how, and therapeutic area expertise. Furthermore, market conditions posing an entry barrier may be access to financing and incentives, exit opportunities through robust stock market exchanges, "buy local" campaigns, or historic barriers.

Suppliers: This is an important force for the biopharmaceutical industry, referring to the bargaining power of industry's suppliers. For biopharmaceutical companies, important suppliers are those providing raw chemicals, or facility constructors, lab tool and reagent providers, contract research organizations (CRO), contract manufacturers, formulation specialists, syringe manufacturers, and others. These suppliers exert a bargaining pressure on biopharmaceutical companies, which is related to the availability of alternative manufacturers, their costs charged, the importance of uninterrupted supply, their desire to forward-integrate (for example a CRO planning to commercialize biopharmaceuticals of its own), and the quality of products and services provided.

Buyers: Biopharmaceutical companies are faced with three different classes of buyers. First, their immediate targets, i.e. physicians prescribing their products. Second, individual diagnosed patients suffering from diseases treated by biopharmaceuticals, often called individual buyers. Third, biopharmaceutical companies often have to convince hospitals, state insurance funds, private insurance companies, or pharmacy benefit organizations (PBOs) to include their products in their critical reimbursement or formulary lists. These buyers are called institutional buyers and also possess a significant bargaining power versus the biopharmaceutical industry.

Substitutes: This force refers to the availability of therapeutic alternatives to the biopharmaceuticals themselves. Substitution may arise from: 1) other branded biopharmaceuticals, 2) branded chemical (traditional) medicines, 3) generic substitutes, 4) diet and exercise, 5) occasionally psychological (non-pharmacologic) support, 6) alternative treatments (e.g. homeopathy, yoga, ancient Chinese medicines, ancient Indian medicines, herbal remedies, meditation, acupuncture, etc.). Although the highly sophisticated technology of biopharmaceuticals, as well as the chronic and severe characteristics of certain indications are not easily substituted or treated by alternatives, the significant level of patients discontinuing their biopharmaceutical therapies due to low tolerance and adherence, makes these patients candidates for alternative (and more "natural") treatments.

STAKEHOLDER AND TREND ANALYSIS

The corporate stakeholder concept

Corporate stakeholders are all those groups of individuals who may affect, or be affected by, the biopharmaceutical company's actions. Stakeholder theory was first popularized by Edward Freeman in 1983, and today is a critical component of a company's strategic management process.[10] The existence of distinct stakeholder groups, their individual needs and wants, their influence on the organization, as well as the means by which a biopharmaceutical enterprise may interact with and manage this relationship for the benefit of both sides is of paramount importance for its long-term success and sustainability.

Who are biopharma's stakeholders?

A biopharmaceutical company stakeholder is any individual or group that can be influenced by, or exert an influence on the company, whether a positive or a negative one. Stakeholders have often been distinguished in: 1) **primary**, that is individuals who are directly affected by an organization's actions, 2) **secondary**, that is those who are indirectly affected, and 3) **key**, that is primary/secondary stakeholders who play a significant role for the organization, either directly or indirectly. Looking into the biopharmaceutical industry, one would quickly identify three major stakeholders, namely prescribers, regulators, and patients.

However, a quick look into Figure 4 would reveal a long list of important stakeholders. For

example, patient families and advocates, primary care physicians, health management organizations (HMOs), nursing homes, pharmacists, social workers, reimbursement funds, national registration and drug organizations, as well as formulary committees, all play an active and critical role in biopharmaceutical industry's regulation, profitability, and sustainability. A thorough identification, characterization, and plan of action for each individual stakeholder category are therefore an integral part of a biopharmaceutical company's strategic planning cascade.

Stakeholder analysis

Stakeholder analysis is the process of identifying each individual stakeholder group, describing their respective role, defining their needs and wants, and predicting their attitude and potential response to a specific action by the biopharmaceutical organization, and managing that response to the benefit of the biopharmaceutical organization. For example, if a biopharmaceutical company plans to launch an innovative and expensive new biopharmaceutical, it needs to identify the potentially positive reaction from patient advocates and assist in having their voice heard by the regulators, while at the same time predicting the objections of a formulary committee and trying to identify ways for potential inclusion and reimbursement. Figure 4 identifies the industry's key stakeholders, and describes their respective roles, needs and critical issues for the industry to manage.

Box 5: Astrazeneca's stakeholders[11]

Health is something that connects us all. In our mission to make a meaningful difference to the world's health, we work closely with governments and regulators, those who pay for healthcare, our partners in industry and academia, and doctors. Through our activities we touch a great number of people's lives and we are acutely conscious of our responsibility to patients and society in general.

When conducting a stakeholder analysis, the biopharmaceutical company executives need to identify the groups involved, what is their reason for existence, what matters, why, and when, and what are the potential consequences for the company. Furthermore, as far as the biopharmaceutical company is concerned, what is their potential sales-impact (upside or downside), how can they be managed, who needs to do what, by when, and at what cost for the organization so that all potential upsides are maximized and downsides are minimized or eliminated, if possible.

Trend Analysis

Completing the first part of their external environment analysis, biopharmaceutical companies then become occupied with what are the expected major trends (societal, governmental, prescriber, patient,

	Patients	Prescribers	Hospitals	Influencers	Financers	Regulators
Who are they	Patient Patient Advocates Patient families	Physicians Non-specialists/ Specialists	Hospitals (State, Private, Military) Clinics HMOs Other	Opinion Leaders Pharmacists Wholesalers Nurses Other	Reimbursement Funds Insurance Companies Employers	Ministry of Health Registration Authority Pricing Authority Patent Office
Needs	Best possible health care Lowest cost Information Choice Privacy Humane treatment Efficacy Safety	Medical rationale Efficacy Safety Tolerability Quality of Life Credibility Practice expansion Information	Increase clientele Increase market share Contain costs	OLs need professional recognition & advancement Healthcare professionals need access to choice Pharmacists need info and protection of profit margin	Protect patient benefits Contain costs	Preserve public health Provide coverage Ensure efficacy & safety Ensure fair pricing

Figure 4: Pharmaceutical environment's major stakeholder characteristics[5]

public) that may affect their strategic planning horizon, and what is their respective expected impact. Having defined these trends, each team then sets about defining internal responsibilities in managing the impact of all major trends, as well as deadlines involved, and resources required to effectively responding and/or adapting to potential marketing environment changes. Figure 5 describes a trend analysis template that may be used by biopharmaceutical industry marketers.

COMPETITIVE ANALYSIS

The competitive analysis process is comprised of knowledge gathering and analysis, competitor identification, strategic rationale analysis (the way each competitor competes), competitive advantage analysis (what makes them unique), and SWOT analysis (their strengths, weaknesses, opportunities, and threats — see below). In addition, product portfolio analysis (their products, price, place, promotion), attribute analysis (customer needs satisfaction), market share and growth analysis, as well as organizational analysis (how big they are, where they are based, functional division, organizational structure, and subsidiaries). The expected outcome of a thorough competitive analysis is the formulation of a robust internal competitive strategy, its implementation, constant monitoring and its adjustment over the planning horizon.

Box 6: Novartis healthcare portfolio[12]

While healthcare remains a growth industry, both positive and negative trends are impacting the way we operate. On one hand, rapid aging of the population, greater access to healthcare in emerging markets and advances in science create opportunities to enhance the lives of patients.

At the same time, an uncertain economy and regulatory reform exert downward pressure. Tensions will grow as healthcare spending outpaces economic growth.

Novartis has a clear vision for how to navigate these pressures to meet changing customer needs and strengthen our leadership over the next five years. Our strategy of focused diversification helps us to fully leverage the changes occurring in our industry, while also balancing risk.

STRATEGIC RATIONALE

A biopharmaceutical competitor's strategic rationale is comprised of their corporate mission (see above), their competitive stance (offensive, defensive, imitator, niche player), their competitive advantages used in the battlefield (product characteristics, price, or cost-base), as well as their chosen image (positioning) in the minds of their customers (see below), and their strategic responses (observed or anticipated) to industry moves (for example how would they react if another biopharmaceutical company reduced the prices of their future portfolio?).

Thorough analysis of a competitor's strategic rationale gives critical insights to every competing biopharmaceutical company. For instance, it reveals their strengths and weaknesses, it predicts their future moves, and it counters their attacks, or maximizes the effectiveness of the strategies chosen to fight them. Figure 6 describes how biopharmaceutical companies analyze their competitors, by rating their organizational and product parameters on a scale of 1 = Lowest to 10 = Highest competitive advantages versus their own profile. Furthermore, as strategic brainstorming continues, a biomarketing core team can come up with

Potential trend	Probability	Impact	Key trends	Type of impact (Volume, Price, Cost)	Size of impact (Upside / Downside)	Effect on segments	Planned action	Action metrics	Responsible	Deadline
TREND A										
TREND B										

Figure 5: Identify important emerging trends for a biopharmaceutical brand[5]

a detailed product head-to-head analysis for their therapeutic area planned for commercial launch (see Figure 7).

INTERNAL ANALYSIS

Resource Analysis

A biopharmaceutical company's resource analysis would not be complete if it did not focus on all three types of resources available, namely tangible assets, intangible ones, and organizational capabilities. A biopharmaceutical company's tangible assets include their land properties, office and laboratory facilities, equipment, reagents and

Box 7: UCB'S strategic rationale[13]

In 2004, UCB was a diversified pharmaceuticals, chemicals and films conglomerate. The transformation of UCB into a biopharmaceutical company, with a development portfolio of small- and large-molecule drugs, began in 2004 with the acquisition of Celltech, the leading British biotech company, and the divestment of noncore businesses in 2005. The acquisition of Schwarz Pharma in 2006 enriched the company's late-stage pipeline, enhancing the company's short- to mid-term commercial potential.

Date / Analyst				
Grading	1 = Lowest, 5 = Average, 10 = Highest			
Aspect	Parameters	Product A	Product B	Product C
Competitor assumptions	New products			
Various				
Positioning	Current			
Various				
SWOT Analysis				
Customer need	Efficacy	5	7	9
Various		8	8	7
Industry competition	Sales volume	5	5	8
Various		8	8	9
Product line competition	Strategy	7	7	5
Various		8	5	9
Organizat competition	Marketing structure	7	8	6
Various		8	8	9

Figure 6: Biopharma competitor analysis[5]

	Product A	Product B	Product C	Product D
PRODUCT COMPARISON				
International Non-proprietary Name				
Other				
CLINICAL DATA COMPARISON				
SIDE EFFECTS				
Hypertension				
Other				
MARKETING				
Positioning				
Other				

Figure 7: Biopharmaceutical head-to-head product analysis[5]

chemicals, raw materials on hand, tissue cultures and test animals, office furniture and supplies, informational technology, communication infrastructure, and more. For a young biopharmaceutical start-up very few of these tangible resources are fully paid-for, while most are leased on a short or longer-term basis.

The respective intangible assets include, first and foremost, its patents, upon which their future product portfolio will be based. In addition to internally created patents, additional patents will have been in-licensed and now belong to the biopharmaceutical company's patent portfolio. Furthermore, several trademarks will by now have been registered, its scientific personnel will definitely be responsible for dozens of trade secrets, while freedom-to-operate will also have been purchased for those missing technologies that are needed for product commercialization.

In addition to tangibles and intangibles, biopharmaceutical companies will also possess certain organizational capabilities that are difficult to match by their future competitors. For example, the companies' founders are all trained molecular biologists and pharmacologists who have a direct in-depth knowledge of the entire R&D process. They also have preferential access to their alma matter's IP portfolio, as well as an impressive scientific publication track record and personal knowledge of the national neurology and immunology medical associations' boards. These are famed opinion leaders with whom they liaise almost daily and plan to use them as future advisors and spokespersons. Furthermore, the company is located at an incubator with superb facilities and shared resources, they have secured exclusivity contracts for their raw materials, they have devised a bioreactor concept that is unique in the industry, and also share a dedication, open communication, camaraderie, and academic atmosphere that makes a biopharmaceutical company an ideal place to work for bright industry scientists and marketers. Taken together, their tangible and intangible assets, as well as their unique organizational capabilities make them an empowered organization that is poised to quickly capitalize on their impressive IP portfolio.

Box 8: Abbott's pharmaceutical portfolio[14]

Humira, Abbott's biologic for six different autoimmune diseases, is approved in 83 countries and treats nearly 500,000 patients worldwide. With the global penetration rates of biologics still low across indications, there continues to be significant potential for many more patients to benefit from treatment with Humira.

Situational analysis

The second component of their internal analysis focuses around the characteristics of the overall healthcare market, their targeted therapeutic area, their unique competitive advantages, as well as every other organizational aspect, and how these characteristics compare with those of the major industry competitors. By identifying and analyzing several of these parameters and comparing them with the competition, a biopharmaceutical company can not only describe their market segment attractiveness, but also their company's position vis-a-vie the competition. Figure 8 provides a detailed example of a biopharmaceutical situational analysis.

SWOT Analysis

Countless models and tools have been proposed to assist marketers in their marketing planning quest. One of the most widely used is the SWOT analysis (stands for Strengths, Weaknesses, Opportunities, and Threats), originally proposed by Albert Humphrey at Stanford University. This analytic process is focused on a given business objective or venture, and analyzes both internal (strengths and weaknesses), and external characteristics (opportunities and threats) that define its probabilities for achievement. For example, a biopharmaceutical SWOT analysis may be associated with the commercial viability of the biopharmaceutical company, or the eventual marketing launch of its leading drug candidate in the United States market. SWOT analysis is a useful strategic analysis tool in biopharmaceutical marketing. It is imperative, that should a SWOT analysis indicate that a given project is not achievable, in a well-thought, objective manner which is validated by all participating organizational functions (R&D, regulatory, marketing, legal), then a different business objective should be pursued instead.

