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Commentary

The other side of innovation

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How do you compare two molecules (or three or more) that have different mechanisms of action for patients that respond differently to different medicines based on their personal genetic make-up?

Comparative effectiveness relies heavily on findings from randomized clinical trials. While these trials are essential to demonstrating the safety and efficacy of new medical products, the results are based on large population averages that rarely, if ever, will tell us which treatments are "best" for any given patient.

Two such studies, the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE), study and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, were two such "practice-based" clinical trials, sponsored in part by the National Institutes of Health, to determine whether older (cheaper) medicines were as effective in achieving certain clinical outcomes as newer (more expensive) ones.

The findings of both CATIE and ALLHAT were highly controversial, but one thing is not: even well-funded comparative effectiveness trials are swiftly superseded by trial designs based on better mechanistic understanding of disease pathways and pharmacogenomics. And, since most comparative effectiveness studies are underpowered, they don't capture the genetic variations that explain differences in response to medicines by different patients. Comparative effectiveness in its current form leads to a "one-size-fits-all" approach to healthcare, which means that it doesn't fit anyone all that well.

As currently organized, comparative effectiveness research will be used to increase government control over the practice of medicine and is a slippery slope towards the introduction of price controls.

Government sponsored comparative effectiveness research is the first step towards allowing Uncle Sam to push a restrictive formulary on more and more Americans—with step one in the process being unfettered (and unregulated) communications efforts (aka "academic detailing"). Unless we are aware and vigilant, such cost-think may very well lead to a single-payer system referred to in cost-think as "universal coverage"—but in reality will be nothing short of healthcare rationing.

There are many dangerous implications, but the most frightening is the chilling effect so-called comparative effectiveness programs will have on the future of healthcare innovation.

Innovation means facilitating the free market's desire and ability to advance the public health through investment in new, exciting, (and expensive) science. But innovation is important—and not just for biopharmaceutical industry profits. Increases in life expectancy resulting from better treatment of cardiovascular disease from 1970 to 1990 have been conservatively estimated as bringing benefits worth more than $500 billion a year. In 1974, cardiovascular disease was the cause of 39 percent of all deaths. Today it is about 25 percent. Cerebrovascular diseases were responsible for 11 percent of deaths back then. In 2004 they caused 6.3 percent of deaths. Kidney diseases were linked to 10.4 percent of deaths and now they are associated with 1.8 percent. And that's just for the United States.

These considerations lead to the conclusion that we must start taking innovation, both incremental and discontinuous, seriously, which means spending more on harder developmental R&D (with concomitant higher investment risks). In the words of Frederick the Great, "L'audace, l'audace, toujours l'audace."

Personalized medicine gives doctors and patients control over health care decisions while comparative effectiveness, as it is now defined, will increase government control over the choices doctors and patients have in the future. The battle over the value of medicine and who decides what is valuable will determine who controls health care in America over the next decade.

A progressive health technology assessment model for the 21st century should reflect and measure individual responses to treatment based on a combination of genetic, clinical, and demographic factors that indicate what keep people healthy, improve their health, and prevent disease.

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A rapidly longer-living society demands a new health care paradigm capable of providing for its needs in the 21st century. Equality of care must be matched with quality of care.

In an era of personalized medicine, one-size-fits-all treatments and reimbursement strategies are dangerously outdated. We are early in this debate, but at least we can all agree that this is not, and must not be, exclusively a debate about saving money. The debate must be about patient care. When it comes to health care reform, this is not even the end of the beginning

To borrow an over-used adjective from the world of global climate change—we must protect "sustainable" innovation. The critical battle, the battle for the heart and soul of 21st century health care is the battle over innovation. And nothing short of victory is acceptable.

Commentary

Fixing a broken drug development process

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ABSTRACT

It costs about $1.2 billion to bring a single new drug to market in the U.S. today. With a combination of high late-stage failure rates and the high cost of drug trials, the number of new drugs being approved by the FDA has flat-lined at historically low levels, falling from 53 in 1996 to just 19 in 2009. If the cost of drug trials doesn't come down, we will see far fewer new drugs on pharmacy shelves.

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Keywords: telehealth; telemonitoring; remote healthcare technologies; remote patient monitoring

It costs about $1.2 billion to bring a single new drug to market in the U.S. today.[1] With a combination of high late-stage failure rates and the high cost of drug trials, the number of new drugs being approved by the FDA has flat-lined at historically low levels, falling from 53 in 1996 to just 19 in 2009.[2] If the cost of drug trials doesn't come down, we will see far fewer new drugs on pharmacy shelves.

Patients awaiting new treatments, pharmaceutical companies and the FDA all recognize that our drug development process is unsustainable. Unless a new compound is a potential blockbuster, no one—no matter how deep their pockets—can afford to risk the hundreds of millions of dollars it costs to find out whether or not it works. As a result, thousands of compounds that have shown promise in animal studies will never be tested in humans or brought to market.

Drug trials are performed in a hopelessly antiquated manner, making them cripplingly expensive in both time and dollars. The electric company can read your meter remotely and your x-rays may be read by a radiologist on another continent, but a patient in a pharmaceutical trial must travel to a doctor's office to have her blood pressure or blood sugar or weight or heart rate checked, and to answer some questions about symptoms and side effects. Then, perhaps once a month, a clinical trial associate travels to the same doctor's office and transfers all that data to a trial database. It's so 20th century…

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Remote technologies used in other areas of healthcare—with the blessing of the FDA—monitor a wide range of physiologic parameters in a patient's home and send them electronically to a central database. The patient doesn't even need a computer or a cell phone. Mobile video enables direct observation, and patients can report symptoms and answer questions about how they feel by telephone, text message or email. Smartphones can send high-resolution pictures of eyes, ears and skin, researchers are using GPS in Smartphones to analyze activity in daily life, and medication dispensers remind patients when it is time to take their study medications and send alerts to researchers when they don't.

Until recently, FDA rules for drug trials discouraged the use of remote technologies, calling for 100% in-person collection and verification of all data. But now, the FDA recognizes that this antiquated approach is too cumbersome and expensive. The agency recently revised its rules to allow remote collection of data.

Of course, some tests will still require a visit—there's no in-home MRI yet—but the vast majority of clinical trial data can be collected remotely, with dramatic savings. Recruiting volunteers for clinical trials has become increasingly difficult, due to lack of patient awareness and the burden of multiple extra doctor visits. Technology can help. In a recent study,[3] the cost of recruiting through the Internet was $4.82 per interested patient, compared with $86.28 for direct mail and $195.65—40 times more—for email.

There are other important benefits to remote patient monitoring. Researchers can collect far more readings at home, and with more data, fewer patients may be needed.

Researchers can see the effects of a drug at different times of day, and they may be able to tell much earlier in a trial whether or not a drug is safe and effective. Automatic reminders before study visits will reduce no-shows, and knowing whether or not patients are taking the medication will help us understand whether or not the drug does any good.

Remote recruitment and monitoring technologies are available today, and the FDA has indicated a willingness to consider trials that are conducted remotely. Now it is up to the pharma companies and the contract research organizations that conduct most drug trials to incorporate these technologies into their trial protocols. Pfizer recently gained FDA approval for a trial that would be conducted entirely in cyberspace, and another major pharmaceutical company will be using remote monitoring in combination with in-person study visits. Just last month, the FDA approved an investigational new drug (IND) application for a Phase 2a trial to study a re-purposed antihypertensive drug, lisinopril, for multiple sclerosis, using several remote technologies to collect objective physiologic data and self-reported outcomes. The sponsor of this study, Transparency Life Sciences, stated that a major part of its strategy "…is to dramatically reduce the cost and patient inconvenience of executing clinical trials by replacing patient site visits with telemonitoring and other measurements obtained from patients' homes. To achieve its goal of 50% or greater reduction in the cost of clinical trials, TLS is partnering with AMC Health. In the proposed twelve-month lisinopril study, patients will visit in-person with clinical trial staff at the start and end of the trial, and all other study data will be collected at home." If we don't take advantage of these technologies to bring down the cost of drug trials, there is a real risk that new drug pipelines may run dry.

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Original Article

Biotechnology valuation and governance: Drug development and board of directors composition

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ABSTRACT

We examine the valuation of biotechnology firms and measure firm value relative to the firms' drug development pipelines, alliances with other firms, and the varied composition of those firms' boards of directors. Unsurprisingly, the advancement of drugs in the pipeline is associated with increased valuation, and the failure of drugs in testing is found to have negative impacts. Our findings do not support the notion that companies engaged in partnerships or alliances have better performance. Extending prior research, we find that the presence of medical doctors on the boards of directors is significantly positively associated with price-to-book ratios and firm value. Drug approvals seemed less likely for small cap firms; this outcome is likely the result of small cap firms with more promising prospects being acquired, and exiting "small cap" status. Smaller firms have lower approval rates—they have fewer drugs in the pipeline—and the risk of these smaller firms is diversified when they are combined with larger firms whose research is spread across many more drugs. We observe a higher number of drug approvals for AIDS and cancer. We also discover a modestly higher approval rate alongside a higher proportion of financiers—such as hedge fund managers and investment bankers—on biotechnology boards. The investor might use our discoveries to better project a firm's success in drug approvals and equity returns; the biotech manager could use our findings to better anticipate market responses to changes in the company's board or research; the regulator could remember to limit the political influences on drug approvals by recalling the potential "favoring" of one disease over another depending upon the political climate. Thus our findings are important to the investor, the biotechnology manager and the regulator.

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Keywords: valuation; board composition; drug development; governance

INTRODUCTION

Recent patterns suggest that the biotechnology industry, and biotechnology investors, may be entering a new financial era; gone are the days of loose venture capital purse strings and generous buyout offers from the "majors." Rockoff and Tam[1] note that "the gravy days are over." Once a "darling" of investors and global pharmaceuticals, newer startups are having to more convincingly show their muster than was the case a decade or less ago. In this light, factors contributing to the valuation of biotechnology firms are key. Given this, we examine the influence of such issues as research, clinical success rates and board composition as they relate to firm value.

Some of our findings are unsurprising, while others are more noteworthy: We find that the advancement of drugs in the pipeline is associated with increased firm values, and that the failures of drugs in testing are seen alongside declinations in those values. A more noteworthy finding is seen where we observe no better performance for companies engaged in partnerships or alliances than is observed for firms striking out on their own. Extending prior research, we find that the presence of medical doctors on the boards of directors is associated

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with higher price-to-book ratios and firm values. Drug approvals seemed less likely for small cap firms; we believe this outcome is the result of small cap firms with more promising prospects being acquired, and exiting "small cap" status. Among other results, a higher number of drug approvals among such targeted diseases as AIDS and cancer are observed; modestly higher approval rates are observed in concert with a relatively higher proportion of financiers—such as hedge fund managers and investment bankers—on biotechnology boards. This is especially meaningful; hedge fund managers and investment advisors would be expected to appreciate whether a drug-development "team" is more or less likely to create value for an investor. However, taking this set of "skills" a step farther leads to a surprising result—that investment advisor seems better able, as well, to influence the selection of the more promising drugs for development in the first place.

The sector has a storied past, with a plethora of factors contributing to the success, and value, of participants in the biotechnology marketplace. The biotech industry emerged in the 1970's. NAICS data and Plunkett Research, Ltd report that this sector witnessed dramatic growth, from less than $10 billion in global sales for publicly held biotech firms in the early 1990's to over $80 billion in 2010. And this is a research intensive industry; near the end of 2011, according to MedTrack,[2] there were 10,000 or more "unique products" under development, with many of these products being drugs in various stages of development. There were over 400 drugs "being tested to treat more than 100 …" diseases, including various cancers, cognitive disorders, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis.[3] A review of *BIO*[4] describes the work of 180,000 employees working towards the combined biotechnology goals of both creating value for investors and discovering remedies for various maladies. Drug breakthroughs may generate considerable value for investors, but most research spending does not result in a drug reaching the market.

Pisano[5] notes that most biotechnology companies do not generate positive cash flows or profit. Thus, traditional financial or economic theory that estimates value as a function of future cash flows is compromised; yet, Bratic et al.[6] and Villiger and Bogdan[7] remind us that the valuation of biotechnology firms is important for capital and investment decisions, and in the division of any value the firm creates between investors and management.

The purpose of this research is to examine—in a new light and with a previously unexamined set of data—factors that impact biotechnology firm value. These factors include the transition of drugs through various phases of clinical trials, the prior experiences of the firms' science and management teams in achieving success with drug development, the diversification of the drug development pipeline, and the firms' alliances and partnerships. Finally, extending the extant research, this study considers the role played by the composition of the firms' board of directors in describing increases in firm value, and in anticipating increases in R&D spending; the likelihood of success with drug approvals is probably framed by these same factors, and tests for that are provided, as well.

Literature that has examined related topics over the past couple of decades is considered next, followed by a description of our data to reveal the importance of such factors as the firm's investment in R&D and the composition of its board of directors in describing the firm's later success, in creating shareholder value and in securing drug approvals. We construct a set of models to test these ideas; results are reported. We then provide a summary along with some concluding remarks.

BACKGROUND AND LITERATURE REVIEW

Industries that are characterized by significant investments in research and development make traditional valuations difficult to apply. Impediments in biotechnology valuation stem from the large initial investments typically required to develop new pharmaceutical products, coupled with the inherent uncertainty that such efforts will yield marketable products; cash flows typically do not occur until years after initial investments, and the application of traditional valuation models is compromised. A review of Microsoft's performance prior to its initiation of a dividend payment in the early 2000's is telling; there, stock price and company value soared through the late 1990's in the absence of distributions to shareholders, yet corporate profits and cash accumulations at the company level were clearly apparent. For the high-tech firm considered here, not even those earnings—much less dividend payments upon which some valuation models depend—are evident.

DiMasi *et al.*[8] and Xu[9] affirm that research and development can be time-consuming, often lasting a decade or more. Estimates of costs per drug are substantial, but vary considerably. Bratic et al.[6] estimate that sixty percent of drugs currently in the market required over $100 million in development costs. This earlier research estimates cash outlays for each successful drug range from $207 million to nearly $900 million; Morgan et al.[10] report that the capitalized costs per drug may be as high as $1.8 billion. DiMasi[11] notes that as new drugs move through the development pipeline, these sunk costs may actually increase, but the probability of garnering FDA approval improves.

There are four phases of clinical trials for prospective drugs, necessary for the drug's approval by the FDA. Phase 1 (or I) trials are the earliest and least structured, and are typically tailored for a cohort of a few dozen (or less) patients that have exhausted traditional treatment options. If non-human laboratory testing has revealed that some new drug or treatment may have potential with humans, the first tenuous steps towards ascertaining safe dosage levels and side effects are taken with the Phase 1 trials. If a new treatment passes muster with the Phase 1 trial, a second phase may be initiated. The Phase 2 (II) trial involves a much larger set of test subjects, further examines dosages and side effects, and often allows the prospective drug to be tested alongside a placebo and contrasted with existing treatments. If positive results are generated with the Phase 2 trial, a Phase 3 (III) clinical trial may be conducted, if the company conducting the trials can justify the often-enormous costs of this third phase. To iron out ideal doses, clearly portray potential side effects, and determine the appropriateness for differing populations (children, adolescents, adults, those suffering from other maladies, citizens of different countries, the thin, the overweight, etc.) of the new treatment, the Phase 3 trial may involve thousands of patients, and cost tens of millions of dollars. Differences in success rates for the given populations may be small, and this phase needs to begin to anticipate those varying success rates prior to FDA approval. Once the FDA has issued a license for a new drug or treatment, Phase 4 (IV) trials are conducted to discover long-range side effects and risks and the suitability of the new drug or treatment for wider populations over a longer period of time.

Using a real options framework, Villiger and Bogdan[7] show that drugs in different phases of clinical trials have different values depending upon the uncertainties attaching to each drug's development. Villiger and Bogdan[12] note that due to breakdowns in efficacy, safety, or economics, many drugs never make it to market. In fact, and according to Bratic et al.[6], only one in five thousand compounds that enter preclinical research and development make it to human testing, and then only one in five garners FDA approval. Pisano[5] observes that, historically, between 10 and 20 percent of drugs that begin clinical trials will become commercially viable.

The development status of a firm's drug pipeline has substantial implications for firm value, as it signals the likelihood that the firm will convert R&D expenditures into viable commercial products. However, unlike a retailer's metric of same store sales, the drug development pipeline of one company is not easily compared to another. Hence, the type, number, and development stage of the drugs in each company's pipeline are germane to valuation.

Competition motivates rapid development, as drugs under development have less value once a competitor's similar drug is FDA-approved. Xu[9] reports that rapid progress through the development process reveals that development is going well; a product is nearing commercialization and is associated with higher valuations. However, given the significant costs of development noted above, rapid progress implies a rapid "burn" or depletion of available cash. Bratic et al.[6] found 33% of the biotechnology firms in their sample had less than one year of cash, with 50% having less than two years. Given the multi-year development witnessed with most drugs, alliances and partnerships with larger more established companies could provide access to needed liquidity, particularly in the latter stages of development. In this vein, and according to the Biotechnology Industry Organization[4], biotechnology companies struck 417 new partnerships in 2007 with pharmaceutical companies and 473 deals with fellow companies. Baum et al.[13] and Agnew[14] note that these alliances facilitate the transition to production and enhance the likelihood of success for new disease therapies. Xu et al.[15] hold that these alliances may also serve to validate product viability to investors, contributing to firm value.

Also important is the composition of the board of directors. As noted in Pisano[5], a biotechnology company presents a unique set of challenges for management and investors; with uncertain cash flows broadcast years into the future, traditional financial modeling falls short. The necessity to manage persistent risk and uncertainty, coupled with a critical need for integration between the disparate disciplines of business, science and medicine suggests that boards may require a special backgrounds and expertise. The presence of medical doctors and financiers on boards may impact spending on R&D and may influence alliances, later influencing firm performance and value.

A broad literature examines the relationships between corporate governance and firm value. Vance[16] and Pearce and Zahra[17] consider the functional backgrounds of directors. Barnhart and Rosenstein[18] find that smaller boards generally outperform larger boards, while Finkle[19] concludes that there is a quadratic relationship between the number of board members and firm valuation—value increases with board size up to a point and then diminishes. While larger boards of directors may allow for a more diverse array of knowledge and perspectives, larger boards suffer from the adverse effects of large group dynamics such as free-riding and fractionalization.[20,21]

Board independence is another area of uncertainty. Jensen and Meckling's[22] seminal work notes that most corporate managers are not shareholders but agents of those owners. As agents, they have little or no personal

wealth at stake and often act in their own self interests. Jensen and Meckling's work has encouraged a number of studies of the behavior of managers, and the importance of board composition in assuring the enhancement of firm value. For example, non-management or outside directorships seem to influence value. Schellenger et al.[23] find a direct positive relationship between outside director's representation on the board and a risk-adjusted measure of stock price performance. On the other hand, earlier work by Vance[24] finds that better financial performance, as measured by net income, sales, and owner's equity, is associated with a high proportion of inside directors. Pfeffer[25] suggests the existence of an optimal insider-outsider ratio. And Dalton et al.[26] and Bosner[27] find that board composition in terms of insiders, outsiders, and CEO/Chair duality has virtually no effect on firm performance.