To perform a biopharmaceutical SWOT analysis four essential steps need to be completed. First, a set of pertinent business parameters need to be selected as indicators of strengths, weaknesses, opportunities, and threats. Second the parameters need to be weighted, in order for a final score to be derived. Third, the relevant business segments need to be chosen for analysis. Finally, all business segments are scored, and are compared with each other for viability and a priority rating is derived. Figure 9 describes a basic SWOT model that can be used for a biopharmaceutical SWOT analysis.

As far as the biopharmaceutical strategic parameters to be used as indicators, Figure 10 lists a large number of the most commonly used indicators for S-W-O-T analysis in the industry.

MARKET SEGMENTATION

What is a market segment

The second phase of strategic analysis, includes the analysis of their market segmentation, profiling, targeting and positioning. Before we can start, we

Factor	Market attractiveness	S	M	W	Company position	S	M	W
MARKET								
Size								
Other								
PRODUCT								
PLC stage								
Other								
COMPETITION								
Concentration								
Other								
PROFITABILITY								
Profit								
Other								
PERSONNEL								
Structure								
Other								
OTHER FACTOR								
Team spirit								
Other								

Figure 8: Biopharma situational analysis[5]

(S:Strong, M:Medium, W:Weak)

		Segment A		Segment B		Segment C	
Strengths & Weaknesses (SW)	**Weight**	**Rating**	**Score**	**Rating**	**Score**	**Rating**	**Score**
Parameter A							
Parameter B							
Total	100						
Opportunities & Threats (OT)	**Weight**	**Rating**	**Score**	**Rating**	**Score**	**Rating**	**Score**
Parameter C							
Parameter D							
Total	100						

Figure 9: Biopharmaceutical SWOT analysis[5]

S (internal)	W (internal)	O (external)	T (external)
Best clinical trial program Contact with Authorities Cost-effective Crosses bodily barriers Disease management program Efficacy Fast onset of action Global reach	Complex dosage scheme Lack of disease expertise Lack of financial resources Lack of human resources Lack of technology know-how Limited clinical data Limited premarketing effort Low acceptance of new drug Low prescriber awareness	Changing epidemiology Changing politics Changing world climate Chronic treatment possibilities Co-marketing with others Competitor withdrawals Discovery of new diagnostic Disease treatment guidelines Globalization	Aggressive competitor campaign Competitor tech breakthroughs Competitive clin. trial program Competitive mergers Entry of generics Eroding market share Government bias to competitor Increased regulation Industry rivalry

Figure 10: Common examples of factors used in a biopharmaceutical SWOT analysis[5]

need to give a brief definition of a market segment. A market segment is a group of individuals or organizations (individual or institutional consumers) that have similar characteristics making them have similar needs for products or services.

Let's think of some potential market segments in the biopharmaceutical industry. First, patients suffering from rheumatoid arthritis, in need for a new safe and effective medicine that will improve their quality of life. Second, private medical specialists in rheumatology who are in need for a new medicine to prescribe to their chronic patients. Third, the state health insurance fund covering all state employees, which is in need for a new safe and effective RA medicine, that will be not only financially beneficial in the long-term, but will also reduce morbidity and absenteeism among the state employee patients. Here's some defining criteria that will reduce their confusion from the outset: 1) a market segment is distinguishable from other segments; 2) a segment is homogeneous; 3) a segment responds similarly to a market action, e.g. a medicine's commercial launch; 4) a segment is reachable by a given market action, e.g. a promotional campaign; 5) a segment is commercially meaningful, e.g. a single global patient with limited adherence to prescribed medicines cannot be a viable commercial segment, 6) a segment may appear, change characteristics or disappear, making market segmentation a continuous and evolving process.

What is market segmentation

Market segmentation is the process of dividing a biopharmaceutical market into distinct market segments. As mentioned above, crude market segmentation would suggest the existence of three groups, namely physicians, patients, and institutional buyers. However, by following the segment criteria described above, the patient group could be further sub-divided into the following segments: 1) never diagnosed, 2) seeking the advice of a physician, 3) newly diagnosed, 4) placed on a diet, 5) prescribed a medication for the first time ("pharmacologically naive"), 6) prescribed a new medication ("switching patients"), 7) patients not responding to therapy ("non-responders"), 8) patients not adhering to therapy ("non-compliant"), and more.

There are multiple variables used for biopharmaceutical market segmentation. The most commonly used are: 1) geographical (e.g. country characteristics, population, climate, etc.), 2) demographic (e.g. age, gender, education, income, standard of living, etc.), 3) psychographic (e.g. personality, lifestyle, values, attitudes, etc.), 4) behavioral (e.g. needs, usage, loyalty, adherence, etc.), 5) technological (motivation, attitudes versus biotechnology), 6) pathological (e.g. signs and symptoms, years after diagnosis, relapsing, morbidity, mortality, quality of life), 7) pharmacological (e.g. previously untreated, on treatment, non tolerated, non-adherent, switching, etc.), and others.

It is imperative that these patient segments are all important to a biopharmaceutical company,

Market potential	Ther Area A	Ther Area B	Ther Area C
Potential market size			
Available market size			
Other			
Opportunity	**Ther Area A**	**Ther Area B**	**Ther Area C**
Market growth			
Number of competitors			
Other			

Figure 12: Biopharmaceutical segment analysis[5]

Product	Your Prescribers		Competitor A		Competitor B	
Attribute	**Importance**	**Score**	**Importance**	**Score**	**Importance**	**Score**
Efficacy						
Safety						
Other						
	Your Patients		**Competitor A**		**Competitor B**	
	Importance	**Score**	**Importance**	**Score**	**Importance**	**Score**
Efficacy						
Safety						
Other						

Figure 13: Biopharmaceutical product attribute analysis[5]

and special marketing plans may be created for each one in the future. In general, a biopharmaceutical marketer is faced with four market segmentation steps: 1) segment identification, 2) segment analysis (profiling), 3) segment evaluation (market attractiveness analysis), and 4) segment selection (targeting). We will study these four steps in detail below. First, we will focus on segment identification and profiling, especially among physicians and patients.

SEGMENT ANALYSIS (PROFILING)

Having identified a series of distinct market segments, industry marketers are faced with the task of analyzing these segments in detail, a process called segment profiling. The goal of profiling is three-fold: 1) identify segment characteristics that are pertinent to a given biopharmaceutical product and rate them for importance (e.g. volume market potential), 2) identify product characteristics that are pertinent to the given segment's needs and rate them (e.g. safety, efficacy), and 3) based on steps 1 and 2, rate the market attractiveness of the chosen segment for the given biopharmaceutical product (e.g. primary, secondary, etc.). Figure 12 provides a template for performing a biopharmaceutical segment analysis (Step 1), while Figure 13 gives an example of a biopharmaceutical product attribute analysis (Step 2).

Based on the above two templates, the case is made for the primary market segments to be targeted. A more detailed segment profiling is then performed, where industry marketers attempt to closely monitor today's market characteristics, and further extrapolate these into the future in an attempt to forecast the market segment evolution over the planning period (usually three, five, or ten years ahead). Based on the above primary segment

Box 9: Roche's Avastin sales performance in 2010[15]

Global sales of Avastin (bevacizumab), for advanced colorectal, breast, lung and kidney cancer, and for relapsed glioblastoma (a type of brain tumour), rose 9% to 6.5 billion Swiss francs, reflecting continued positive uptake of the product overall. Sales growth in Western Europe (7%) was driven primarily by continued uptake for breast cancer and improved uptake for colorectal and lung cancer.

	Weight	Segment A	Segment B	Segment C	Segment D
Criteria	1=High, 5=Low	GP	OB/GYN	Paediatric	Oncology
Disease incidence					
Disease prevalence					
Other					

Figure 14: Identifying biopharmaceutical market segment attractiveness[5]

Total population		100%
Potential market	Disease sufferers	20%
	Asymptomatic	5%
Available market	Symptomatic	15%
	Not seeking treatment	5%
Qualified available market	Seeking treatment	10%
	Put under observation	11%
Target market	Treatment compliant	7%
Penetrated market	Receiving biopharmaceutical	3%
	Competitive biopharmaceutical	2%
Our market share		1%

Figure 15: Defining sub-segments of a biopharmaceutical brand's potential market[5]

profiling, marketers can then derive the biopharmaceutical product's global market potential over the planning period, by incorporating even more prescriber-, patient, and product attributes and assumptions.

Identifying a market segment's attractiveness

When biopharmaceutical market segments, for example several disease indications, are profiled in detail, comparisons can be made as far as their respective market attractiveness is concerned. Figure 14 provides a useful market segment attractiveness template for comparing four separate therapeutic indications with each other while Figure 15 provides insight in defining sub-segments of a biopharmaceutical brand's potential market, a basic parameter in identifying a market segment's attractiveness.

The marketing literature abounds with several market attractiveness models in the form of matrices. Two of these, originally proposed by business consultants The Boston Consulting Group (BCG, www.bcg.com) and McKinsey & Company (www.www.mckinsey.com/) are especially well-known in the biopharmaceutical industry, and are shown in Figures 16 and 17, respectively. In the first, products are rated as "stars, cash-cows, question marks, or dogs" for their respective market attractiveness, while in the second the products' market attractiveness (high, medium, low) is plotted versus their respective marketing position (high, medium, low) to give a nine-square product comparison matrix.

Physician profiling

The American Medical Association (AMA) reports 815,000 US-licensed physicians in 2009, belonging to dozens of medical specialties. This group is a definitive market segment for the biopharmaceutical

Box 10: Abbott's pharmaceutical pipeline[16]

- 18 million people have Alzheimer's disease. This figure is expected to double by 2015 as worldwide populations continue to age.
- 100 million women worldwide suffer from endometriosis, a condition that can cause pain and infertility.
- 50 million adults in the United States and Europe have chronic kidney disease, and the number of patients is rapidly increasing.
- 80% of hepatitis C infections become chronic, which can potentially lead to long-term complications.

MARKET GROWTH RATE (Cash usage)	RELATIVE MARKET SHARE (Cash generation)	
	Low	High
High	QUESTION MARKS	STARS
Low	DOGS	CASH COWS

Figure 16: The BCG matrix

COMPETITIVE POSITION Criteria: First-in-class, efficacy, safety, tolerability, onset of action, duration of action, formulation, frequency of administration, contra-indications, company brand, product brand	MARKET ATTRACTIVENESS Criteria: Disease prevalence and incidence, healthcare dollars, pharmaceutical treatment dollars, patent protection, disease awareness, disease diagnosis, in-patient beds, access to care, market growing, reimbursement available		
	High	Medium	Low
High	Invest	Selective Growth	Grow or Abandon
Medium	Selective Growth	Grow or Abandon	Harvest
Low	Grow or Abandon	Harvest	Divest

Figure 17: The GE/McKinsey matrix

industry; however, detailed market segmentation is essential before any biopharmaceutical company embarks on marketing its products and services to the entire group.[17] A simple calculation will verify the importance of physician market segmentation and profiling.

Biopharmaceutical products often target small patient populations (small market segments are called specialty or niche), biopharmaceutical companies are typically small organizations, and the available sales and marketing budgets and organizations are limited. It becomes apparent that physicians need to be carefully identified, profiled, segmented, and the ideal segments to be preferentially focused on, so that the biopharmaceutical companies involved manage to achieve the optimal promotional presence ("share of voice") with every physician involved.

Prescribing physicians can be segmented according to multiple variables, for example:

- Attitudes versus biopharmaceutical companies, e.g. apathetic, hostile, friendly, enthusiastic, collaborative.
- Attitudes versus patients, e.g. remote, strict, communicative, friendly.
- Benefits sought, e.g. efficacy, safety, tolerability, savings, adherence, and formulary.

- Brand loyalty, e.g. only others, only ours, mixed, balanced.
- Brand usage, e.g. light, medium, heavy, and dedicated.
- Disease characteristics, e.g. chronic, severe, debilitating, relapsing, progressive, final-stage.
- Prescriber readiness to prescribe, e.g. unaware, aware, interested, prescribing.
- Product specific, e.g. chemical, traditional, reference, biochemical, revolutionary, experimental, most effective, safest.

Box 11: Amgen's business overview[19]

We maintain sales and marketing forces primarily in the United States, Europe and Canada. We have also entered into agreements with third parties to assist in the commercialization and marketing of certain of our products in specified geographic areas. Together with our partners, we market our products to healthcare providers, including physicians or their clinics, dialysis centers, hospitals and pharmacies. Most patients receiving our principal products for approved indications are covered by either government or private payer healthcare programs, which influence demand. The reimbursement environment continues to evolve with greater emphasis on both cost containment and demonstration of the economic value of products.

Creating a biopharmaceutical product strategy

Having segmented their target physicians with some of the variables mentioned above, biopharmaceutical marketers may then set-out to create targeted promotional strategies geared at satisfying the individual needs and wants of each prescriber group identified and profiled. For example, science-based prescribers may be offered access to clinical trials, inclusion into advisory boards or as trainers and speakers, or scientific journal subscriptions. Therapy-minded prescribers may be offered scientific bibliographies, medical reference textbooks, diagnostic tools and charts, and patient diaries and information to distribute. Finally, economy-minded prescribers may be targeted with patient adherence guidelines, pharmacoeconomic analyses, generic alternatives, etc.

Patient profiling

According to the U.K.'s Multiple Sclerosis Society (MS, www.mssociety.org.uk/), the disease is the most common disabling neurological condition affecting young adults. Around 100,000 people in the UK have MS, of which approximately 20% have benign MS, 15% have primary progressive, and 65% eventually developed secondary progressive disease.[18]

One of the most widely used methodologies for patient profiling includes the epidemiology tree analysis (commonly referred to as "patient flow" analysis). This is a method following every single patient along their disease progression, starting from undiagnosed patients, and moving into those seeking medical advice, those referred to a specialist, those not assigned to therapy, the patients receiving therapy, dropping out of therapy, switching medications, relapsing, worsening, etc. If every single disease probability is plotted on an epidemiology tree, complete with detailed statistics and validated from various sources (medical societies, patient associations, medicines prescribed and consumed, patient hospitalizations, etc.) then a detailed patient profiling emerges.

Armed with epidemiology tree information, biopharmaceutical marketers may create targeted promotional actions tailored at individual segments. For example, for undiagnosed patients a campaigns urging them to visit a physician, for patients on medication an adherence-improving campaigns, for patient families an educational campaign, etc. Let's not forget that biopharmaceutical marketing may depend on occasional market assumptions, but is far from being an abstract and subjective procedure. Instead, it is science-based, depends on continuous prescriber and patient surveys, is validated with multiple inputs, and tries to eliminate subjectivity and bias everywhere these may occur. Besides, the rise and fall of young biopharmaceutical companies, relies on the careful strategic analysis, including market segmentation, targeting and positioning we are studying.

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From the Classroom

The University of Colorado Certificate Program in Bioinnovation and Entrepreneurship: An interdisciplinary, cross-campus model

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ABSTRACT

In keeping with an emerging literature on the role of business education in the development of entrepreneurially-intentioned biotechnologists, this paper describes the actions and experiences of a non-traditional entrepreneurship program that began in the late 1990's. Along the way, it illustrates how a business-centric approach can shift the budding bioentrepreneur's perspective from a product to a market orientation when considering an innovation's commercialization. While the developmental timeline and specific stages of the adoption process for biotechnology-based products vary from traditional consumer or industrial products, there many similarities, foremost is the notion that to be successful the market must perceive significant advantage to the new offering. Lastly, this paper provides thoughts on potentially profitable areas for program expansion and new foci, especially regarding the globalization of biotechnology innovation and international opportunities.

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INTRODUCTION

In the 21st Century, it is imperative that we break down the barriers between intra-university entities as well as between university and industry, so we can develop entrepreneurial scientists and engineers. As emphasized by Friedman, the growing industries around the world, involve the STEM (Science, Technology, Engineering, and Mathematics) disciplines[1]. Scientists and engineers need to understand business principles and our business students need a basic understanding of science and technology. In today's world, we need innovative entrepreneurs, who are adaptable to changing world economies. As Pink states, both left brain and right brain skills are needed. Technical skills with no social, emotional and business intelligence will not lead to success[2].

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While suggestions for changes in business education's role in the development of bioentrepreneurs are few, a small number of recent articles have created the beginnings of a research stream in this area. For instance, working from the premise that the most deficient of bioentrepreneurship's three pillars is "scientific and managerial" talent, Meyers and Hurley present a review of bioentrepreneurship programs in the USA and identify skill sets needed to improve commercial success.[3] In a similar vein, York, McCarthy and Darnold state that there is a lack of the types of business skills needed for successful commercialization of bioscience endeavors and that the development of these skills is often (more out of necessity) a function of experiential than rote knowledge.[4] In other words, being able to "see" situations or issues from an appropriate business perspective is often more critical than knowing about those situations and issues. They suggest that acquisition of these skills is aided by appropriate bioscience entrepreneurship education. Progressing a bit further, Brown and Kant discuss how students, who identified deficiencies in their programs of study, created organizations to aid themselves in overcoming these business-based knowledge deficits.[5] The authors' qualitative research endeavor also suggests that biotechnology researchers often lack core new-business-development skills, especially in the areas of marketing, operations and project management, legal issues, and finance, all required to create a competitive business plan. Together these studies suggest that a deeper, and perhaps formal, understanding of basic entrepreneurial business principles and their application can facilitate efforts at commercializing biotechnology-based innovations.

Using a grounded theory type approach that focuses on the activities at a given institution, similar to that used by Allan et. al.,[6] this paper attempts to build on this emerging literature by examining the actions taken in the process of developing an bioentrepreneurship program at the University of Colorado-Denver, a large western state university (with more than 28,000 students, $375 million in grants, and over 12,000 employees). It proceeds by providing a brief history of the Bard Center for Entrepreneurship program at the University of Colorado Denver, its evolution into bioentrepreneurship education and its plans for meeting future challenges. In the process it describes the program's non-traditional business model, the value proposition it offers its target audiences, its progress in fulfilling its goals, planned future expansion, and lessons learned in the process (and hence tips for other fledgling bioentrepreneurship programs).

STAGE ONE: VISION AND START-UP

The University of Colorado Denver's Business School is a young entity having gained independence from its sister campus in Boulder in 1974. The college has maintained its sister campus' research mission, but given its proximity to local businesses in and around the downtown Denver area, has also developed more of an applied focus designed to aid students seeking masters degrees in business disciplines. In addition to the MBA degree, the college offers Master of Science degrees in the functional areas of Accounting, Decision Sciences, Finance, Information Systems, Management and Marketing. There are over 1,000 graduate students and 1,400 undergraduate students enrolled at the Business School. It is the 9th largest AACSB-accredited business school in the United States among schools that offer a full time specialized masters degree program. The school, which currently operates at 6 different locations, is scheduled to consolidate its separate locations and move to a single 99,000-square-foot (9,200 m^2) building in early 2012.

Responding to requests from students and local business leaders, the college created a center for entrepreneurial education. In 1996, this nascent organization, named in honor of the family that provided the initial endowment, became known as the Bard Center for Entrepreneurship.

The Business Model

While seen as an important element in providing a complete business education, University-based budgetary constraints meant that there would be no faculty lines, staffing support or facilities provided by the campus to develop entrepreneurial education. This meant that, to survive, the center had to implement a non-traditional business model. Endowments from the business commu-

nity covered the facilities and some staffing needs, but faculty would have to be compensated on that portion of student tuition the University allowed the center to retain. Lacking a rostered faculty, but needing to meet AACSB accreditation standards for course coverage by academically and professionally qualified faculty, the entrepreneurship program built its instructional team by getting interested fulltime college faculty to teach on an overload basis and by hiring part-time lecturers from the business community. Given its hybrid faculty, offering a Master of Science degree in entrepreneurship was not viable. Further, it was deemed that entrepreneurship students were more concerned with learning the essence of business startups and less concerned with titular issues. Hence, an educational program was created whereby MBA students could select entrepreneurship as their degree specialization and, upon completion of three classes would receive a certificate of entrepreneurship. Subsequently, this certificate was made available to non-degree graduate students (e.g., students from non-business disciplines). This certification is now identified in the graduate's permanent transcript.

The Value Proposition

Offering an average of 12 entrepreneurial classes per year the program attracts an average of 350 master's level students and awards over 100 certificates per year, making it the most popular MBA specialization at the University of Colorado-Denver. Clearly, business students want to learn about the entrepreneurial process, but the value provided by the program goes beyond formal education. To help students develop critical "soft skills" (York et. al.[2]), the center has an active board of advisors consisting of successful entrepreneurs assigned the task of mentoring students, a popular speaker series, an active alumni association, a venture capital fund administered by students, an incubator to assist student's nascent startup efforts, and an annual business plan competition with prizes worth over $50,000.

STAGE TWO: CONSOLIDATION AND THE BIOENTREPRENEURSHIP PROGRAM

In 2004, the governing entity of the University of Colorado campuses, the Board of Regents, decided to merge the University of Colorado Health Sciences' medical school and related colleges with the traditional schools and colleges (e.g., Arts and Sciences, Business, Engineering, etc.) of the University of Colorado Denver. The resulting institution of 13 schools and colleges, situated in two unique locations, offers 132 degree programs to over 28,000 students. One expectation of this merger is the realization of program synergies across the two campuses.

The Target Audience

Given this consolidation, one area of synergy that the Bard Center envisioned was the integration of entrepreneurship education with a variety of cross-campus disciplines (e.g., dentistry, architecture, engineering, arts and media, and biotechnology). It was hoped that this would enable entrepreneurship education to be accessed by a variety of students, especially in disciplines where a large proportion of graduates start their own businesses or are affiliated with entrepreneurial ventures started by others. Of these collaborations, the bioscience and entrepreneurship initiative was considered the most viable, due to considerable interest shown by all parties, including biotechnology faculty and researchers, business faculty, students, and the center's advisory board. It was envisioned for those interested in starting biotechnology companies, or those with science, business, and engineering backgrounds who wanted to be active in a biotechnology firm's new business creation process.

As indicated in the papers previously cited in the Introduction, there is a lack of understanding by scientists of what makes a biotechnology offering successful, beyond having a product that does what it is supposed to do and that has passed the appropriate regulatory hurdles. Further, one-on-one interviews conducted by the authors amongst 6 prospective bioentrepreneurship students revealed great (and consistent) deficiencies in their knowledge of core business concepts, most importantly finance, marketing, and legal issues. For instance from a financial perspective, many in this

target market did not appreciate the cost and risk imposed by the regulatory process and the importance of securing funding able to cover these costs and support the innovator for extended periods of time. Further, there is the risk that at the end of the development process, having cleared the regulatory hurdles, the product is not viable. Another issue associated with this target market is that its members also lacked a grasp of both industry and market realities. A better product might not be enough to change potential customers' behaviors in its favor and, even if it can, competitors are unlikely to allow the new product to take share away from its products without a fight. Too often entrepreneurs developing innovative new products become product-oriented rather than being market-oriented. Using a market orientation during the product development process can reduce the risk of post-development failure by addressing critical market acceptance and competitive response obstacles beforehand. Given the lack of core business knowledge among this group, it was determined that the core concepts be taught by business school faculty with expertise in these specific areas, not by medical researchers with an interest in business. The pros and cons of this "specialist" vs. "generalist" model are further discussed in a subsequent section of the paper.

The Bioentrepreneurship Program

In discussing conditions favorable to the creation of a bioentrepreneurship program, Back talks about the importance of biotechnology clusters in establishing demand for the program's graduates.[7] Fortunately, a rather large biocluster and life-science eco system exists in Colorado that is fueled by a large number of aspiring bioentrepreneurs.

Colorado's bioscience industry encompasses biotechnology, medical devices, pharmaceuticals and agricultural biotechnology. Colorado companies are engaged in research, development and production in all of these areas. Colorado's world-class university and private-sector research facilities, an educated and highly skilled labor force, a critical mass of existing firms and a strong statewide commitment to the industry provide an environment that is especially conducive to continued growth and excellence in bioscience. The cluster includes about 400 medical device and biopharmaceutical companies, employing 16,000 people. In addition, accelerating Colorado's biotechnology position is the $4.3 billion redevelopment of the former Fitzsimons Army Medical Center into one square mile dedicated to life science research, education and patient care. It is the first of its kind west of the Mississippi, and by far the largest single, integrated redevelopment dedicated to bioscience. The new 217-acre campus of the University of Colorado Health Sciences Center and the 160-acre Colorado Bioscience Park in Aurora anchor the project.[8]

Thus, tremendous demand and hence a great need for bioentrepreneurship education exists in Colorado. Further, another viable market was determined to be MBA students who wish to specialize in the Health Sciences area (over 200 of them). It was thus determined that, even within the Denver Metro geographical area, enough demand existed for a bioentrepreneurship certificate program to be viable.

STAGE THREE: STRATEGIC PLANNING AND MOVING FORWARD

The Bard Center recently underwent a change of leadership and management restructuring. Previously, the two leadership positions involved an academic director and an executive director. The executive director's position was eliminated, replaced by an interim administrative director, who was also academically qualified with a Ph.D. in Information Systems. The new academic director had a Ph.D. in Marketing, and immediately started envisioning the development of the Bard Center brand. The most notable and relevant aspect of these changes was a refocus in the Directors' knowledge base from the sciences to academics. It was anticipated that this seemingly minor difference, a PhD in Biology to a PhD in Marketing / Information Systems with an understanding of science, would have a significant impact on the program's focus going forward. The advisability of this change was in part reflected in the center not moving forward or marketing itself as hoped. As part of this change the center's leaders determined that a more formal strategic planning process would be beneficial.

The Strategic Plan

The planning process involved the faculty, the advisory board, and the business school deans. The faculty concluded that the Bard Center, despite its excellent, albeit migrant, faculty and reputation, had not effectively leveraged its core areas of distinction. These were identified as international entrepreneurship and (after the consolidation of the campuses) bioentrepreneurship, with an understanding that there were synergies between these two seemingly diverse areas. International entrepreneurship made logical sense, as the University of Colorado-Denver was one of only 33 schools awarded the federal CIBER (Center for International Business Education and Research) grant. Further, since the University of Colorado-Denver, especially the Anchutz Medical Campus, had several biotechnology researchers and an excellent world-renowned bioentrepreneurship leader in Professor Arlen Meyers, a synergy between the Bard Center for entrepreneurship and the medical campus naturally existed.

The new Bard Center academic director made it a priority to surmount inter-campus hurdles. The biggest barrier was that the downtown campus and the Anchutz Medical campus had different budgetary systems, making it impossible for the Bard center to pay biotechnology faculty recruited from the medical campus. Innovative thinking by the academic director and the key bioentrepreneurship faculty member helped resolve this problem by getting the graduate school (which is a completely independent school within the system, separate from the business school and the school of medicine) to sponsor the core bioentrepreneurship course taught at the medical campus. The academic director then worked to get the certificate approved by the business school and "officialized" at the registrar's office, and the biotechnology core course approved as an MBA elective. Since all the Bard Center classes were already approved for the MBA program, this process enabled business students to complete an AACSB accredited MBA degree with a specialization in bioentrepreneurship. The result was that the new certificate in "bioinnovation and entrepreneurship" became a reality, starting Fall 2011. This program is unique in that it is one of the very few offered at an AACSB accredited business school open for graduate students of any discipline, certainly the only *certificate* being offered of the kind. Further, it enables MBA students to specialize in bioentrepreneurship making the certificate doubly lucrative to them as they would, upon completion of the MBA requirements, get two official University of Colorado certifications: an MBA degree and a certificate in bioentrepreneurship. Marketing materials (please see appendix for a flyer) were prepared and a grand launch "event" is planned in October 2011.