In a study of Canadian firms, McIntyre et al.[28] find that firm performance as measured by Tobin's Q is highly correlated with the board levels of experience, team size, variation in age, and team tenure. Among other results, they suggest that peers of similar age work better in increasing firm value, than boards comprised of generational age differences. Markarian and Parbonetti[29] classified board members according to four typologies developed by Baysinger and Zardkoohi[30]: insiders, business experts, support specialists, and "community influentials." They find that a higher proportion of support specialists on the board is associated with larger R&D expenditures per employee, but they do not discover such relationships for the other three board typologies.

Drug therapies designed for specific conditions (e.g. cancer, diabetes) might also create value. Targeting high-profile diseases may be a promising strategy. Among the diseases targeted by sample firms, cancer, cognitive disorders, pain, heart disease, diabetes, and AIDS have the greatest number of drug indications under development. Market valuations of these R&D investments may be associated with high market valuation due to the potential for substantial new revenues. This is especially true for drugs in the advanced stages of development, and those that target multiple high-profile diseases.

DATA

The importance of several factors influencing company valuation is measured. Drug development success, strategic alliances, board composition, pipeline diversity and specific disease targets are considered. The sample includes 163 biotechnology companies with market capitalizations greater than $30 million over the period from the first quarter of 2007 to the first quarter of 2009. The sample consists of 116 firms with less than $1 billion in market capitalization and 47 worth over $1 billion.

Firms in the sample have Standard Industrial Classification (SIC) codes between 2830 and 2836. These firms discover, develop, produce, and sell drugs for the treatment or diagnosis of human diseases; 199 firms meeting this criterion were initially identified; 29 firms were omitted due to incomplete or inaccessible financial data and seven firms were excluded due to incomplete or inaccessible clinical trial data. Financial data were collected from Bloomberg, clinical trial and strategic alliance data were collected from Inteleos, and board of director information was gathered from company websites.

Firms in the sample have an average of more than five drugs in phase II clinical trials and more than three in phase III trials. Phase II appears to be a critical turning point in the drug development pipeline, as firms have modestly more drugs discontinued in phase II, than in phases I and III combined.

Disease indications are grouped into seven categories: cancer, cognitive disorders, pain, heart disease, diabetes, AIDS, and bone disorders. The total number of drug indications under development by firms in the sample, in each of these categories is, respectively, 842, 199, 106, 102, 99, 67, and 48. Cancer therapies dominate the pipeline for firms in the sample with a mean of 5.17 drugs per company. Firms also have an average of 1.22 drugs that target cognitive disorders and an average of 0.65, 0.63, and 0.61 drugs for pain, diabetes, and heart therapies.

Board members are classified into five categories: medical doctors, business experts, scientists, financiers, and support professionals. They are classified as medical doctors regardless of whether or not they are still practicing. Business experts are consultants or managers of biotechnology/pharmaceutical companies. If the director possessed specialized knowledge outside of the biotechnology industry (lawyers, accountants, chemical engineers, etc.) they are classified as support. Scientists are those who hold PhD's. Financiers belong to a venture capital group, hedge fund, or investment bank.

The typical size of boards of directors in the sample is approximately eight individuals, with an average of 3.45 business experts, 1.47 financiers and 1.3 medical doctors per board. There is an average of nearly seven males in each group and roughly 42 percent of the boards in the sample are chaired by the CEO. On average, boards contain approximately 1.5 members who are current or previous employees of the company.

The average change in market capitalization for firms in the sample over the time period Q1 2007-Q1 2009 is -3.28% with a median of -43.69%, indicative of the recessionary climate during the sample period. Yet, on average, changes in research and development expenditures

are 26.12%. Price-to-book ratios at the end of the sample period exhibit considerable variation across firms.

Pipeline success is measured, as in Dimasi[11] using the probabilities of drugs passing through the various stages of development, and calculate the percent of a firm's total pipeline that is expected to be FDA approved. The total number of drugs in the pipeline expected to be FDA approved is estimated as:

(1) $E[Approved\ Drugs] = Prclinic\ (n_1)*.1936 + PhaseI(n_2)*.2391 + PhaseII(n_3)*.3188 + PhaseIII(n_4)*.6375 + Pending(n_5)*.75$

Where $n_1 - n_5$ are the number of drugs the firm has at the associated stage of development.

The percentage of the total pipeline that is expected to be FDA approved is estimated as:

(2) $E[Approval\ Rate] = E[Approved\ Drugs]\ /Total\ drugs\ in\ the\ pipeline$

Accordingly, a drug in the preclinical trial has a probability of 19.36% to pass the FDA final approval; this probability is 23.91% for a drug in Phase I trial, 31.88% for a drug in Phase II trial, 63.75% for a drug in Phase III trial and finally, 75% for a drug in the final FDA approval process.

Using the function above, firms in the sample expect to have 5.47 drugs FDA-approved, on average (with a median of 2.34). This suggests that on average roughly 33% of drugs in the associated pipelines can be expected to be approved.

To quantify pipeline diversity, the number of drug indications in each of the phases of development and phases of discontinuance is measured, extending the measures of diversity used in Guo et al. [31] and Xu et al.[15] Those measures accounted for differences in expected returns across target diseases. Guo et al.[31] used the total number of drugs being developed by a firm to assess pipeline diversification; Xu et al.[15] measured the level of diversification using the number of different drug therapies the firm had in development. To account for the importance with alliances and mergers, we measure the number of alliances per firm that were in effect at the end of the most recent pipeline development phase; the pipeline report revealed firm alliances.

Table 1: Variable names and definitions

Board of Director Variables	
Director	Number of directors on board of directors
Medical	Number of medical doctors on the board
BsExpert	Number of business experts on the board (consultants, managers, VP's, CEOs, etc of healthcare, pharma, or biotechnology companies)
Finance	Number of financiers on the board (bankers, hedge fund managers, institutional investors, venture capitalists)
Scientists	Number of scientists on the board (scientists, PhDs)
Support	Number of support professionals on the board (attorneys, accountants, etc)
CEODual	= 1 if CEO is also the chairman of the board, = 0 otherwise
Male	Number of males on the board
PhDFinance	Number of financiers who hold PhD's
PhDExpert	Number of business experts who hold PhD's
Insider	Number of current or previous employees of the company that reside on the board
Performance Variables	
MktCap0709	The change in the market capitalization of the company from Q1 2007 to Q1 2009
RD0709	The change in research & development expenditures from Q1 2007-Q1 2009
PBratio	Price-to-book ratio as of Q1 2009
PTBratio	Price-to-tangible book ratio as of Q1 2009

Table 1: continued

Drug Pipeline Variables	
Prclinic	Number of drugs in preclinical trials Q1 2009
PhaseI	Number of durgs in Phase 1 clinical trials Q1 2009
PhaseII	Number of drugs in Phase 2 clinical trials
PhaseIII	Number of drugs in Phase 3 clinical trials
Pending	Number of drugs pending FDA approval
Approved	Number of drugs approved since 1998
PhaseIV	Number of drugs in post-marketing surveillance trials[32] since 1998
DsconPre	Number of drugs discontinued during preclinical trials since 1998
DisoconI	Number of drugs discontinued during phase 1 trials since 1998
DisconII	Number of drugs discontinued during phase 2 trials since 1998
DisconIII	Number of drugs discontinued during phase 3 trials since 1998
DisconPA	Number of drugs discontinued during the pending approval stage since 1998
Suspend	Number of drugs in development temporarily put on hold by the company
Withdraw	Number of approved drugs pulled from the market (e.g. Vioxx)
Licensed	Number of drug indications approved and that are being marketed and/or were developed with more than one firm
Solo	Number of approved drug indications that were developed and are marketed by one company
DrugAppr	Number of drug indications approved and on the market since 1998
AIDS, Bone, Cancer, Cognitive, Diabetes, Heart, Pain, Other	Number of drug indication therapies in development targeted at each ailment as of Q1 2009

A full list of variable names and definitions is provided in Table 1. Descriptive statistics are shown in Table 2. The size and composition of the boards of directors are considered, along with the number of doctors, financial experts, scientists, PhD's, and insiders on the boards. Over the period of the study, from the first quarters of 2007 through 2009, prosaic measures of market capitalization, research expenditures, and price-to-book ratios are gathered. Clinical factors include measures of the numbers of drugs in various testing phases, the successes and failures of drugs in the various company pipelines and the diseases targeted by the drugs in the pipeline. In Table 2, the average board has seven or eight members, most of whom are male and one or two of which are founders or other insiders. Three or four of the board members are "experts" in the industry; those experts might also be founders or insiders. The typical firm has between three and six drugs in various stages of development; some have as few as one, and some over 100, using the generous descriptions used by firms when identifying the different compounds they have in various stages of testing; the drugs being developed are designed to treat a panoply of ailments, from AIDS to cancer, heart disease, cognitive disorders, diabetes and pain.