This new certificate requires prospective students to take a fundamental core class at the Anchutz Medical Campus titled "Building Biotechnologies: Fundamentals of Life Science Technology Innovation and Entrepreneurship" taught by a global leader in bioentrepreneurship education, Dr. Arlen Meyers, and two entrepreneurship classes at the Bard Center. Students will have to consult with the academic director to determine which two courses would be the most suitable for them, given areas of deficiency and ultimate goals.

All the aforementioned classes are graduate level seminars and involve group work and case analyses. An effort is made to form multi-disciplinary groups depending on the makeup of the students in the class. In addition, locally famous entrepreneurs are invited as guest speakers to the classes. Some of these guests are members of the advisory board of the Bard Center.

Competitive advantages and threats

As part of the strategic planning process and to help determine the size of the market for the bioentrepreneurship certificate program, the academic director assigned a research team to conduct a market research project to determine the core strengths, and weaknesses of the endeavor, as well as the target areas for future promotion. While the study is ongoing, preliminary analysis identified the following:

Strengths:

1. Unique: only AACSB accredited bioentrepreneurship certificate program in the world;
2. Tremendous market need in the Denver area;

3. Only 3 graduate courses required to get a certificate, not the 10 to 16 courses, typical of a master's program;
4. Certificate appears in the student's official transcript;
5. Taught by world-renowned bioentrepreneurship faculty;
6. Low risk;
7. Tailored to each student's needs and goals;
8. Low cost; only about $4000 for the entire certificate program (often further reduced by scholarships).

Weakness:
1. New program has not yet developed brand equity;
2. Focus is on the local market;
3. Lacks the gravitas of a true master's degree.

Opportunities:
1. The market for bioentrepreneurship education is global and expanding;
2. If the certificate can be offered globally, demand will be unprecedented;
3. The certificate can help enhance the Bard Center's reputation as a global entrepreneurship center;
4. The certificate can attract large scale donations and endowments.

Threats:
1. Can potentially be emulated by other schools with strong biotechnology programs;
2. Other schools may be able to offer a similar program at lower cost.

STAGE FOUR: IMPLEMENTATION AND FUTURE EXPANSION

The aforementioned SWOT analysis, while preliminary, does suggest that the Bard Center must capitalize on the uniqueness of the certificate program, especially the fact that students only need to take 3 courses to get an official graduate certificate from the University of Colorado. This opens up the market to students who otherwise could not afford to spend the time and the money to pursue a master's degree in bioentrepreneurship. It is contended that most bioentrepreneurs care less about the titular nature of the degree per se, and more about quickly learning the basic concepts necessary to start or grow their entrepreneurial ventures. Hence, a meaningful certificate program, customized to their particular needs, is likely to be more to their liking than a degree program. The support and mentorship available from the Bard Center's Board of Advisors, which includes experts in the realm of finance, marketing, and law, will make the experience unique for the students. Further, students can participate in the Bard Center's business plan competition and also qualify to seek financing through the center's venture fund. Finally, students can conceivably complete all the certificate requirements in one semester.

Given this, and ever growing global demand, it is imperative that the center expand the certificate offerings globally. There are two ways in which this can be accomplished. First, the certificate can be offered online. This is theoretically the easiest and also the most convenient way to open up the program to larger, perhaps even global, audiences, especially given that the Bard center already offers several of its courses online. However, the nature of the core bioinnovation class, with its hands-on focus, may make it difficult to translate effectively to the online platform. Further, students often learn much from speakers who share their entrepreneurial experiences, both positive and negative, and this experience is hard to replicate in an online format. Finally, support from mentors and participation in the business plan competition is more difficult to accomplish in the online format, especially to non-local students.

Second, the core class can be offered in several countries. Indeed, over the summer, it is quite conceivable that Professor Meyers travels to European and Asian destinations and offers the course in an intense 3-week session. This would expose foreign students to University of Colorado classes, and also serve to enhance the reputation of the Bard Center globally. Students could then take the entrepreneurship classes online, and then finally visit Denver to get their certificate and participate in a capstone project or the business plan competition. Once again the cons of online education partly manifest themselves here as well.

Finally, the Bard Center can partner with other schools to give credit to students who have taken the equivalent of the core class elsewhere, as long as they participate in at least one or two classes at the Bard center. Details of such a collaboration will have to be worked out individually with these other schools.

DISCUSSION AND SUMMARY

The previous account described a new bioentrepreneurship certificate program launched by the Bard Center for Entrepreneurship at the University of Colorado Denver, despite its non-traditional academic model and its business school (not medical school) affiliations. The intention is to encourage others considering a foray into bioentrepreneurial education at their institutions to proceed with the planning process even if all of the traditional resources are not available. Viable educational programs take many years to become recognized entities and the Bard Center, using a non-traditional approach, is hoping to soon leapfrog into the class of successful entrepreneurial programs. There are two realities worthy of further discussion associated with enacting a non-traditional approach. One is that it has provided considerable administrative flexibility. The other is that it has limited development of academic stature, an issue further complicated by giving provenance to the business school.

Traditional vs. non-traditional approach to entrepreneurship and bioentrepreneurship

Does the non-traditional approach fit entrepreneurship and bioentrepreneurship better than a traditional model with dedicated faculty and departments? The non-traditional entrepreneurship program at the Bard Center has no faculty to call its own, but rather borrows faculty from individual departments including (now) biotechnology. The financial model is based on the tuition dollars that the center is allowed to keep (around 75 percent), augmented by endowments and donations by community members. These monies are then used to finance the center, e.g., pay the rent, the staff, the faculty, and sponsor any events (such as the business plan competition).

The main advantages of the non-traditional model are first, faculty members are paid on an overload basis and hence have the opportunity to supplement their base pay. The compensation structure offered by the Bard center to the faculty is generous, and often exceeds the overload salary that their home departments would offer. Thus the center is able to attract the very best faculty. Second, the center has a greater control of where revenue dollars are spent and has independence in sponsoring events without the approval of a larger, bureaucratic authority, as long as reasonable financial solvency is assured.

The primary disadvantage of the non-traditional model is that tenure-track professors have little incentive to conduct topical research, since their research expectations, especially with respect to tenure and post-tenure decisions, are aligned more closely with their home departments. While faculty do get credit for publishing in the entrepreneurship field, the weight assigned to such research may not be quite equivalent to the weight assigned to research in their core area of specialization. One way to surmount this problem is to offer faculty grants for conducting research in entrepreneurship. Further, a realization campaign must be initiated to convince faculty that entrepreneurship research does not have to be at odds with their core area of study; thus for example, a marketing researcher could well conduct a study on marketing issues associated with small business, and could thus get credit for research in both areas.

Specialized vs. generalized approach to entrepreneurship and bioentrepreneurship education

Are bioentrepreneurship programs best taught at medical schools or business schools? Should courses be taught by medical faculty or business faculty? The consensus among the faculty and the academic director of the entrepreneurship program is that Bard center must adopt a specialist approach, with the realization that the best teachers are those that specialize in their narrow field of study. Thus a faculty member teaching, say, marketing, typically will hold a doctorate degree in that area, or would otherwise be professionally qualified with several years of experience in the field. The advan-

tages of this approach are that rigor, quality and usefulness of the material to the students can be maintained. With this approach, the core bioentrepreneurship course is taught at the medical campus by Dr. Arlen Meyers who is a global leader in biotechnology education and an expert in the area. The business courses are then taught at the Bard center, by dedicated business faculty. One possible disadvantage of this approach is that the business faculty are less able to use biotechnology examples in class, since their knowledge of the biotechnology field is limited. This gap must be bridged by the selection of guest speakers from the biotechnology field, biotechnology cases, and the invitation of industry leaders in the field for speaker events.

To recap, the Certificate Program in Bioinnovation and Entrepreneurship at the Bard Center for Entrepreneurship at the University of Colorado, a collaboration between our Business School and Graduate School, was created to take advantage of local strengths using a business model that is unique to our campus. As this has been (and continues to be) a learning experience, we can offer the following suggestions to those with limited financial resources who are interested in creating such a program:

1. Create a program that satisfies a defined need and that is structured to be sustainable given local conditions and administrative barriers.
2. Be sure the program is perceived to create enough value to justify the time and expense of taking it.
3. Aggressively market the program to interdisciplinary students in science, engineering, dentistry, healthcare professionals, law, and business students.
4. Prototype smaller offerings before jumping to major programs. Demonstrate student interest and demand and build on the success.
5. Create a business model that will cover administrative costs and faculty salaries and will build revenue streams to expand the program.
6. Bioentrepreneurship is a global discipline and elements of international business and entrepreneurship could be integrated into the program.
7. Education is not enough to assure student success. In addition, graduates need experience provided by knowledge transfer and exchange programs with industry, mentoring, strong internal and external networks, and career development support.
8. Incentives are needed to reward innovative faculty for participating in the program and to entice them into conducting appropriate academic research.
9. Entrepreneurial faculty should be recruited and developed for participation in bioentrepreneurship education programs.
10. Faculty should share their domain expertise and life science courses should be incorporated into standard business school courses at the Masters level.

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APPENDIX

PDF flyer available at: http://www.ucdenver.edu/academics/colleges/business/about/Centers/bard/Education/Pages/Certificate.aspx

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ABSTRACT

UK and European content is compiled and written by Bird & Bird LLP, an international law firm which advises Life Sciences clients on:

- **licensing intellectual property and know-how**
- **R&D agreements and other commercial contracts**
- **clinical trials**
- **regulatory issues**
- **risk management**
- **private equity, venture capital, joint ventures, strategic alliances, mergers & acquisitions and stock exchange listings**
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This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought.

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PATENTS COURT RULES ON BIOTECHNOLOGY DIVISIONAL PATENTS DISPUTE

On 5 July 2011 Arnold J gave judgment in the case of MedImmune Limited against Novartis Pharmaceuticals UK Limited and Medical Research Council ("MRC") before the Patents Court. The judgment extensively reviews many of the issues encountered in biotechnology patent disputes.

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Background

MedImmune (formerly Cambridge Antibody Technology) and MRC (joined as a Defendant rather than as a Claimant because it took no part in the proceedings) were joint proprietors of two divisional European Patents (UK) 0774511 ("511") and 2055777 ("777") (together, "the Patents"). The invention disclosed in the patents consisted of a particular technique (phage display) for selecting a binding molecule of interest (such as an antibody) from amongst a potentially large population of other binding molecules. MedImmune alleged that Novartis (the First Defendant) had infringed the Patents by sales of the pharmaceutical product ranibizumab, sold under the trade mark Lucentis, which is an approved treatment for the eye condi-

tion known as wet age-related macular degeneration. Novartis disputed infringement and counterclaimed challenging the validity of the Patents.

The Skilled Person

Following a comprehensive introduction in his judgment into the science and technology behind the Patents, Arnold J commenced his discussion of the law by identifying the skilled person (here a team of people), focussing on the required degree of specialisation of the team in the field of antibody engineering. The Judge referred to Jacob LJ's discussion in *Schlumberger Holdings Ltd v Electromagnetic Geoservices AS* [2010] EWCA Civ 819, [2010] RPC 33 (which applied the reasoning in *Dyson Appliances Ltd v Hoover Ltd* [2001] EWCA Civ 1440, [2002] RPC 22) and held that the Patents were addressed to a team of scientists with differing backgrounds in areas such as immunology (in particular antibody structural biology), molecular biology and protein chemistry, but with a common interest in antibody engineering. It was reiterated that the notional skilled team must be deemed to lack inventive capacity and therefore a distinction must be drawn between routine experimental work not requiring invention and scientific research which does require invention. This was consistent with the EPO TBA decision in T 500/91 'Biogen II' where it had been stated that "the average skilled person operated at a practical level, and the technical development normally expected of him did not include solving technical problems through scientific research".

Expert Witnesses

The Judge considered in much more detail than is usual in such cases the duties and responsibilities of the expert witnesses. Arnold J explained that the nature of patent cases typically meant that experts had little or no prior experience of this role and emphasised that the lawyers who instruct expert witnesses bear a heavy responsibility for ensuring that an expert witness is not put in a position where he can be made to appear to have failed in his duty to the court. The courts should also be cautious of criticising an expert witness for omissions from their report unless it is clear that the fault lies with the expert and not those instructing him. This case provides important guidance as to the approach that lawyers should adopt in instructing expert witnesses and emphasis the importance of ensuring that the expert report is drafted in a manner as to accurately reflect the way the expert was instructed by the lawyers, and in particular the order in which the expert was shown the documents.

Priority

MedImmune conceded that if the claims in the Patents could not properly claim priority from the third of the priority documents they were invalid. Reference was primarily made to the judgment by Arnold J in *Intervet UK Ltd v Merial* [2010] EWHC 294 (Pat), which both parties agreed was an accurate summary of the relevant principles relating to priority. Accordingly, a claimed invention will be entitled to priority from an earlier application, if it is supported by matter disclosed in the earlier application. In the present case Arnold J accepted Novartis' argument that claim 8 of 511 and claim 1 of 777 were not entitled to priority from the third priority document due to differences in disclosure, particularly in terms of scientific content. Applying *Abbott Laboratories Ltd v Evysio Medical Devices plc* [2008] EQHC 800 (Pat), [2008] RPC 23 the Judge concluded that the third priority document had not as a whole disclosed, directly and unambiguously, information to the skilled person that was in the claims of the Patents that were in question.

Obviousness

Despite the fact that the priority finding rendered both Patents invalid, the Judge went on to consider the obviousness attack in the event that they could properly claim priority, applying the approach established in *Pozzoli v BDMO SA* [2007] EWCA Civ 588 (a reformulation of the classic *Windsurfing* test). Arnold J focused his assessment of obviousness on two pieces of prior art. The first was a pa-

per referred to as "Parmley & Smith" published in 1988. The Judge considered that the Patents were not obvious over the published paper because it did not provide the skilled reader with an opinion that there was a reasonable expectation of success within a reasonable time frame, because of a lack of information as to matters such as infectivity, breakdown and folding of the antibody fragments (applying the principles established in *Condor Medsystems Inc v Angiotech Pharmaceuticals Inc* [2008] UKHL 49, [2008] RPC 28; Biogen/Hepatitis B [1995] OJ EPO 627) . This decision was consistent with that of the Opposition Division concerning 877.

The second piece of prior art was a talk delivered by a Professor Smith at a conference in 1990. The Judge deemed that the talk provided a sufficient enough explanation to make it obvious to try the techniques claimed in the invention and thus the skilled team would have believed that there was a reasonable expectation of success within a reasonable time. Arnold J based this decision on the fact that Professor Smith, displaying a consistently positive and encouraging tone, demonstrating his underlying confidence in success, had explicitly proposed carrying out the claimed invention. He furthermore addressed the concerns raised in Parmley & Smith, put forward a number of solutions to potential problems and provided reasons as to why he considered nevertheless that the experiment was worth carrying out. His decision as to this was in contrast to that of the Opposition Division who had rejected the allegation that 877 was obvious over the talk on the basis that the contents of the oral disclosure had not been sufficiently substantiated.

Insufficiency and Added Matter

The Judge also considered and rejected attacks of insufficiency and added matter. As to former the attack was on the broad scope of the claims and the judgment reviews in considerable detail the UK and EPO case law on this issue, which has long troubled the English courts, particularly in biotechnology cases. In the light of that review he held that the invention disclosed in the Patents was a principle of general application that did not depend on the precise identity of the binding molecule employed, and so the insufficiency attack failed.

Infringement

The claims asserted to be infringed by the production of ranibizumab were to the production of binding molecules (such as antibodies) within a recombinant system into which nucleic acid isolated from particles selected by means of the claimed phage display technique had been inserted. Based on his construction of certain scientific phrases in the claims that described how the phage display technology was employed (taking into account the specification, applying the principles established in *Virgin Atlantic Airways Ltd v Premium Aircraft Interiors UK Ltd* [2009] EWCA Civ 1062, [2010] RPC 8), and on the balance of probabilities, the Judge held the process of production of ranibizumab did not fall within claim 5 - 8 of 511 or claim 1 of 777 and therefore there was no infringement by Novartis.

Despite this finding, the Judge then went on to consider, in the event that he had incorrectly construed the claims, whether ranibizumab, which was manufactured in the USA, was obtained directly by means of the patented process in claim 8 of 511 and claim 1 of 777, and so, according to section 60(1)(c) 1977 Act its import into the UK would infringe. This involved detailed consideration of the case law on this section and the leading case under it, *Pioneer Electronics Capital Inc v Warner Music Manufacturing Europe GmbH* [1997] RPC 757. Novartis in effect argued that it did not infringe because the invention, if any, lay in the use of the phage display aspect of the claims and that it was only as a result of adding a conventional manufacturing process (production in a recombinant system) that MedImmune were able to allege infringement. Although he accepted that this was an attractive argument Arnold J rejected it because the case law that bound him was expressed in terms of how the claims were drafted rather than what was the inventive concept. Thus he con-

cluded that if ranibizumab had been produced by a process falling within claim 8 of 511 and claim 1 of 777, it would be a product obtained directly by means of that process. He also went onto consider Novartis' further argument, based on Article 8(2) of the Biotechnology Directive, but held that Article 8(2) could not apply to the relevant claims because the processes claimed by claim 8 of 511 and claim 1 of 777 were not processes that enable a "biological material" as defined in the Biotechnology Directive to be produced.

Conclusion

This case provides a thorough review of many aspects of current English patent case law and discusses some interesting questions, particularly in relation to "claim scope" insufficiency and the issue of when a product is obtained directly from an infringing process. It also provides extensive guidance as to the duties of both experts and their lawyers have during the presentation of expert evidence, and from which lawyers in future will stray at their peril.

EMA GIVES FIRST POSITIVE OPINION FOR A PAEDIATRIC USE MARKETING AUTHORISATION (PUMA)

Regulation (EC) No. 1901/2006 (the Paediatric Regulation) sets out the incentives for applicants complying with the paediatric investigation plan (PIP) which is intended to provide health care professionals and patients with information on the safe and effective use of medicines in the paediatric population.

The incentive for authorised products no longer covered by patents and supplementary certificates is a new type of marketing authorisation, called the Paediatric use Marketing Authorisation or PUMA. Although the provisions in the Paediatric Regulation covering the PUMA (Articles 30 and 31) came into force on 26 July 2007, the first positive opinion for a PUMA was given by the CHMP in June 2011.

The PUMA is for a product with the brand-name Buccolam® which contains the active ingredient midazolam. The applicant ViroPharma SPRL has developed a paediatric formulation for prolonged, acute, convulsive seizures in children aged from 3 months to 18 years. In return for undertaking the clinical studies in children ViroPharma will obtain "8 + 2 + 1" years' data exclusivity once the Marketing Authorisation is granted.

Midazolam is also the active ingredient in the Roche product Hypnovel® which has been authorised in the UK since 1984 and is used for sedation e.g. as a pre-medication before anaesthesia.

The positive opinion for Buccolam® has taken under two years from the approval of the PIP by the Paediatric Committee (PDCO) on 11 August 2009. The Marketing Authorisation application was submitted on 22 September 2010 and had an active review time of 210 days. The positive opinion of the CHMP was given at its meeting on 20-23 June 2011.

The EMA states that another 25 applications for PIPs for PUMAs have been received and seven opinions have been given by the PDCO.

EU: REVISION OF EMA QUALITY GUIDELINE REGARDING BIOSIMILARS

On 7 February 2011 the EMA released a concept paper for consultation on the revision of the quality guideline on Biosimilars (Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues, EMEA/CHMP/BWP/49348/2005).

The guideline addresses what steps should be taken to show quality during the demonstration of comparability for Similar Biological Products containing recombinant DNA-derived proteins. It particularly provides guidance on:

1. the manufacturing process;
2. differences in impurity profiles and product-related substances;
3. the choice of the reference product; and
4. the analytical methods and procedures used for the comparative testing.

The current version of the guideline addresses the comparability exercise of the biosimilar against the reference product but not the comparability exercise for manufacturing process changes, either during development or post-authorisation. Since the guideline was published, this has been recognised to as an area where guidance is necessary. Changes to the manufacturing process for both the reference products and the biosimilar products are frequent, and such changes can have a significant effect on the quality profile. Therefore, as the quality profiles of the reference and biosimilar products evolve, the results of the initial comparability exercise between the two may no longer be accurate.

The EMA's Biologics Working Party has therefore recommended in this concept paper that the current guideline be revised to ensure that the evolution of the quality profiles of both reference products and the similar biological medicinal products is captured throughout their respective lifecycles.

The deadline for comments on the concept paper EMA was 31 May 2011. It is anticipated that the draft revised guideline will be released for consultation in the last quarter of 2011.

A potential development from this recommended revision may be a step towards strategic manufacturing process revision by manufacturers of original reference products, in order to increase the comparability burden that rests on the manufacturer of a biosimilar at present.

UK PATENT BOX PROPOSALS

On 10 June HM Treasury published a consultation document on a patent box in the UK. Broadly speaking there is to be an optional 10% tax rate on patent profits (including those arising on sale of a patent) in the UK arising after 1 April 2013. This is to be achieved by a tax deduction in the corporation tax return of the relevant company.

It was initially proposed that the regime should apply to patents commercialised after 29 November 2010. However, the Government is now instead consulting on whether to apply the regime to all patents (whenever first commercialised) but phase the benefit of the regime in over a 5 year period. Therefore 60% of the benefit will be available in 2013/14 and 100% will be available by 2017/18.

The regime is to apply to worldwide income relating to qualifying patents. It is initially proposed that qualifying patents are to be those granted by the UK Intellectual Property Office and the European Patent Office. The regime will also extend to supplementary protection certificates which extend such patents as well as regulatory data protection and plant variety rights. To benefit from the regime the relevant company needs to have legal ownership of the patent or an exclusive license to exploit a patent (although such licence can be limited by territory or field of activity provided it procures market exclusivity). Interestingly a company which has full beneficial ownership of patents without legal title or an exclusive licence would not seem able to qualify on the basis of the current condoc.

The rationale for restricting the benefit to UK IPO and EPO patents is that these have been "independent validated as innovative and useful". Additionally certain other regimes include a wider scope of inventions which may be patented (eg business models). The Government is, however, consulting on bringing other patents into the regime.

A requirement of the regime is that the company claiming the benefit of the regime will need to remain actively involved in the ongoing decision making connected with the exploitation of the patent. In addition the company or another group company must have performed significant activity to develop the patented invention or its application. In this respect account will be taken of management of risks as well as R&D activity – although it is specifically stated that subcontracted R&D will not necessarily prevent a group from meeting the requirement. It remains to be seen how the group provisions will work in detail without draft legislation (eg does one look at the group relationship at the time of the development activity or at the time of making the claim). Groups should therefore be careful when looking at structuring and post

structuring M&A activities to ensure that they do not lose the benefit of the regime in respect of target companies.

Qualifying income under the regime is to include royalties and licence fees as well as income embedded in patented products. The focus of the regime is on products as this should allow companies to calculate profits from embedded patents more easily. The regime will apply to all income from a product if it incorporates at least one invention covered by a current valid qualifying patent. The incorporation of the patent must be commercial and not simply to benefit from the regime. In this respect the consultation document refers to "parts, components or separate items...aggregated for sale" and which "constitute a single composite product in which they are functionally interdependent". So in this respect a patent in a car radio is unlikely to make the whole car qualify, whereas a patented product in the engine should make the car qualify. On the definition in the document, a patented invention in the car wheel would seem to make the whole car qualify. It will be interesting to see if the final draft legislation is as generous in this respect.

As well as the products themselves spare parts (which could potentially cover consumables such as ink cartridges for printers) should be covered by the regime.

Patents used in industrial process are not covered. However, it should be noted that companies would be allowed to "divisionalise" such that a deemed division of the company would be treated as licensing such process patents. The royalty income in this division should then qualify under the rules. Divisionalisation will be mandatory in some cases and in others will not be available. It is not entirely clear yet as to the boundaries of the rights and obligations to divisionalise in this respect.

The regime will apply from date of grant of a patent. However, once a patent is granted it will be possible to look back to the date of the application (up to four years) and obtain a benefit for any income in such period. The benefit is however taken in the tax year in which the grant is made.

To avoid complex transfer pricing issues as to the level of income that relates to patents, a more mechanical formulation is suggested whereby patent box income is calculated as follows:

1. Calculate the profit attributable to qualifying income. This is achieved by allocating profits and expenses pro-rata between qualifying income (i.e. from patents/patented products) and non qualifying income
2. Deducted from this profit is the profit that the company would have made without the valuable IP. It is suggested that this "routine profit" is calculated by applying a mark up of 15% on costs. However certain costs are excluded from this calculation. Notably costs of outsourced supplies, inventory and licence fees. It is not clear whether amortisation of capital expenses is subject to the mark up or not. The "residual profit" which arises after deduction of the "routine profit" is what goes forward to stage 3 of the calculation
3. Finally, the profit from patents is separated from the profit from other valuable IP. As a measure of this it is suggested that the profit is split pro-rata according to the level of R&D spend against marketing spend. The amount allocated to the R&D side is then subject to the patent box.

   It is envisaged that losses in the patent box should effectively be used against current year non patent box profits if any. If that is the case they would be carried forward to reduce future patent box profits. This in turn would increase future non patent box profits and therefore recoup the additional tax deduction obtained in the year of first offset.

As always, it is proposed that anti-avoidance rules may be required to avoid manipulation of

the rules, eg by artificially including patented inventions in products, artificial manipulation of income and expenses and avoiding restrictions on losses through intra-group transfers.

The patent box must be seen in light of other Government developments which are making the UK's corporation tax regime significantly more business friendly. As well as a reduction in corporation tax rates to 23% by 2014/15 and the recent dividend exemption rules, the Government is also consulting on the CFC rules with further proposals on this imminent.

COURT OF JUSTICE JUDGMENTS IN *SYNTHON* AND *GENERICS* SPC REFERENCES

On 28 July 2011, the Court of Justice of the European Union handed down its decision in *Synthon v Merz* (C-195/09) and *Generics v Synaptech* (C-427/09).

Summary

The Court of Justice held that medicinal products placed on the market within the Community prior to having obtained a marketing authorisation in accordance with Council Directive 65/65 and, in particular, without undergoing safety and efficacy testing, are not within the scope of Regulation No 1768/92 and may not, therefore, be the subject of an SPC.

Background to the Synthon reference

Merz had been marketing memantine (Akatinol) in Germany since before 1 September 1976 in accordance with the national system in force at that time. The continued placing on the market of memantine was authorised on the basis of Article 3(7) of the German AMG 1976 (the national medicines act). In 1983, Merz was also granted an authorisation in Luxembourg to place memantine on the market, on the basis of the earlier German authorisation. It was admitted that both authorisations were granted without carrying out the product efficacy and safety tests required under Directive 65/65. In April 1989, Merz filed for a European second medical use patent for the product memantine hydrochloride for the treatment of cerebral ischemia and Alzheimer's disease. The patent was granted in September 1993 and expired in April 2009. In May 2002, Merz were granted by the EMA a series of marketing authorisations for memantine in the treatment of Alzheimer's disease. At this time the German and Luxembourg marketing authorisations were withdrawn. In November 2002, Merz applied for an SPC in the UK, citing the 2002 authorisation, but not the earlier German or Luxembourg authorisations as the *first* authorisation to place the product on the market in the Community, despite the fact that the product had been on the market in Germany since at least 1976. The SPC was granted for 5 years to expire in April 2014.