METHODS

Relationships between the several explanatory variables and performance and valuation are examined. Explanatory variables include measures of drug development success, strategic alliances, board composition, pipeline diversity and specific disease targets. Given the wealth of research describing a relationship between firm size and market performance, we created a small

Table 2: Descriptive statistics

Variables	Mean	Median	Minimum	Maximum	n
Board of Director Variables					
Director	7.85	8	3	15	163
Medical	1.3	1	0	6	163
BsExpert	3.45	3	0	7	163
Finance	1.47	1	0	7	163
Scientist	0.52	0	0	4	163
Support	1.16	1	0	8	163
CEODual	0.42	0	0	1	163
Male	6.98	7	2	13	163
PhDFinance	0.24	0	0	2	163
PhDExpert	0.78	0	0	4	163
Insider	1.46	1	0	6	163
Performance Variables					
MktCap0709	–23.28	–43.69	–98.54	418.36	162
RD0709	26.12	4.11	–161.34	627.82	160
PBratio	13.22	3.22	0.176	553.15	135
PTBratio	11.85	3.99	0.817	321.35	117
Drug Pipeline Variables					
Prclinic	3.5	2	0	31	163
PhaseI	2.79	1	0	71	163
PhaseII	5.68	2	0	120	163
PhaseIII	3.02	1	0	101	163
Pending	0.51	0	0	6	163
Approved	3.21	0	0	85	163
PhaseIV	1.13	0	0	35	163
TotPipes	5.47	2.34	0	128.4	163
PipeFDA	33.08	30.82	0	75	163
DsconPre	2.89	1	0	41	163
DisconI	2.01	0	0	61	163
DisconII	3.55	1	0	91	163
DisconIII	1.48	0	0	43	163
DisconPA	0.18	0	0	8	163
Suspend	0.37	0	0	7	163
Withdraw	0.25	0	0	19	163
Licensed	11.69	4	0	191	163
Solo	17.79	8	0	493	163

Table 2: continued

Variables	Mean	Median	Minimum	Maximum	n
DrugAppr	8.74	5	0	157	163
AIDS	0.41	0	0	8	163
Bone	0.29	0	0	5	163
Cancer	5.17	0	0	111	163
Cognitiv	1.22	0	0	41	163
Diabetes	0.61	0	0	17	163
Heart	0.63	0	0	21	163
Other	7.04	4	0	115	163
Pain	0.65	0	0	23	163

cap indicator variable to control for differences in market capitalizations. A differentiation was made between companies that exhibited positive growth in market capitalization over the period of study and those that experienced a decline.

An array of measures to proxy for performance and valuation were employed, including price-to-book ratios, changes in market capitalization, changes in R&D spending, the number of expected drug approvals and the expected approval rate. The price-to-book ratio and changes in market capitalization served as measures of changes in firm size or value. Because data were collected during a recessionary period, changes in capitalization for the sample may not be indicative of firm success.

Changes in research and development expenditures over the period of the data (first quarter of 2007 to first quarter of 2009) influence the drug development pipeline; this simply assumes that higher R&D expenditures are indicative of more drugs in a company's pipeline and progression through the pipeline toward commercialization.

Finally, it is hypothesized that firms with a larger number of expected drug approvals and greater drug approval rate will have more favorable measures of success and higher valuations. Indeed, drug approvals can be viewed as both a quantifiable measure of success and a causal factor in explaining other valuation measures. However, endogeneity may confound the empirical estimation of the effect of pipeline success on firm performance and valuation. For example, higher expenditures on research and development may lead to larger number of total approvals or a higher probability of pipeline success, yet as drugs near the approval stage, R&D spending may increase. This potential for endogeneity prompts the use of an instrumental variables approach when using one of these variables as an explanatory factor in modeling the other.

RESULTS

Results in Table 3 are fairly straightforward; the price to book ratio is positively and significantly related to having a board chairperson that is also the CEO; the number of insiders and doctors on the board share this relationship. Echoing an extensive literature, the smaller firm is expected to outperform the larger one. Squared insider and doctor variables are also positive; this suggests that the importance of those parties being on the board, towards the enhancement of firm value as measured by the price-to-book, increases as insiders and doctors are added to the board. This is modestly surprising; an analyst might expect that with more insiders and doctors on the board, the diversity of opinion on the board might be reduced, negatively impacting firm value and the price-to-book ratio. Such is not the case with the firms in the sample.

Extending this discovery concerning the number of insiders and doctors on the board, Figure 1 portrays the predicted price-to-book ratio using the medical doctor and insider coefficients from Model 2 in Table 3. The quadratic relationship between insiders, doctors and the price-to-book ratio is revealed. It is likely that the newest firms, with the lowest earnings and the smallest book values, have a greater preponderance of doctors and founding partners (insiders) on their boards than do "older" more established firms. With the "number of insiders" becoming a proxy for the newer smaller firm with the lower book value, the linear and quadratic relationships observed between the number of insiders (and doctors) and the price-to-book ratio is less surprising.

Extending the "stories" of Table 3 and Figure 1, in Table 4 the price-to-book ratio is measured against additional descriptive features of the board of directors. The importance of board composition as measured by the percentage of total membership comprised of

Table 3: OLS results for price-to-book ratio

	Model 1	Model 2	Model 3	Model 4
Variable	Coefficient (standard error)			
Intercept	–42.28*** (13.14)	–25.88*** (10.27)	–34.28*** (11.32)	–33.71*** (12.31)
CEO Dual	13.39+ (8.71)	15.48* (8.62)	15.05* (8.62)	13.98+ (8.70)
Small Cap	19.99** (9.30)	22.06** (9.25)	22.31** (9.26)	19.93** (9.28)
Insider	14.48*** (5.02)			13.21*** (5.06)
Insider^2		3.25*** (1.04)	3.54*** (1.03)	
Medical Doctor	11.20*** (3.95)		11.85*** (3.89)	
Medical Doctor^2		2.80*** (0.90)		2.72*** (0.92)
R-Squared	0.1448	0.1675	0.1656	0.1495

**Indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level*

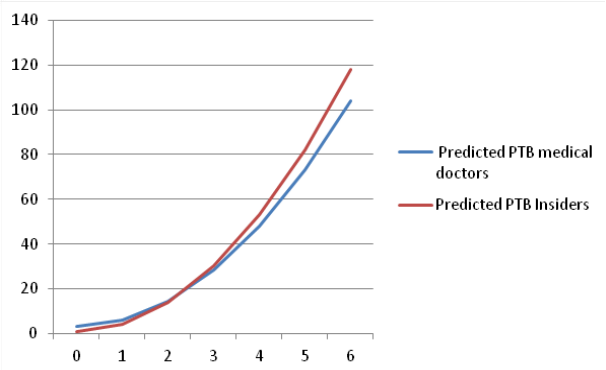

Figure 1: Predicted price-to-book ratio as a function of the number of medical doctors and insiders

individuals with different backgrounds is examined. Given an increase in the growth rate of the relative portion of the board made up by doctors, the presence on the board of men (without over-representation), and the inclusion of finance experts on the board (without over-representation), the price-to-book ratio increases. For the firm seeking to enhance its attractiveness to buyers (both buyers of its stock, and potential buyers of the entire firm), these findings are not critical, but they are telling; the firm should exhibit a growing board presence of doctors, and should include but not overweight men and "experts" in finance.

Results in Tables 3 and 4 relate board features to firm value. Increasing equity values, as firms mature and expand, are characterized by a number of the variables. Most of the features of the board members (MD's, insiders, gender, etc) do not regularly influence the firm's market cap or firm size, but they are often associated with equity *returns*. In a set of unreported tests, it is found that only the finance PhD's and scientists appeared to play any significant role in describing market cap.

But between 2007 and 2009, two difficult years for most equities across the world, the examinations of R&D expenditures reveal several patterns: In Table 5, for example, the influence of doctors and business experts in directing firm resources towards greater expenditures on research is affirmed. In a broad set of unreported tests, no separable statistically significant influence of scientists or insiders, in directing the firm towards greater R&D expenses, is observed over those years. One might have expected the influence of those stakeholders to increase during that time period, but such is not the case.

Changes in research and development expenditures are associated with efforts to move drugs through the development pipeline, and those changes influence firm value. In Table 6 below, the number of drugs in the pipeline pending FDA approval (*Pending*) has a negative

effect on *RD0709*, the R&D expenditures between 2007 and 2009. This may at first seem counterintuitive, but on reflection it makes sense: Having invested in a given drug in the past, as that drug moves through the pipeline, companies seem to pause on other, newer, R and D efforts, as the decisions attaching to the existing drug(s) develop.

Table 4: OLS results for price to book ratio with board composition measured as a percentage of the board

Variable	Coefficient (standard error)
Intercept	–120.89* (65.22)
CEO Dual	–0.76 (4.14)
Insider	0.11 (0.18)
Medical Doctor	–1.46* (0.77)
Medical Doctor^2	8.47** (3.82)
Medical Doctor^3	–11.93** (5.09)
BsExpert	–0.21 (0.14)
Finance	0.14 (0.17)
Scientist	–0.05 (0.24)
Male	10.84** (5.18)
Male^2	–19.19** (9.18)
Male^3	9.75** (4.64)
PhDFinance	–0.44 (0.35)
PhDExpert	1.52** (0.78)
PhDeExpert^2	–7.29 (4.64)
PhDExpert^3	8.28 (6.57)
R-Squared	0.1441

*Indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level

Table 5: OLS results for change in R&D expenditures with board composition measured as a percentage of the board

Variable	Coefficient (standard error)
Intercept	–142.85 (92.10)
Medical	–2.95 (2.94)
Medical^2	23.03* (14.02)
Medical^3	–26.55 (17.59)
BsExpert	1.4*** (0.56)
Finance	1.32* (0.72)
Scientist	0.79 (0.95)
CEODual	9.12 (16.73)
Male	3.69 (2.66)
Male^2	–3.78 (2.42)
Male^3	0.56 (0.42)
PhDFinance	0.69 (1.45)
PhDExpert	4.12 (3.23)
PhDeExpert^2	–18.51 (19.52)
PhDExpert^3	22.53 (28.25)
R-Squared	0.1245

*Indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level

Results in Table 6 suggest that higher R&D expenditures are influenced by higher expected approval rates, as calculated using Equation 2, but the *direction* of that relationship should be kept in mind; higher R&D expenditures likely lead to higher approval rates and the higher approval rates themselves influence R&D. As the FDA moves a drug past various phases of approval, additional R&D spending ensues, as those approvals themselves mandate additional expenditures by the drug developer.