Synthon brought proceedings before the High Court in the UK seeking revocation of Merz's SPC or a declaration that it should have a term of zero years. Synthon argued that the 2002 Authorisation was not the first marketing authorisation for memantine and so the SPC was therefore invalid or has zero term pursuant to Article 13 of the Regulation (governing SPC duration), because the first marketing authorisation in the Community predated the filing of the patent application. In the further alternative, Synthon argued that the SPC was invalid because the first marketing authorisation in the Community was obtained before 1 January 1985 in breach of Article 19(1) (the transitional provision), or because memantine was placed on the market as a medicinal product before authorisation was obtained in accordance with Directive 65/65, in breach of Article 2 (governing scope of SPC availability).

The questions referred

The High Court referred a number of questions to the CJEU:

1. For the purposes of Articles 13 and 19 of Council Regulation (EC) No 1768/92, is an authorisation a 'first authorisation to place ... on the market in the Community', if it is granted in pursuance of a national

law which is compliant with Council Directive 65/65/EEC, or is it necessary that it be established in addition that, in granting the authorisation in question, the national authority followed an assessment of data as required by the administrative procedure laid down in that directive?

2. For the purposes of Articles 13 and 19 of Council Regulation (EC) No 1768/92, does the expression 'first authorisation to place … on the market in the Community' include authorisations which had been permitted by national law to co-exist with an authorisation regime which complies with Council Directive 65/65/EEC?
3. Is a product which is authorised to be placed on the market for the first time in the EEC without going through the administrative procedure laid down in Council Directive 65/65/EEC within the scope of Council Regulation (EC) 1768/92 as defined by Article 2?
4. If not, is an SPC granted in respect of such a product invalid?

The CJEU decision

The Court considered the Third Question first. Article 2 provides that:

> *"Any product protected by a patent in the territory of a Member State and subject, prior to being placed on the market as a medicinal product, to an administrative authorization procedure as laid down in Directive 65/65… may… be the subject of a certificate."*

The Court considered the Third Question to be asking, in essence, whether Article 2 of the Regulation must be interpreted as meaning that a product which was placed on the market in the Community as a medicinal product *without* first being subject to an administrative authorisation procedure as laid down in Directive 65/65, and, in particular, to safety and efficacy testing, is within the scope of the Regulation and may, therefore, be the subject of an SPC.

The Court considered that it was not apparent from the wording of Article 2 alone whether in using the concept of *'placing … on the market'* the legislature intended to refer to the Community market or just the market of the Member State in which the SPC application was submitted and in whose territory the patent is valid. Merz contended that it referred only to the market of the Member State in which the application was submitted whereas Synthon contended that it referred to the placing of the product on the market *anywhere* in the Community.

In finding that the concept of 'placing the product on the market' referred to the Community market, the Court found the following points persuasive:

1. to limit the concept of 'placing the product on the market' to the Member State in which the SPC application is made would result in Articles 3(a) and (b) (i.e. the conditions for the grant of an SPC) simply replicating Article 2, thereby depriving Article 2 of purpose, which was unlikely to have been the intention of the legislature;
2. the objective of the Regulation, as is apparent from its recitals, is to compensate the patentee for loss of effective protection as a result of the time required to acquire the authorisation to place the product on the market. It would be contrary to that objective of offsetting the time taken to obtain a marketing authorisation – which requires long and demanding testing of the safety and efficacy of the medicinal product concerned – if an SPC, which amounts to an extension of exclusivity, could be granted for a product which has already been sold on the Community market as a medicinal product before being subject to an administrative authorisation

procedure as laid down in Directive 65/65, including safety and efficacy testing;

3. In addition, the interpretation of Article 2 put forward by Merz would give rise to a difference in treatment between certain products placed on the market before the transitional date laid down in Article 19(1), which is not justified in the light of the objective of the Regulation. If Merz were correct – as a result of Article 19(1) – products issued with a compliant marketing authorisation before that date cannot be granted an SPC even if that authorisation was issued in accordance with Directive 65/65, whereas products marketed before that date on a non-compliant basis which would have obtained a marketing authorisation in a Member State in accordance with Directive 65/65 after that date could be granted an SPC.
4. It was common ground that memantine was marketed as a medicinal product in the Community under the German and Luxembourg authorisations without having first undergone safety and efficacy testing as prescribed by Directive 65/65. Such testing was only carried out for the first time when the 2002 marketing authorisation was issued. It followed that memantine was not within the scope of Regulation No 1768/92, as defined by Article 2 thereof, and may not, therefore, be the subject of an SPC.

The Court therefore answered the Third Question accordingly:

> *"Article 2 of Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products, as amended by the Act concerning the conditions of accession of the Republic of Austria, the Republic of Finland and the Kingdom of Sweden and the adjustments to the Treaties on which the European Union is founded, must be interpreted as meaning that a product, such as that at issue in the main proceedings, which was placed on the market in the European Community as a medicinal product for human use before obtaining a marketing authorisation in accordance with Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products, as amended by Council Directive 89/341/EEC of 3 May 1989, and, in particular, without undergoing safety and efficacy testing, is not within the scope of Regulation No 1768/92, as amended, and may not, therefore, be the subject of a supplementary protection certificate."*

With regard to the Fourth Question, the Court answered that:

> *"A supplementary protection certificate granted for a product outside the scope of Regulation No 1768/92, as amended, as that scope is defined in Article 2 of that regulation, is invalid"*

In view of its answers to the Third and Fourth Questions, the Court declined to answer the First and Second Questions.

The Generics reference

The Court also handed down its judgment in the *Generics v Synaptech* (C-427/09) reference at the same time holding, for the same reasons as those in *Synthon*, that as galantamine had already been placed on the market in the Community before undergoing the safety and efficacy testing required by Directive 65/65, it was outside the scope of Regulation, as defined in Article 2, and may not be the subject of an SPC.

DATA EXCLUSIVITY AND DEFINITION OF A NEW ACTIVE SUBSTANCE

On 4 July 2011, the General Court ordered that the action brought by Sepracor Pharmaceuticals (Ire-

land) against the Commission (Case T-275/09) be dismissed as inadmissible.

Background to the Sepracor action

Sepracor Pharmaceuticals (Ireland) submitted an application for a marketing authorisation for Lunivia (containing the active substance eszopiclone) to the EMA on 23 July 2007, and in October 2008 received a positive opinion from the CHMP that it should be granted a MA, but the CHMP also recommended that it should not be granted "new active substance" status. The CHMP confirmed this opinion in February 2009, and as a result Sepracor withdrew its application in May 2009, before the Commission decision to grant the MA.

The reason that the CHMP determined that eszoplicone should not be granted new active substance status was because Sepracor failed to prove relevant and clinically meaningful differences between eszopiclone and the racemate of which it was the active enantiomer, zopiclone in an adequate planned clinical trial with direct head to head comparison.[1] No relevant differences had been demonstrated in properties with regard to safety or efficacy. Therefore eszopiclone was considered as a known active substance.

Sepracor withdrew their application before the marketing authorisation was granted and brought the action to annul the decision by the Commission that the "eszopiclone" contained in it was not a new active substance under Article 3(2) (a) of Regulation N° 726/2004.

Inadmissibility of the Sepracor action

An order was made by the 4th Chamber of the General Court on 4 July 2011 that Sepracor's application is inadmissible. It was held that a "simple letter" from the Commission's services expressing the position to be taken following the CHMP opinion cannot be regarded as a decision producing legal effects regarding the applicant. Only decisions which have legal effects may be the subject of an action for an annulment. The Commission would be required to formalise the CHMP opinion in order for it to have legal effect on the applicant.

If Sepracor had not withdrawn its MAA it would have had a decision on which to challenge both the CHMP's refusal to recognise eszopiclone as a new active substance and the legal test applied by the CHMP to reach that conclusion. The reason Sepracor withdrew the application was that it took the view that that its pre-clinical and clinical data would become immediately available to manufacturers of generic products. In its withdrawal letter Sepracor says "the absence of NAS status leads to uncertainty as to whether the extensive research data underlying the application, and upon which the CHMP formed the opinion that the criteria for safety and efficacy were met, are entitled to a 10 year period of regulatory data protection".

Sepracor was therefore unsuccessful in its application and the issue of the criteria to determine what is a new active substance remains open.

Escitalopram

On 6 July 2011, shortly after the Sepracor challenge was dismissed, the Raad van State in the Netherlands rendered its decision in another regulatory dispute concerning enantiomers, this time in relation to escitalopram, the active enantiomer of the racemate citalopram. The Division of the Dutch Council of State upheld an appeal by Lundbeck A/S and found that the Dutch regulatory authority (the MEB) should not have conducted its own investigation into whether escitalopram is a new active substance, but should have followed the assessment as to this made by the Swedish agency (MPA) as Reference Member State. As a result generic marketing authorisations for escitalopram which had been granted in the Netherlands were suspended by the Division of the Council of State.

The MPA had informed the MEB that the Cipralex (escitalopram) was classified as a new active substance according to the classification made by the applicant on the application form. The MPA at the time of the application did not consider it necessary to consider whether escitalopram constituted a new or previously known active substance. Lun-

1 Withdrawal Assessment Report for Lunivia (INN: eszcopiclone) Procedure No. EMEA/H/C/000895

dbeck submitted further information at the time of renewal of the authorisation for Cipralex from which the MPA concluded that *"Although these data are insufficient for a firm conclusion of superior effect of escitalopram compared with citalopram, they were considered strong enough to indicate that an effect difference in favour of escitalopram is not unlikely"*. [2]

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) had previously noted that there is a need to harmonise the decisions taken in European Union (EU) Member States involved in the decentralised procedure on whether to maintain or suspend the marketing authorisations of medicines. The CHMP had reviewed group of generic escitalopram-containing medicines that were authorised via a decentralised procedure following a reference by the UK under Article 30 of Directive 2001/83/EC. The CHMP concluded that marketing authorisations for the generic medicines should be suspended based on an assessment using only data which was not subject to data protection provisions, and would thus have excluded data relating to escitalopram, as opposed to that for citalopram alone[3].

New Active Substance Status

At the present time the CHMP have considered the case of two isomers (eszopiclone and escitalopram) and released a draft reflection paper "*Reflection paper on considerations given to designation of a single stereo isomeric form (enantiomer) as new active substance in relation to a reference active substance which is a racemic mixture of enantiomers*" on 23 November 2010[4] following endorsement by the CMD(h) at its meeting in November. The EMA indicated in its news bulletin to SMEs that this paper "provides details on evidence that would be required to support the designation of a single stereoisomeric form (enantiomer) as a new active substance in relation to a reference active substance which is a racemic mixture of enantiomers. The document is intended to provide advice on aspects related to data exclusivity, data requirements and access to the centralised procedure". Therefore the scope of this paper is restricted to consideration of differences in isomeric composition of a product compared to a racemic reference active substance. The question addressed is "*when should an enantiomer be regarded as a new active substance (NAS) in relation to a reference active substance which is a racemate and what level of evidence would be required to confirm the designation as a new active substance*"? It observes that the "*default position is that an enantiomer is not different from the racemate, unless proven otherwise.*" The consultation period closed on 28 February 2011, and the outcome of the consultation and the final version is yet to be published.

Significance of New Active Substance Status

The significance of new active substance status becomes apparent when the legal definitions of reference and generic medicinal products are considered:. Thus Article 10(2) of Directive 2001/83/EC states (emphasis added):

. *For the purposes of this Article:*

1. *"reference medicinal product" shall mean a medicinal product authorised under Article 6, in accordance with the provisions of Article 8;*
2. *"generic medicinal product" shall mean a medicinal product which has the same qualitative and quantitative composition in terms of active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product had been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance unless they differ significantly in properties with regard to safety and efficacy. In such cases, additional information providing proof of the safety*

2 Decision of the MEB of 25 February 2010

3 EMA/89593/2010 EMEA/H/A/1231 18 February 2010 Questions and answers on generic escitalopram-containing medicines

4 EMA/651649/2010

and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant.

Sepracor's concerns regarding early generic competition for eszoplicone containing medicinal products if eszoplicone was to be treated as the "same active substance" as zoplicone would have arisen from the possibility that applicants could have applied for generic medicinal products containing eszopiclone using Zimovane (zopiclone) as the reference product (which has long been authorised for much the same indication, and for which data protection has long expired) and show through a bioequivalence study that the products were clinically equivalent. Lundbeck's initial experience in the Netherlands with escitalopram shows that such a concern is not unfounded.

Comment

The differing outcomes in these two cases in Europe, which concerned the narrow situation of the racemate and the optically active isomer, indicate that there is legal uncertainty around the issue of new active substance status. This issue is not limited only to racemates and enantiomers. Although the regulatory authorities through the CHMP have attempted to provide some guidance through their reflection paper on enantiomers, this, like the guidance set out in Notice to Applicants is not legally binding. The *Sepracor* decision evidences the absence of a legally binding mechanism by which new active status can be determined in advance of the grant of a marketing authorisation. Without such certainty companies which invest in clinical trials to bring medicines to the market lack the reassurance that their investment will be protected by regulatory data protection. Sepracor failed to "prove relevant and clinically meaningful differences between eszopiclone and the racemate zopiclone in an adequate planned clinical trial with direct head to head comparison."[5] Companies in this position will need to include in their development programme suitable studies to show that there are differences in safety and efficacy.

5 CHMP Withdrawal Assessment Report for Lunivia Procedure No. EMEA/H/C/000895 confirming Opinion of the CHMP of October 2008

SPANISH GOVERNMENT APPROVES A NUMBER OF MEASURES TO IMPROVE THE MANAGEMENT OF PHARMACEUTICAL SPENDING

On 19 August 2011, the Spanish Government approved a new regulation: Royal Decree-Law 9/2011, regarding *measures to improve the quality and cohesion of the National Health System, contributions to fiscal consolidation, and provisions to increase the maximum amount of state guarantees for 2011*. This Royal Decree-Law brings changes to medicinal product pricing and reimbursement in order to reduce pharmaceutical spending. This is a highly controversial measure as it implies dramatic discounts to medicinal products in addition to those formerly imposed by the Spanish Government in 2010 (specially, the mandatory 7, 5% discount on the price of medicinal product which are not subject to reference prices).

The main issues of Royal Decree-Law 9/2011 can be summarised into three fundamental steps:

- It requires the prescription of medicinal products according to the name of the active substance as opposed to by the trade mark. This prioritises the prescription of the medicinal products or medical devices with the lowest prices.
- It sets forth a number of amendments in the reference prices system.
- It establishes a reduction of 15% to the price of medicinal products that do not have a generic or biosimilar in Spain, provided 10 years have passed since the decision to invest public funds in the product was taken. This is without prejudice to patent protection which is explained below.

1) Prescription of medicinal products according to the name of the active substance

In this regard, Article 85 of Law 29/2006, of 26 July on guarantees and rational use of medicinal product and medical devices, is amended in order to widen the prescription of medicinal products according to the name of the active substance, and to ensure that pharmacists supply the appropriate medicinal product or medical device with the lowest price.

Therefore, the prescription of medicinal products and medical devices shall be carried out, respectively, according to the name of the active substance or regarding to their common or scientific name (i.e. according to the product characteristics). This is subject to the two following cases (in which case, the prescription could be carried out by identifying the medicinal product or medical device according to their trade mark):

- Where therapeutic needs that justify prescription by trade mark exist; and
- Where the medicinal products belong to groups which are composed solely of the original medicinal product and its licenses (without generic medicinal products). This applies provided the licenses have the same price as the reference medicinal product.

For a given prescription, as a starting point the lowest-priced presentation of the medicinal product or medical device shall be supplied by the retail pharmacy. Even when the prescription is processed by identifying the medicinal product or medical device according to its trade mark, the pharmacist should dispense such medicinal product or medical device prescribed by the doctor, provided that it is the lowest-price product of its group. Otherwise the medicinal product or medical device prescribed shall be replaced by the one with the lowest price, in such a way that the medicinal product with the lowest price within its group shall always be the one supplied.

The "Dirección General de Farmacia" shall periodically establish the lowest prices of the different homogeneous groups of medicinal products and medical devices and provide the necessary information about them.

In the light of the above, these amendments shall cause both medicinal and original products to maintain lower prices in order to qualify for public financing.

2) Reference prices

In addition, Royal Decree-Law 9/2011 establishes a number of amendments to the reference prices system (Article 93 of Law 29/2006, on medicinal products) on the basis of the following purposes:

- To clarify the meaning of the "reference prices system".
- To speed up the procedure for establishing new homogeneous groups of medicinal product and their reference prices.

Pursuant to these purposes:

- The reference price shall be the maximum amount to which the presentations of medicinal products, included in each of the groups to be determined, will be financed, provided that they are prescribed and supplied through public funds (instead of the former regulation: *"provided that they are prescribed and supplied through an official medical prescription of the National Health System")*.
- Each new group of medicinal products and its reference price shall be established immediately following the inclusion of the first generic of the reference medicinal product in the financing of the National Health System.

- The current option of implementing the reduction in price of a medicinal product as it is incorporated into a group with a reference price gradually over two years is removed. From now on, such a reduction must be immediate with no transitional period.
- Galenic innovations are maintained in the current regulation. However they shall be included in the reference group should a generic medicinal product with the same qualitative and quantitative composition in active substances and the same pharmaceutical form be included in the financing of the National Health System.
- Finally, sections 6 and 7 of Article 93 are removed (these removed sections formerly provided for a reduction of 30% in the price when there was no generic product in Spain but there was in Europe).

3) Reduction of 15% in the price of the generic medicinal product

The most significant change to medicinal products pricing follows the amendment of Article 10 of Royal Decree 8/2010 of 20 May (on urgent measures to reduce the public deficit) to implement the aforementioned reduction of 15%.

Royal Decree-Law applies a reduction of 15% to the prices of medicinal products that do not have a generic or biosimilar in Spain once 10 years have passed since the decision to invest in it with public funds has been taken (or once 11 years have passed where a new indication has been authorised). Only those medicinal products, even where meeting the conditions above, that prove "reliably" that they are protected by patent in all Member States of the European Union, are excluded from this deduction.

4) Other relevant measures

In addition, Royal Decree-Law sets forth other important measures on pharmaceutical issues:

- The discounts for "*orphan medicinal products*" shall be 4%; and
- Article 3.6 of Law 29/2006, is amended in order to increase the percentage discount available from distributors to retail pharmacies for non-generic medicinal products from 5% to 10%. This establishes the same legal regime for generic and non-generic medicinal products.

EUROPEAN COMMISSION PUBLISHES SECOND REPORT ON MONITORING PATENT SETTLEMENTS

On 6 July 2011, the European Commission published its second monitoring report of patent settlement agreements covering the period 1 January to 31 December 2010. The Commission concludes that the number of settlement agreements that are potentially problematic, from a competition law perspective, have decreased significantly, despite an overall increase in the number of patent settlements. The report compares the 2010 situation with that for the eight and a half years to 2008 covered in its Final Report on the pharmaceutical sector, and the position in 2009 covered in its first monitoring report, on which we reported in our September 2010 issue of this Bulletin.

Background

The Commission's Final Report following its pharmaceutical sector enquiry noted that certain patent settlements in the pharmaceutical sector may give rise to competition law concerns, in particular those that lead to a delay in generic entry in return for a value transfer (such as a monetary payment, a grant of a licence, or some kind of side deal) by the originator company. The Commission therefore announced in its press release accompanying the Final Report that it would continue to monitor settlements between originator and generic drug

companies. For our analysis of the Commission's first monitoring report please see http://www.twobirds.com/English/News/Articles/Pages/EC_report_monitoring_Patent_Settlement_Agreements.Aspx

The second report's findings

The Commission states that there has been a marked increase in patent settlements in the last two years (89 in 2010 compared with 73 in 2009) attributable to the following factors: the increased number of medicines losing patent protection; a general increase in litigation and disputes which in turn leads to a higher number of settlements; and an increased readiness for parties to settle. The total number of settlements reviewed by the Commission was 89. Those Member States identified in the Final Report as having comparably high numbers of patent settlements (relative to other Member States), such as Portugal and Germany continue to do so.

The majority of patent settlements reviewed by the Commission (61%) concerned settlements that do not restrict the generic company's ability to market its own product (referred to as A-type). 76% of A-type settlements were concluded on a 'walk away' basis i.e. the parties agreed to discontinue litigation without any further commitment/obligation on either party. Seven, out of a total of 54 of the A-type settlements included a value transfer from the originator to the generic company with six including a value transfer from the generic company to the originator. In the former case the Commission noted that whilst damages suffered by the generic company might be fully recompensed, the settlement would not reimburse the damage suffered by consumers and health insurers/public health schemes caused by delayed generic entry.

Of those settlements that do limit generic entry the overwhelming majority (91%) did not involve a value transfer (so called BI-type). With reference to the percentage of A-type and BI-type settlement agreements, the Commission notes that its increased scrutiny of settlements has not hindered companies from concluding settlements in general, and therefore concludes that concerns that the Commission's scrutiny would force companies to litigate patent disputes until the very end has proved unfounded.

There were three patent settlement agreements where the agreement limits generic entry and there was a value transfer from the originator to the generic company (BII-type). In the eight and a half years of the sector report such settlements accounted for 22% of the total, but this was down to 10% in 2009 and is only 3% for 2010. It is these settlements that the Commission has consistently identified as being the most likely to attract the highest degree of competition law scrutiny as they may be designed to keep competitors out of the market. However, the Commission's monitoring report makes no judgment as to whether the B-II type settlement agreements mentioned in the report are in fact problematic - it merely reports their existence. The Commission concludes that there has been a significant decrease in the number of B.II type settlements compared to the period investigated in the course of the sector enquiry, which may be attributable to increased awareness by companies and their legal advisors as to the fact that such agreements might raise competition law issues.

Comment

The Commission intends to continue monitoring patent settlement agreements for at least another year. In the meantime we await the Commission's conclusions in its patent settlement investigations against *Les Laboratoires Servier* and *Lundbeck*. In the UK it has been reported that the NHS has launched legal proceedings against Servier, in relation to its drug perindopril, alleging a number of abuses of a dominant position including that Servier paid other pharmaceutical companies in return for agreement that they would not supply the UK market with perindopril. The NHS also alleges that the Servier applied for patents which it knew to be invalid. It is not clear whether this action re-

lates to the same conduct that the Commission is investigating.

MEDICINAL PACKAGING AND PARALLEL IMPORTS. JOINED CASES OF *ORIFARM AND PARANOVA V MERCK SHARP & DOHME, CASES C-400/09 AND C-207/10*

This reference to the CJEU concerned the interpretation of Article 7(2) of the Trade Mark Directive. The ECJ has previously specified the conditions under which a parallel importer may market repackaged medicinal products bearing a trade mark, without the consent of the trade mark proprietor (the BMS Criteria).

Merck owned, or under licence agreements was entitled to bring judicial proceedings in relation to, trade marks on certain medicinal products. In the separate cases the relevant medicinal products were parallel imported onto the Danish market by members of the Orifarm and Paranova groups.

In each case, Merck brought an action on the grounds that the name of the actual repackager did not appear on the packaging of the medicinal products in question. The Danish Supreme Court referred questions to the ECJ asking whether the BMS Criteria meant that the name of the entity that physically carried out the repackaging had to appear on the repackaged product.

The CJEU considered that the requirement that the importer's name appear on the product was to protect the trade mark proprietor's interest that the consumer or end-user should not be led to believe that it was responsible for the repackaging. The other BMS Criteria and other legal instruments protected the trade mark owner's and consumers' other legitimate interests. Accordingly the new packaging did not need to state the name of the actual repackager: this interest was sufficiently protected if the repackaged product indicated as the repackager the undertaking which held a marketing authorisation for the product, on whose instructions the repackaging was carried out, and which assumed liability for the repackaging.

OLIVER BRÜSTLE V GREENPEACE E.V. (C-34/10)

The CJEU has handed down its decision in *Brüstle* on the interpretation of Article 6(2)(c) of the Biotechnology Directive (98/44EC), relating to the concept of a 'human embryo' and its patentability.

Background

Greenpeace applied to invalidate a German patent held by Oliver Brüstle, filed in 1997, which concerned isolated and purified neural precursor cells, processes for their production from embryonic stem cells, and the use of neural precursor cells for the treatment of neural defects.

Greenpeace asserted that Brüstle's patent was invalid on the basis that its claimed invention was contrary to TRIPS and the EPC which permit signatories to exclude an invention from being patented if its commerical exploitation would be contrary to *ordre public* or morality, and that it fell within Article 6(2)(c) of the Biotech Directive which provides that in particular this exclusion is satisfied if human embryos are used for industrial or commercial purposes. The Bundesgerichtshof stayed proceedings and referred a number of questions to the CJEU concerning the definition of a 'human embryo' and its application in these circumstances.

Stem Cells

A distinction can be made between 'totipotent' and 'pluripotent' stem cells. The former arise after fertilisation and are capable of dividing and developing into a complete individual. A few days after fertilisation a blastocyst is formed consisting of the latter, which although capable to developing into any type of cell, cannot develop into a complete individual.

The CJEU's decision

The definition of a 'human embryo' in Article 6(2)(c)

The CJEU considered that although member states should have wide discretion to interpret *ordre public* and morality, Article 6(2) sets out particular ex-

clusions from patentability. Therefore, the concept of a 'human embryo' for these purposes should be interpreted uniformly across the EU rather than leaving this to member state courts. The Biotech Directive aimed to remove obstacles to trade and smooth the functioning of the internal market. This aim would not be achieved if some member states chose a narrow interpretation which would result in a liberal patenting regime whilst others interpreted the exclusions more broadly.

The CJEU noted that although the Biotech Directive seeks to promote investment in biotechnology, the use of biological material originating from humans had to be consistent with regard to fundamental rights and, in particular, the dignity and integrity of the person. Therefore, the concept of a 'human embryo' should, for these purposes, be interpreted in a wide sense. Accordingly, the CJEU ruled that, for the purposes of Article 6(2)(c), a 'human embryo' constituted any (i) any human ovum after fertilisation, and (ii) any non-fertilised human ovum (a) into which the cell nucleus of a mature human cell has been transplanted or (b) for which further development has been stimulated by parthenogenesis. However, it would fall to the relevant national Court to ascertain whether a stem cell obtained from a human embryo at the blastocyst stage fell within this definition, in light of scientific developments.

The stem cells in question in Brüstle's patent were pluripotent cells. Advocate General Bot had recommended that these should not be regarded as a 'human embryo' as they do not have the capacity to develop into a human being, although if obtained from a blastocyst they could only be patentable if they could be obtained without detriment to the embryo (which was not the case at the priority date). However, the CJEU's broader definition of a human embryo means that pluripotent cells could fall within the concept of a 'human embryo', depending on how a member state's national Courts interpret this ruling in light of scientific developments.

Use of human embryos for scientific research

The second question referred asked whether the 'use of human embryos for industrial or commercial purposes' covered the use of human embryos for the purposes of scientific research. The CJEU noted that the purpose of the Biotech Directive was not to regulate the use of human embryos in scientific research, but to the patentability of biotechnology inventions. However, the use of a human embryo for scientific research implies its industrial or commercial application: even if the aim of scientific research was different, such use of a patent's subject matter would fall within the exclusion. This is subject to the clarification in Recital 42 of the Biotech Directive, that therapeutic or diagnostic purposes which are to be applied to the human embryo and are useful to it are patentable.

Invention requires destruction of human embryos

The third question asked whether an invention would be unpatentable if it necessitated the destruction of a human embryo, even if its purpose is not the use of human embryos. In answering this question, the CJEU reached essentially the same conclusion as the Enlarged Board of Appeal had in *WARF* (G 2/06) in relation to the EPC. If the implementation of the invention required the destruction of human embryos, it had to be concluded that human embryos must have been said to have been used within the meaning of Article 6(2)(c). It was irrelevant if the claimed invention was implemented at a stage long after the destruction of such embryo. Moreover, it does not matter whether the invention as claimed referred to the use of human embryos – a contrary conclusion could enable a patent to avoid the exclusion and be valid by skilful drafting, rather than because the invention itself does not fall within the exclusion.