Interestingly, the number of professional support personnel in Table 6 (lawyers, accountants) exhibits a quadratic relationship with changes in R&D spending. This relationship, represented in Figure 2 (with other dependent variables evaluated at their means), signifies that as more professional support personnel are added to boards, R&D spending may decrease at first, but will eventually increase with additional support personnel. This is an absolute and relative relationship; we find that as either the total number of these personal or their percentage representation on the board increases, the effect in Figure 2 is observed. Notably, boards with between two and seven professional support personnel appear to decrease spending on R&D on average, while those with fewer than two or more than seven support personnel appear to increase spending on R&D. This changing spending, in turn, influences firm value and the attractiveness of the firm to stockholders and potential acquirers.

Expected drug approvals, the hoped-for outcome of the R&D expenditures, are associated with several distinct factors, as shown in Table 7. Following an exhaustive set of tests encouraged by prior research and anecdotal comment in the press, one finds the likelihood of drug approvals characterized by the number of prior approvals, the alliances in which the firm is engaged, and the duality of the CEO's role with the firm. The expected approval rate is higher for the firm with a history of drug approvals (this is unsurprising), that is not a member of a drug development alliance but is working on its own, and whose CEO is not also the board chairman; this contrasts with the higher price-to-book ratios observed for firms with a board chairman who is also CEO. The greater likelihood of success among firms going "solo," suggests that perhaps the firms seek partners for the less promising endeavors, saving the better prospects for independent development. As well, the greater success of firms that have earlier had drugs approved may contribute to a snowball effect—the firms with greater prior success have enhanced later success, and in turn invest more in R&D, perpetuating the cycle.

A multitude of tests were conducted, encouraged by the financial press, to ascertain the importance of firm foci on various diseases in both motivating research and in contributing to the firm's growth and overall equity values. In Table 8 below, it is shown that additional R&D spending is associated with those firms that are moving drugs through the FDA pipeline, with those companies that have recently discontinued work on a drug, and for those firm's engaged in bone work. A review of the p-values in the right-hand column of Table 8 suggests that, for the sample, research is conducted across a broad area of medical maladies, with only bone research being associated with statistically significantly increased R&D expenditures for the small cap firms in the sample. Note also the marginal significance of the relationship between market cap and R&D. In another set of tests, not detailed here in the interest of brevity, no single disease and its adjacent treatments are statistically significantly

Table 6: OLS results for percent changes in R&D expenditure

Variable	Coefficient (standard error)
Intercept	–0.62* (0.38)
Pending	–0.15* (0.09)
Expected approval rate	1.54** (0.66)
Director	0.09** (0.04)
Support	–0.35*** (0.12)
Support^2	0.04** (0.02)
R-Squared	0.1133

**Indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level*

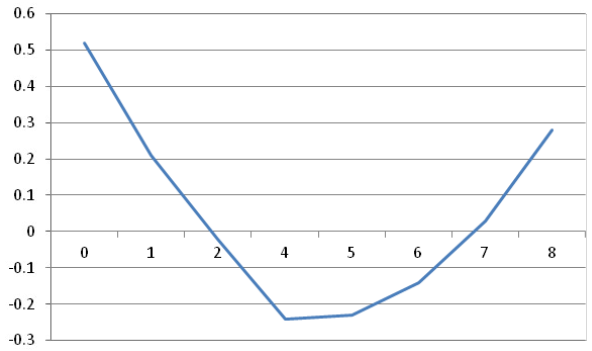

Figure 2: Predicted percentage change in R&D expenditure as a function of professional support personnel

Table 7: OLS results for expected drug approval rate

Variable	Coefficient (standard error)
Intercept	0.34*** (0.01)
Approved	0.007*** (0.002)
Solo	–0.001*** (0.0004)
CEODual	–0.04** (0.02)
Finance[2]	0.002[+] (0.0016)
R-Squared	0.1270

**indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level, [+]indicates significance at the 15% level*

Table 8: OLS results drug data-small capitalization firms

Variable	Coefficient (standard error)
Intercept	–37.71 (39.26)
MktCap0709	0.19 (0.12)
Prclinic	25.17 (26.00)
PhaseI	7.45 (30.94)
PhaseII	21.31 (39.02)
PhaseIII	51.78 (72.22)
Pending	12.82 (82.85)
Approved	35.32 (30.31)
PhaseIV	–3.55 (26.45)
TotPipes	–68.81 (109.03)
PipeFDA	2.6*** (1.09)

Table 8: continued

Variable	Coefficient (standard error)
DsconPre	34.3 (28.38)
DisconI	30.32 (30.89)
DisconII	29.15 (29.77)
DisconIII	50.6* (31.05)
DisconPA	121.65** (56.09)
Licensed	–34.34 (28.48)
Solo	–34.97 (28.34)
AIDS	40.92 (32.53)
Bone	71.58** (37.04)
Cancer	36.17 (28.17)
Cognitive	20.44 (29.86)
Diabetes	48.82 (31.99)
Heart	43.67 (36.00)
Other	30.35 (28.03)
Pain	37.25 (31.99)
DrugAppr	–4.55 (5.69)
R-Squared	0.2886

**Indicates significance at the 10% level, **indicates significance at the 5% level, ***indicates significance at the 1% level*

associated with the equity values and market caps of the sample firms.

CONCLUSIONS AND ENCOURAGEMENTS FOR SUBSEQUENT RESEARCH

Factors associated with the success of the biotechnology industry are examined, with particular attention paid to board structure and the firm's alliances, as those issues receive only limited consideration in the prior research. Employing a sample of biotechnology firms, between 2007 and 2009, alternative measures of firm valuation are modeled based upon board composition and characteristics of the drug development pipeline. Over 1,000 directors are classified by specialty and degree earned, alongside a sub-classification of close to 5,000 drug treatments under development by the examined firms. Findings show that:

- A CEO who is also board chairman appears to have a positive relationship with the price-to-book ratio, but is negatively associated with the drug approval rate.
- Similarly, small cap firms have higher price-to-book ratios (this is unsurprising and a pattern revealed in a broad research), but lower expected approval rates. Approvals for these smaller firms have a much larger relative impact, and that larger impact may account for this observed relationship. This "relative impact" influences the likelihood of acquisition; as smaller and smaller firms are influenced to a greater and greater degree by the success or failure of a given drug, the attractiveness of being acquired (and of subsequently diversifying the firm's operations over all the activities of the acquirer) increases. As well, recent changes in new equity-issue regulations have been onerous, and the desirability of being acquired over going public has become clear.
- Insiders and medical doctors on the board are associated with higher price-to-book ratios, but have no significant relationships with the number of approvals or approval rates.
- A critical mass of support personnel on the Board appears to have a significant impact on R&D spending and subsequent drug approvals.
- History of success matters.
- Volume matters; more going into the pipeline means there is a higher chance of something making it through to the market.
- Having the capital to operate independently is important; firms appear to keep the best prospects "at home," and enter alliances with poorer development candidates; this becomes risky where the firm is not independently able to fund the better prospects.

The investor could use our findings to frame a firm's success in drug approvals and equity returns, encouraging or discouraging investment. A biotech manager might anticipate market responses to changes in the company's board or research plans using our study's results. And, finally, a regulator is encouraged to maintain—with our findings—his or her sensitivity to the approval of a drug for any non-scientific or political reason. Thus our findings are important to all three of these stakeholders—the investor, the biotechnology manager and the regulator. While these findings are in no way exhaustive, and clear avenues for additional research are evident, the results shared here can assist the investor, manager, mergers and acquisitions specialist and regulator in motivating the best allocations of capital, and the most promising directions for research and development. Later research could refine some of this work—value enhancements provided by research into varied diseases is one area inviting additional tests—and assist the manager or clinician in better creating value with the biotechnology firm's resources.

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32. These drugs are already approved. The company continues to maintain and update data on the drugs. This phase may or may not be FDA mandated. Not all companies administer PhaseIV trials on their drugs.

APPENDIX

List of all biotechnology companies in this study

Company Name	Ticker Symbol
Aastrom Biosciences	ASTM
Abott Labs	ABT
Abraxis Bioscience	ABII
Acadia Pharmaceutical	ACAD
AchillionPharma	ACHN
Acorda Theraputics	ACOR
Acura Pharmaceutical	ACUR
Adolor Corp	ADLR
AffymaxInc	AFFY
AlexionPharma	ALXN
Alexza Pharmaceutical	ALXA
Alkermes, Inc	ALKS
Allos Therapeutics	ALTH
Alnylam Pharmaceuticals	ALNY
Amag Pharmaceuticals	AMAG
Amgen, Inc	AMGN
Amicus Therapeutics	FOLD
Amylin Pharmaceuticals	AMLN
Anadys Pharmaceutical	ANDS
Ardea Bioscience	RDEA
Arena Pharmaceutical	ARNA
Arqule, Inc	ARQL
Array Biopharma	ARRY
Auxilium Pharmaceutical	AUXL
AvanirPharma, Inc	AVNR
AVI Biopharma	AVII
Avigen, Inc	AVGN
Biocryst Pharmaceuticals	BCRX
Biodel, Inc	BIOD
Biodelivery Science	BDSI
Biogen Idec, Inc	BIIB
Biomarin Pharmaceuticals	BMRN
BiosantePharma	BPAX
Biospecifics Technologies	BSTC
Biotime, Inc	BTIM
Bristo-Myers Squibb	BMY
Cadence Pharmaceuticals	CADX
Cardiovasuclar Sys	CSII
Celgene Corp.	CELG
Celldex Therapeutics	CLDX
Cel-Sci Corp	CVM
Cephalon, Inc	CEPH
Chelsea Therapeutics	CHTP
Comumbia Laboratories	CBRX
Combimatrix Corp	CBMX
Corcept Therapeutics	CORT
Cornerstone Therapeutics	CRTX
Cubist Pharmaceuticals	CBST
Curis, Inc	CRIS
Cypress Bioscience	CYPB
Cytokinetics, Inc	CYTK
Cytrx Corp	CYTR
Dendreon Corp	DNDN
Discovery Labs	DSCO
Durect Corp	DRRX
Dynavax Technologies	DVAX
Eli Lilly & Co.	LLY
Emergent Biosolutions	EBS
Enzon Pharmaceuticals	ENZN
Epicept Corp	EPCT
Forest Labs, Inc	FRX
Genta, Inc	GNTA
Genvec, Inc	GNVC

Company Name	Ticker Symbol
Genzyme Corp	GENZ
Geron Corp	GERN
Gilead Sciences	GILD
GTX Inc	GTXI
Halozyme Therapeutics	HALO
HemispherxBiopharma	HEB
Hospira, Inc	HSP
Human Genome Sciences	HGSI
IdenixPharma	IDIX
Idera Pharmaceuticals	IDRA
Immunogen, Inc	IMGN
Insite Vision	INSV
Inspire Pharma	ISPH
Intermune, Inc	ITMN
Javelin Pharmaceuticals	JAV
Jazz Pharmaceutical	JAZZ
Johnson&Johnson	JNJ
KeryxBiopharma	KERX
King Pharmaceuticals	KG
KV Pharm	KV/A
Ligand Pharma	LGND
Mannkind Corp	MNKD
Map Pharmaceutical	MAPP
MDRNA Inc	MRNA
Medarex, Inc	MEDX
Medicinova, Inc	MNOV
MedicisPharma	MRX
Merck & Co.	MRK
Micromet, Inc	MITI
MiddlbrookPharma	MBRK
Molecular Insight	MIPI
Momenta Pharmaceutical	MNTA
Mylan, Inc	MYL

Company Name	Ticker Symbol
Myriad Genetics	MYGN
NabiBiopharma	NABI
Nektar Therapeutics	NKTR
Neurocrine Biosciences	NBIX
Neurogesx, Inc	NGSX
Nexmed, Inc	NEXM
Novavax, Inc	NVAX
NovenPharma, Inc	NOVN
NPS Pharma, Inc	NPSP
NymoxPhamaceutical	NYMX
Obagi Medical Products	OMPI
OncogenexPharma	OGXI
Oncothyreon, Inc	ONTY
Onyx Pharma	ONXX
Opko Health	OPK
Optimer Pharmaceutical	OPTR
Orexigen Therapeutics	OREX
OSI Pharmaceuticals	OSIP
Osiris Therapeutics	OSIR
Oxigene, Inc	OXGN
Pain Therapeutics	PTIE
Par Pharmaceuticals	PRX
PDL Biopharma, Inc	PDLI
PenwestPharma	PPCO
Peregrine Pharma	PPHM
Perrigo, co	PRGO
Pfizer, Inc	PFE
Pharmacyclics	PCYC
Pharmasset, Inc	VRUS
Poniard Pharmaceutical	PARD
Pozen, Inc	POZN
ProgenicsPharma	PGNX
QuestcorPharma	QCOR

Company Name	Ticker Symbol
Quigley Corp	QGLY
Regeneron Pharm	REGN
RegenerxBiopharma	RGN
Repros Therapeutics	RPRX
Rexahn Pharmaceutical	RNN
Salix Pharma	SLXP
Sangamo Biosciences	SGMO
SantarusInc	SNTS
Schering-Plough	SGP
Sciclone Pharm	SCLN
Sepracor, Inc	SEPR
Siga Tech, Inc	SIGA
Spectrum Pharmaceutical	SPPI
Stemcells, Inc	STEM
SucampoPharma	SCMP
Supergen, Inc	SUPG
Synta Pharmaceutical	SNTA

Company Name	Ticker Symbol
Targacept, Inc	TRGT
Theravance	THRX
Titan Pharmaceuticals	TTNP
Trubion Pharmaceutical	TRBN
Unigene Labs, Inc	UGNE
United Therapeutics	UTHR
Valeant Pharmaceutical	VRX
Vertex Pharmaceutical	VRTX
Vical, Inc	VICL
Viropharma, Inc	VPHM
Warner Chilcot	WCRX
Watson Pharmaceutical	WPI
Wyeth	WYE
Xenoport, Inc	XNPT
Xoma, Ltd	XOMA
Ziopharm Oncology	ZIOP
Zymogenetics, Inc	ZGEN

Original Article

NPV modelling for the selection of value-creating biosimilar development candidates

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ABSTRACT

The purpose of this study was to apply net present value (NPV) modelling to evaluate the financial attractiveness and business risk of different categories of biosimilars. Challenges and opportunities of biosimilars are compared with those of standard small molecule generics. Minimum peak sales levels are required to create financial value were determined in order to derive recommendations for the selection of commercially rewarding biosimilar development candidates.

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INTRODUCTION

Biologic drugs are increasingly gaining importance for the pharmaceutical and biotech industry. Whereas the market share of biopharmaceuticals sales was only 6 % of total pharmaceuticals sales in 1999, its share grew to around 22 % in 2009[1], indicating that biologics are growing twice in magnitude compared to small molecule drugs. This trend will likely continue because biotech drugs represent more than 50 % of new molecular entities in development[2]. The number of biologic drugs that have reached blockbuster sales of more than US$ 1 billion is also constantly increasing with Aranesp® (darbepoetin alpha) being the front runner with sales above US$ 10 billion. The growing success of biologics has inevitably been paralleled by an increasing cost burden to health care systems worldwide. Biologic products are highly effective, life-altering therapies, but unit costs are high, and the products are often used for chronic diseases that require continuous treatment[3]. Annual treatment cost ranges from around US$ 10.000 for Rituxan® and the beta interferons up to US$ 40.000 for Herceptin® and Avastin®, and even reach US$ 200.000 for orphan drugs such as, e.g., Myozyme®. Based on these factors, global sales of biosimilars are expected to achieve up to US$ 25 billion in the year 2020[4].

Although the expenses for pharmaceuticals represent only around 8-10 % of overall health care cost in the major markets, the increasing use of high price biologics is a significant driver of health care budgets. The top six biologics already consume 43% of the pharmaceuticals budget for Medicare Part B[5]. In the year 2011, global biologics sales totalled around US$ 108 billion, and they are expected to grow at 8% per year up to US$ 160 billion in 2016[6].

It is therefore obvious why there is a pronounced interest in developing biosimilars. However, the exact definition of biosimilars differs among regulatory agencies. EMA defines biosimilars as similar biological medicinal products[7]. The FDA has introduced the expression follow-on biologic[8]. In the present paper, we use the expression biosimilar, and the assumptions we make in this analysis are considered to be similarly relevant for both territories. Some studies suggest that the worldwide market for biosimilars which was below US$ 100 million in the year 2009 may grow up to US$ 2 billion by the year 2014, potentially reaching US$ 20 billion by 2020 when more lucrative biologics will lose market exclusivity[9]. In view of this outlook there is increasing political pressure on regulatory agencies to install an effective regulatory framework enabling the launch of generic versions of

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Table 1: Biologics sales per disease category *vis-a-vis* the years over which product patents expire

Disease category	2009 sales (US$ billion)	Patent expiration in	
		US	EU
Oncology	23.8	2012-2019	Expired/n/a
Immunology & inflammation	22.6	2012- 2016	n/a
Diabetes mellitus	14.0	2013-2017	2010-2014
Multiple Sclerosis	9.2	expired-2026	expired-2015
Diseases requiring stimulation of erythropoiesis	9.1	2015-2024	expired-2014
Other Categories	22.0		
Total	100.7		

biologics. It is expected that such biosimilars will bring along substantial savings in health care costs[10], as this had happened when small molecule generics were introduced in the past[11].

The significant commercial potential of biologics attracted many companies to start working on biosimilars already at a time when there was no regulatory pathway for the approval of such products. The European Medicines Agency (EMA) has paved the way for the approval of biosimilars by issuing guidelines for the first product categories to lose patent protection, i.e., erythropoietin and GM-CSF. This is the reason why European countries were pioneers in applying biosimilar versions of such products. On November 18th, 2010, the EMA published a draft guideline on similar biological medicinal products containing monoclonal antibodies[12]. Thus, it can be expected that in the foreseeable future a regulatory pathway for this commercially meaningful but also more complex class of drugs will be available in Europe.

FDA's biosimilars pathway has officially been opened in March 2010, when a legislation called the Patient Protection and Affordable Care Act passed the congress. However, it has not yet been enacted until today. Companies developing biosimilars in the USA are therefore just beginning to understand what the agency will actually expect for approval[13]. The FDA has created a two–step process. Companies will first have to submit analytical data showing how similar their compounds actually are compared to the FDA-approved innovator version. On this basis the agency will determine, case by case, which preclinical and clinical data shall be required for approval[14]. With the currently available information about the impact of the first biosimilar products on the market the time is mature to reanalyze the economic potential of such products.