Conclusion

On the face of it, the CJEU's decision in Brüstle is likely to be disappointing for those engaged in stem cell research in the EU. The CJEU has chosen to define a 'human embryo' broadly for the purpos-

es of Article 6(2)(c) and given national courts discretion only to decide how this is to be interpreted in light of scientific developments.

However, the CJEU has not ruled that pluripotent cells per se must be regarded as a human embryo. Moreover, since 1997 new methods have been developed for the production of stem cell lines that do not require the use or modification of human embryos but instead rely on 'reprogramming' differentiated cells to revert to a pluripotent state. Companies will also be able to rely on confidentiality rather than the patent system to protect techniques developed in this area of research.

Legal & Regulatory Update

Post-grant review: The good, the bad and the ugly for biotechnology companies

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ABSTRACT

This paper summarizes the Post-Grant Review process, one of the many interesting aspects of patent reform brought about by the enactment of the America Invents Act, and the effect it may have on how Biotechnology companies conduct business and manage their intellectual property.

The content of this paper is intended to only provide a general guide to the subject matter. The views expressed in this paper are the personal views of the authors.

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INTRODUCTION

After many years of congressional talk about patent reform, the America Invents Act (AIA)[1] was finally enacted in law on September 16, 2011. The substantial changes

1 Leahy-Smith America Invents Act, H.R. 1249 (112th Congress, First Session), enacted (President Obama) 16 September 2011, available online at http://www.govtrack.us/congress/

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it brings to the U.S. patent system will have far reaching effects on biotechnology companies and the way they do business, particularly with regards to drafting patent applications, protecting their patents, keeping a watchful eye on similar technologies of competitors and leveraging their patent portfolios to attract investment.

A noteworthy change heralded by the AIA is a much expanded base on which patent challengers can attack patents, including "Post-Grant Review" (PGR) proceedings before the United States Patent & Trademark Office (USPTO). Section 6 and 18 of the AIA introduce new statutory provisions §§ 321-329 to Chapter 32 of Title 35 of the United States Code (U.S.C) which have similarities to Opposition Proceedings under European practice.[2] Under PGR, a person who is not the patent owner may petition the USPTO to review the validity of an issued patent within nine months of its grant or issuance of a reissue patent.[3]

Under the PGR process, a petition will be granted if the petitioner shows that "if such information is not rebutted, [it] would demonstrate that it is more likely than not that at least one of the claims challenged in the petition is unpatentable."[4] Invalidity can be asserted on any grounds of patentability that one can raise as a defense in patent infringement litigation before the Courts under § 282 of Title 35, U.S.C, including failure of the claims to define subject matter eligible for patenting, lack of novelty, obviousness, and to provide a written description or enablement under §§ 101, 102, 103, and 112 of Title 35, U.S.C. However under PGR, the petitioner need only bear the burden of proving invalidity by the lower standard of "by a preponderance of the evidence" in contrast to the "clear and convincing" evidentiary standard for proving invalidity that follows from the Supreme Court decision on *Microsoft Corp. v. i4i Ltd. Partnership*.[5]

Biotechnology inventions are commonly challenged on the basis of the written description and enablement requirements. A patent application must contain an adequate description of the invention under the first paragraph of § 112 of Title 35, U.S.C. for issuance of a patent in accordance with the *quid pro quo* policy objective of the patent system of encouraging disclosure of inventions in return for exclusive rights.[6] Section 112, of Title 35 in pertinent part will read:

> *The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.*

A review of court decisions will impress the fact that the written description requirement is applied with much greater frequency and scrutiny in biotechnology cases due to the inherent unpredictability and uncertainty in these fields. In *Ariad Pharms., Inc. v. Eli Lilly & Co.*, after eight years of expensive litigation, the Court of Appeals for the Federal Circuit (CAFC) confirmed *en banc*, in favor of Eli Lilly, that §112 Title 35, U.S.C contains a written description that is separate from the enablement requirement and that the asserted claims were invalid for lack of written description[7]. On February 23, 2011, the CAFC overruled the District Court's decision in *Centocor v. Abbott*

billtext.xpd?bill=h112-1249 (last accessed 31 October 2011).

2 *Id.*

3 PGR rules go into effect September 16, 2012 (12 months after the enactment of the AIA) and are applicable to business method patents under the transitional program, however, the PGR process only goes into effect as to "first-to-file" paragraph 3(n)(1) patents, which are patents that are filed on or after March 16, 2013.

4 H.R. 1249 § 324 (a)

5 *Microsoft Corp. v. i4i Ltd. Partnership*, 564 U.S. _____ (2011).

6 35 U.S.C. § 112

7 *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010)

Labs and set aside a $1.67 billion jury verdict in favor of the patentee (Centocor) and finally held the patent claims at issue were invalid for lack of written description[8]. These decisions, among many others, reflect a recent trend of the Federal Circuit to invalidate patents on the grounds of written description.

However, the litigation route is not available as an option unless there is "actual controversy".[9] If one opted not to go that route, patents could only be challenged post grant through reexaminations at the USPTO. Reexaminations had their limitations as only patents or printed publications eligible under §§ 102 and 103 of Title 35, U.S.C, that raise a substantial new question of patentability (SNQ) are considered. With the present possibility of attacking patents for the lack of written description under PGR at the USPTO itself, biotechnology companies will have to pay keen attention to when they think an invention is patentable and if there is sufficient description in the specification of a patent application to withstand the lower cost, expedited process now available to any third party to challenge their patents post grant.

The AIA has put in place a number of checks and balances that allow for "enhancing patent quality and the efficiency, objectivity, predictability, and transparency of the patent system" as stated by Biotechnology Industry Organization (BIO) President and CEO Jim Greenwood. While this is indeed a good thing, in the short term it may place tremendous pressure on smaller biotechnology companies and start ups with limited resources that rely heavily on their patent portfolio to attract investment, primarily from the venture capital industry. Easier options of knocking down patents, such as through PGR, may make investments in developing innovative technologies much more riskier and possibly untenable for venture capitalists. The flip side of the coin, however, is that companies that have so far been cowed into not taking action based on the prospect of expensive litigation now have a broader avenue for taking down weak patents of larger competitors if doing so is advantageous to their business.

The availability of PGR may indeed compel biotechnology companies to build up their defensive strategy and ensure that the patents in their portfolio are strong and enforceable, especially with adequate written description support. Provisions of the PGR process, such as, submission of the petition within a short time span of 9 months from patent issuance; availability of PGR only if the challenger has not already initiated a civil action in District Court; parties being able to settle the issue before the USPTO makes a final decision and the estoppel associated with the challenger at the USPTO, the District Court and the International Trade Commission (ITC) in asserting invalidity on any ground that could have been reasonably raised during PGR, makes for very important questions of timing that must be considered by biotechnology companies in using PGR as an offensive strategy. With the right decisions made at the right time, biotechnology companies, irrespective of their size, will find PGR to be a very important and powerful resource.

8 *Centocor Ortho Biotech, Inc. v. Abbott Lab.*, No. 2010-1144 (Fed. Cir. Feb. 23, 2011)

9 *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007).

Book Review

Constructing and deconstructing patents

Irah H. Donner

BNA Books, Arlington, 2010, hardcover, 656pp., $255.00 ISBN: 9781570189340

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Particularly in biotechnology, patents serve as the defensive wall that lets innovators reap the rewards of their discovery while keeping competitors at bay. Drafting a patent can be a difficult proposition because the author needs to simultaneously explain what the idea is, while providing a legal definition of what has been invented. In other words, anything you say can be used against you.

Constructing and Deconstructing Patents covers each of the topics needed for someone to begin drafting patents (Mr. Donner has a separate book on how to argue for the allowance of patents). The book is divided into three sections: an overview of drafting (or constructing) a patent; drafting a patent; and a discussion of case law relating to interpreting (or deconstructing) a patent. The book is complemented by extensive appendices and a CD-ROM of the appendices. There is both a summary table of contents and a detailed table of contents in the beginning, and a table of cases and glossary at the end. As laid out in the detailed table of contents, the book is broken into a series of discrete sections of not more than a few pages each. The extensive use of headings and subheadings also contributes to the book's organization.

The overview section begins by comparing patent protection to the other types of intellectual property protection, to explain why one would use one type of protection versus the patent, or both types together. The section continues with a chapter on how to write a patentability opinion and provides an overview of drafting a patent.

The second section covers how to construct a patent and is divided into nine chapters corresponding to the steps one takes in drafting an application. The appendix includes materials relating to three inventions: one mechanical; one combination of mechanical and circuitry; and one chemical invention. The book applies the lessons on how to draft a patent to each of the inventions, such that the reader can see how the techniques are applied. The book includes disclosure materials and drawings for each invention, and a prior art reference for the two mechanical designs. This allows the reader to read materials, such as an interview with the inventor, and then try their hand at the various tasks in drafting a patent. I found this hands on approach helpful when I was learning to draft patents.

Deconstructing a patent is three chapters: interpreting the scope of a patent; inventorship and exceptions to patentable subject matter share a chapter; and disclosure requirements. Though not necessarily apparent from the table of contents, the third section includes many lessons that someone drafting a patent application would benefit from, such as how to evaluate the subject matter eligibility of an invention. This last section reads much like a law school casebook, where the reader is presented with key sections of important cases and a discussion of how each influenced the development of the law. The practice tips included at the end of some chapter subsections are perhaps closer to summaries of the law than ways around a problem.

Given the length of the book, the lack of advanced pointers surprised me. For example, chapter nine discusses how to draft the claims, which create the legal definition of the invention that the

patent covers. The chapter does not discuss how to draft claims for inventions where patent subject matter eligibility might be a concern (fields such as business methods, software or medical diagnostic methods). The relevant law is covered under chapter 16, but the author never opens the kimono to suggest techniques or claim language that he has used to handle such inventions.

Constructing and Deconstructing Patents provides thorough coverage of the basics of writing a patent application, and a targeted legal treatise. While I would have liked Mr. Donner to share more of the strategies that he uses, reading this book will serve as a good first step to a career constructing patents.

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Book Review

Plunkett's biotech & genetics industry almanac 2012

Jack W. Plunkett

Plunkett Research, Ltd., Houston, 2011, hardcover, 554pp., $299.00 ISBN: 9781608796496

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When asked to review the 2012 Plunkett's Biotech & Genetics Industry Almanac I knew from past experience that I would be receiving a comprehensive reference manual. Plunkett Research, Ltd. is a leading provider of industry sector analysis and research, industry trends and industry statistics.

The 2012 Almanac is the 10th edition of the Almanac and presents a complete overview of the entire biotechnology and genetics area and industry. The Almanac, truly a reference book, is designed to be used as a general source for those in the industry or seeking information about the industry. The Almanac provides a vast amount of relevant and timely information for the biotech industry researcher and/or business executive as well as anyone else seeking up-to-date industry information. There is a copious amount of information to assist with market research, strategic planning, and employment searches. The Almanac further provides contact information to facilitate prospect list creation as well as serve as a repository of facts and figures for financial research.

Before even turning to the "Introduction" in the Almanac, Plunkett provides 20+ pages of definitions in a short biotech and genetics industry glossary. Having this right up front is a huge plus. Next a very helpful "How To Use This Book" follows. Plunkett then launches into an extremely comprehensive Chapter I that discusses 28 major trends affecting the biotech and genetics industry, including sections on "The State of the Biotech Industry Today," discussions on numerous timely topics, such as gene therapies, stem cells, biogenerics, vaccines and technology discussions on a number of the most common biotech and genetic technologies in use today (e.g., SNPs, proteomics, synthetic biology and PCR, just to name a few). Many of the chapters discussing the major trends further provide internet links to additional information on the topic as well as links to assist with further research, selected company spotlights and informative Plunkett commentaries.

Chapter 2 provides a plethora of extremely useful industry statistics, graphs and charts including statistics related to drug discovery and approvals, U.S. Pharmaceutical R&D spending versus the number of new molecular entities, prescription drug expenditures, industry employment stats, patent information, domestic and foreign drug sale information and a great deal more.

Chapter 3 is an encyclopedic list of important biotech and genetics industry contacts that includes addresses, telephone numbers and internet site addresses. This list includes industry associations, research organizations, patent organizations and resources, career and professional reference tools and associations, market and research organizations, U.S and global health facts and much more invaluable sources to find out just about anything one needs to in the biotech and generics industry.

The final chapter of the Almanac is devoted to "The Biotech 350." Plunkett explains that the companies chosen to be listed in the Biotech 350 (Plunkett acknowledges that the actual list comprises 367 companies) were chosen specifically for their dominance in the many facets of biotechnology and generics in which they operate. In a nutshell, the list contains 367 of the largest, most successful

and fastest growing firms in the biotechnology and related industries in the world. This final chapter starts with a chart of the Biotech 350 and provides 2010 Sales and Profit figures. An index of the companies by state or country is provided, followed by an individual profile of each company on the list. Each company profile provides a one-page comprehensive snapshot including details about business type, brands, divisions, and affiliates. Executive names and contact information is provided along with company growth plans and other special features. Company financial information is also included along with salary/benefits information and some statistics about women and minority hiring.

Plunkett provides a unique and extremely comprehensive almanac that saves time and effort for competitive intelligence, market research, vertical industry marketing data, or industry trends analysis. The purchase of the 2012 Biotech & Genetics Industry Almanac also includes free 1-year access to book data and exports online (with registration) Simply put, Plunkett's Biotechnology & Genetics Industry Almanac 2012 is an invaluable resource and reference tool for anyone operating within the biotechnology and pharmaceutical industry.

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