THE SMALL MOLECULE GENERICS BUSINESS MODEL

The generics business model for small molecules requires only one successful bioequivalence study for approval. Small molecule generics are interchangeable with their reference originator products. Interchangeability as defined in the BPCIA (Biologics Price Completion and Innovation Act) allows a pharmacist to substitute the originator drug with a generic product without the intervention of the prescribing physician. Development costs are usually small (in the range of US$1-3 million), and development time is short. In addition, marketing costs are low. As a consequence, barriers to market entry are relatively low. This leads to intensive competition with often more than 10 generic products competing with the originator's brand. Generics that are just copycats of the original drug can only differentiate through price. Every newly launched generic competitor fuels the downward price spiral, leading to a price erosion of around 85% of the original and razor-thin margins[15]. Generics companies manage the destructive competition by taking advantage of two options: 1) position as first approved generic, securing a 6-month exclusivity period in the USA, and 2) move into complex products requiring special know-how and technologies such as, e.g., transdermal delivery formulations.

In spite of the above mentioned challenges the generics business model is interesting because of[16]

- Short development times
  < 3 years
- Limited investments
  US$ 1-3 million
- High probability of development success
  > 95 %

The attractiveness and the overall success of the generics business model for small molecules are driven by low entrance hurdles and minimal development risk. The business approach is well established, and the approval process is described in guidelines[16]. Expanding the business model from small molecule drugs to biologics was therefore an obvious strategic move for generic companies, and some have started working on such products early on[17]. It was assumed that fewer generic versions would be launched for individual biologics because of the larger development challenge, leading to a longer maintenance of higher profit margins.

THE BIOSIMILARS BUSINESS MODEL

As outlined above, there is a higher barrier to market entry for biosimilars compared to small molecule generics. Entering the biosimilars market is associated with higher costs and risks, longer development time, and greater required expertise for the clinical development of such products. Furthermore, the launch and marketing of biosimilars requires a different strategy.

When approved, most of the biosimilars are not considered to be identical to the originator product and are therefore not interchangeable at the pharmacy level. This will probably apply to all monoclonal antibodies, based on their complex structure[18]. Effective detailing and patient support are required to maximize the market penetration of biosimilars. Based on these requirements, companies with extensive financial resources and experience in the marketing of branded products have a considerable competitive advantage in the development and commercialization of such products[19].

Although there is as yet limited experience with the development of biosimilars, some characteristic parameters have been reported by numerous parties. For example, there appears to be general agreement that the overall development time is in the range of 7 to 9 years. Development costs are project specific and therefore different numbers were quoted, but there appears to be consensus across the industry that total development costs should at minimum amount to around US$ 50 million and could go up to US$ 150 million or even exceed US$ 250 million for substantially more complex products[16, 20, 21]. In addition, the risk of development failure is substantial higher compared to small molecule generics[16].

Information about cost of goods and probability of development success is scarce. The available information is conclusive for cost of goods sold (COGS), whereas the high probabilities of success that were quoted earlier appear to reflect the less complex molecular makeup of the first generation biosimilars[16].

In summary, the following assumptions characterize the development of biosimilars:

- Long development times
  7-9 years
- Substantial investments
  US$ 50-200 million
- COGS
  17 – 43% (after 10-30% price reduction vis-à-vis the innovator, if innovator COGS ranges between 15-30%)
- Lower probability of success
  50- 75%

High COGS can particularly be expected in the class of monoclonal antibodies in which treatment doses of established originator products are in the range of up to several hundred milligrams. This applies, for example, to Enbrel®, Rituxan®, Herceptin®, and Avastin®. Furthermore, for the more complex class of monoclonal antibodies, lower probabilities of success can definitely be expected, based on the much more complex structures and more challenging clinical studies in therapeutic areas such as, e.g., oncology and inflammatory diseases, in which attrition rates are generally high. A robust conclusion that can be drawn from the above: the biosimilars business model is distinctly different from the original generics business model and mimics more the one of a subclass of the specialty model, such as the reformulation of established drugs[22].

SCOPE OF ANALYSIS AND METHODS

Financial models are commonly used to determine the value of investment projects in order to facilitate strategic decisions. Thus, financial valuations were also published for biosimilars. For example, Grabowski[23] has investigated factors influencing return on investment for a representative portfolio of biological R&D projects with different cost/risk/return characteristics, leading to conclusions about an appropriate period of data exclusivity to enable overall value creation. The current analysis does not investigate portfolio returns but rather focuses on the question under which conditions individual biosimilar projects are expected to create financial value. In particular, it was considered which sales level would have to be achieved in order to yield positive NPVs. It can be expected that for each biological innovator product that has an annual sales volume exceeding US$ 1 billion, several biosmilars would eventually be launched, leading to considerable competition. Therefore, the decision for

which original product the development of a biosimilar should be initiated is to be made carefully.

The present analysis focuses on the question under which conditions a minimum acceptable NPV can be expected. The minimum acceptable expected NPV at the time of decision making, i.e., at the start of development, was assumed to be US$ 10 million. We used the expected NPV algorithm reflecting the risk of development failure at each development milestone, while cost and revenue uncertainty was reflected in one-way sensitivity analyses. This methodology was preferred over Monte Carlo simulation because the intention was to demonstrate, for individual assumptions, at which level of deviation from the likely value the NPV falls below the comfort level for making a 'Go' decision. This illustrates on which uncertainties managers should focus most of their attention.

The applied expected NPV model was described in detail previously[24]. It reflects the impact of probability of success and managerial Go/Stop decisions at each development phase. Taking into account the sensitivity analyses, it is a suitable basis for comparing the differences in commercial and financial value of different classes of biosimilars.

The following parameters were defined (see Table 2):

- Development time
- Development cost
- Probability of development success (PoS)
- COGS
- Peak sales and product life cycle dynamics
- Marketing and sales (M&S) cost
- Discount rate

The base case assumptions provided in Table 2 [16, 25, 26, 27] are blended with the professional experience of the authors. Experience from the past[26] suggests that the main development risk is failure of clinical development, in particular, Phase III, where uncommon side effects may emerge. The approval rate for products that have been submitted in Europe was 92%[26]. The present analysis applies a more conservative assumption as base case (80%), because the more complex molecules that are expected as biosimilars in the future may give rise to a larger rate of inconsistencies and issues vis-à-vis the original, leading to a slightly higher regulatory failure rate and a potentially longer period of time for regulatory review[26] .

We assume total development costs of US$ 100 million as base case (inflated at a yearly rate of 2%, see below). However, depending on the complexity of both technical and clinical development, and on the number of patients required in the clinical trials, costs may be double as high. It is, for example, still uncertain how many clinical trials will have to be conducted for originals with several approved indications. In order to ensure competitiveness, it will be mandatory that the biosimilar will cover the identical spectrum of indications. This might lead to large differences of development costs among products.

Table 2: Assumptions applied for the valuation. Alternative scenarios were also evaluated (see Table 3).

	Investment (US$ million)	Probability of success	Development time (years)
Process R&D (up to pilot scale)	12	90%	2-3
Preclinical Dev.	8	85%	1
Formulation Dev.	5	95%	
Scale up (GMP)	10	95%	(parallel)
Ph I	8	90%	1
Ph II	-	-	
Ph III	55	75%	3
Reg	2	80%	1,5
S,G&A (% of sales)	20%		
CoGs	30%		
Peak sales to achieve an eNPV of US$ 10 m	**180 million**		
eNPV (discount rate: 8%)	**10 million**		

Figure 1: Expected life cycle curve for a biosimilar
It is assumed in the base case that after 6 years of marketing of the biosimilar, the overall life cycle of the product (which includes the original) will be impacted by innovative treatment alternatives, leading to a gradual decline of sales (10% per year).

Scenario	Development Time (years)	Development Cost (US$ million)	PoS	Peak Sales (US$ million.)	Yearly Sales Decline in Years 6-12	Discount Rate	CoGs (% of Sales)	SG&A Cost as % of Overall Sales	Risk-adj. NPV (US$ million)	NON Risk-adj. NPV (US$ million)
1	9	100	37%	180	10%	8%	30%	20%	10	68
2	9	100	37%	180	10%	10%	30%	20%	0	37
3	9	100	37%	180	10%	15%	30%	20%	-11	2
4	9	100	37%	135	10%	8%	30%	20%	0	41
5	9	100	37%	180	10%	8%	17%	20%	35	134
6	9	100	37%	180	10%	8%	43%	20%	-15	1
7	9	100	37%	450	10%	8%	43%	20%	11	71
8	9	130	37%	180	10%	8%	30%	20%	2	55
9	9	200	37%	300	10%	8%	30%	20%	11	100
10	9	100	45%	180	10%	8%	30%	20%	18	68
11	9	100	37%	180	10%	8%	30%	30%	-9	16
12	9	100	37%	335	10%	8%	30%	30%	10	69
13	9	100	37%	155	5%	8%	30%	20%	10	68
14	9	100	37%	130	0%	8%	30%	20%	10	68
15	9	100	37%	236	20%	8%	30%	20%	10	68

Table 3: Scenario 1 shows the major value determinants for the base case NPV calculation of a biosimilar project at the time of project initiation.

A peak sales level of US$ 180 million (and total life cycle sales according to the graph indicated in Figure 1) would be required to obtain an expected NPV of US$ 10 million. Scenarios 2-15 demonstrate the sensitivity of the base case NPV to distinct variations of individual parameters that are within the margins of common market, development, and financial uncertainties.

Other potential uncertainties, such as, e.g., manufacturing plant inspection failures or recalls due to product quality problems were not individually assessed, because such considerations are not commonly driving the decision in favour of or against the development of a particular product. They are rather a task for risk and quality management.

The NPV model includes all project related cash flows from the start of preclinical development up to 12 years after launch. Cash flows beyond year 12 of marketing are modelled as terminal value, assuming a continuous decline of 10% yearly. Cash flows are inflated by 2% per year. The tax rate is 40%. Peak sales are achieved in year 5 on the market and maintained for 2 years. A sales decline of 10% per year thereafter was assumed due to emerging new treatment options, given the long overall product life cycle that shall include the exclusivity period of the original product.

The influence of the different input parameters was investigated to understand the value drivers and to address the question under which conditions an expected NPV of US$10 million would be achieved or missed.

RESULTS

In the first three scenarios the influence of the discount rate was investigated. At a discount rate of 8 % that would be appropriate for established pharmaceutical companies, peak sales of US$ 180 million are to be achieved in order to accomplish a positive NPV of US$ 10 million. For biotech companies, higher discount rates are applied based on their higher cost of capital. At a discount rate of 15 %, a similar peak sale level would lead to a negative NPV of US$ -10 million. Peak sales levels below US$ 135 million would lead to negative NPVs at a discount rate of 8 %.

CoGs have a substantial influence on the attractiveness of specific projects (see scenarios 5, 6, and 7). An increase of CoGs from 30% in the base case up to 43% would make a project financially unattractive whereas a decrease in CoGs by the same percentage leads to a robustly positive NPV of US$ 35 million. In the high CoGs scenario, peak sales of US$ 450 million would be needed to reach a mildly positive NPV of US$11 million.

The influence of higher development costs is investigated in scenarios 8 and 9. An increase of development costs by 30% up to US$ 130 million would actually lead to an NPV close to zero. In the case of doubling development costs to US$ 200 million, peak sales of US$ 300 million would be required to keep an expected NPV of US$ 10 million.

While development risk is only moderate in the base case scenario, an increase in probability of success from overall 37% to up 45% leads to an only slightly increased NPV of US$ 18 million.

In scenarios 11 and 12 the influence of higher marketing and sales cost is investigated. An increase of marketing and sales cost from 20% to 30% in the standard scenario would lead to a negative NPV of US$ -9 million, or alternatively, the peak sales would need to grow to US$ 335 million in order to keep the NPV level of US$ 10 million.

It is uncertain to what extent innovative treatment paradigms will affect the life cycle curve of biosimilars. In scenarios 13 and 14 the impact of a reduced sales decline in the years 6 to 12 was investigated. At a yearly decline of 5% instead of 10%, peak sales of only US$ 155 million would be required to yield an expected NPV of US$ 10 million, while a plateau (0% decline) at a level of US$ 130 million until year 12 would lead to the same result. If the competition were more pronounced than anticipated, resulting in a steep decline by 20% in the years 6 to 12 (scenario 15), sales would have to peak at US$ 236 million to compensate for the losses in the later years.

DISCUSSION

The most relevant question resulting from the present analysis is how likely it will be to achieve peak sales of US$ 180 million, and to maintain a product life time of more than 12 years of substantial sales for biosimilars after the patent of the original has expired, at a time where new treatment principles may have reached the market.

In order to evaluate this question the following parameters are considered most important:

- Market size of the pioneer product
- Total market share that the biosimilars marketed for a particular pioneer will achieve
- Number of biosimilars for a particular pioneer and order of market entry

In the current investigation market sizes of individual pioneer product ranging between US$ 1-5 billion are considered.

Given the lack of interchangeability for biosimilars at present, the market uptake of such products will be significantly slower compared to small molecule generics. In addition, the company marketing the pioneer may decide to offer significant price discounts to maintain its share. Combined with the still existing concerns of physicians and patients regarding potential side effects, this will lead to considerably smaller market shares for biosimilars in comparison to interchangeable small molecule generic products. In the current analysis, total market shares for biosimilars of 10-30 % at peak penetration are considered, in accordance with a report published by the U.S. Federal Trade Commission[28].

The lack of interchangeability and the resulting need for companies to detail their products will most likely lead to a brand-to-brand competition between biosimilars and the originators.

For such market conditions the dependence of market share on the order of market entry has been investigated[29, 30]. The relative shares of individual products are shown in Table 4. For our investigation only the relative market shares of the individual biosimilars are considered.

In order to investigate the attractiveness of biosimilars, sales of three categories of pioneers achieving US$ 500 million, US$2,5 billion, and US$ 5 billion per

Order of Market Entry	Share of 1st	2nd	3rd	4th	6th	7th
First	100%	-	-	-	-	-
Second	59%	42%	-	-	-	-
Third	44%	31%	25%	-	-	-
Fourth	36%	25%	21%	18%	-	-
Fifth	31%	22%	18%	16%	14%	-
Sixth	27%	19%	16%	14%	12%	11%

Table 4: Market research has indicated that, if product properties, price, and marketing strength are comparable, the order of market entry determines relative market shares.

Generics Companies	Pharmaceutical Companies	Asian Companies
Sandoz	Abbott	Fuji Pharmaceuticals
Teva	Astra Zeneca	Samsung/Biogen Idec Joint Venture
Hospira/ Stada	Novo Nordisk	Biocon
Mylan	Sanofi Aventis	Celltrion
Ranbaxy/ Daiichi Sankyo	Baxter	Biocon/Mylan
	Eli Lilly	Intas/Apotex
	Merck	Ranbaxy/Phenex
	Pfizer	Dr. Reddy's
	Roche	
	Boehringer Ingelheim	

Table 5: Companies that have publicly announced their engagement in the development of biosimilars

year, respectively, are assumed. The commercial target of achieving US$ 180 million peak sales is evaluated, related to varying numbers of competing biosimilar products.

For biological drugs with pioneer sales of around US$ 500 million, a biosimilar company could only reach sales of US$ 150 million if a total biosimilar share of 30% could be reached and if there were only one marketed biosimilar. At this peak sales level, the expected NPV would be US$ 3 million. All other investigated scenarios lead to negative NPVs. In conclusion, a decision to develop a biosimilar for an original product with yearly sales of US$ 500 million would be associated with high uncertainty.

For biological drugs with sales around US$ 2,5 billion the situation is more favorable for biosimilars companies, but only in case the total market share of that class would reach the upper margin of 30%. In this scenario, all biosimilars companies could exceed the target peak sale level as long as there were only three competing products. If, however, the number increased to six, only the first market entrant would be able to exceed the target peak sale level modestly, whereas four out of six would fall short in a meaningful way. Finally, if a class share of only 10% were achieved, there would again only be room for one profitable biosimilar product.

In the US$ 5 billion scenario for the originator product, all biosimilars could reach or exceed the US$ 180 million target peak sale level if their total market share amounted to 30% and a maximum of six biosimilars were marketed. If the total biosimilars share would, however, only amount to 10 %, there would only be room for two profitable products. In case there were four or more competitors, no company would be able to reach the target peak sales level of US$ 180 million.

In conclusion, as long as analytical science hasn't reached a state at which, also for biological drugs, similarity with respect to composition of matter, efficacy and safety can be demonstrated to an extent that interchangeability on the pharmacy level is approved, biosimilars have to be marketed as distinct brands. This will most likely lead to relatively low market shares of biosimilars vis-à-vis the pioneer drug. The value of individual biosimilar products will therefore strongly be driven by the sales volume of the originator at the end of its lifecycle, and by the number of biosimilar market entrants.

Since recently, not only generics companies but also established pharmaceutical companies approach the biosimilars business. Table 5 provides an overview of companies that publicly stated their engagement in this field.

This list is certainly not complete, especially with respect to companies in Asia and Latin America that have gained experience from supplying their less strongly regulated home markets with biosimilar products for some time and consider entering the more attractive western markets in the future. In any case, the number of contenders clearly shows that there is the potential that for the next wave of patent expiries there will be many companies chasing the same high value products such as., e.g., Rituxan®, leading to a challenging decision making process for every company based on the considerable level of investment and the uncertain market environment at launch and beyond.

Another aspect to be considered is how long the originator's technology will remain standard of care. Given the twelve years exclusivity for innovative biologics in the USA plus the expected time of five years to reach peak sales for the biosimilars, any technology has to be competitive for nearly 20 years. Looking at the first generation of biologics including, e.g., beta interferons for multiple sclerosis and alpha interferons for hepatitis C virus (HCV) infections, they maintained their gold standard status for approximately 20 years. Now, small molecules are approved or are in late stage clinical development to replace these products. It remains to be seen whether the next generation of biologics will enjoy the

same predominant position for such a long period of time. However, there is clear evidence that their leading position is not only challenged by upcoming biosimilars but also by so-called biobetters , i.e., modified molecules with superior properties, and by innovative therapeutic principles.

At first glance it looks like a 'no-brainer' to enter the biosimilars space. However, the present analysis indicates that this is not the case. It rather appears that the decision whether or not to engage in the development of a particular biosimilar requires a careful and thorough analysis. The following aspects should be evaluated:

- Likelihood to be the first or second market entrant,
- Low threat of substitution by improved 'biobetter' products or innovative technologies,
- Efficient production process to ensure low CoGs,
- Efficient sales organization.

In essence, the biosimilars business model can be financially rewarding, offering specialty pharma-like returns with a significantly higher probability of success compared to new chemical or biological entities. However, based on the significantly higher investments needed to bring such products to the market it is likely that not all companies currently engaged in this field will finally accomplish their expected returns based on the high number of competitors. Only companies with significant financial, technological, and marketing and sales resources will be able to compete successfully in this area.

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Original Article

China's heparin revisited: What went wrong and has anything changed?

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ABSTRACT

China is the world's largest producer of crude heparin. In 2007, tainted Chinese crude heparin made its way into the global finished heparin supply chain killing 149 persons in 11 different countries including 81 deaths in the US. While China never formally admitted that it was the source of the tainted heparin, US and European regulatory officials determined that adulterated crude heparin was intentionally introduced (for economic gain) into the Chinese heparin supply and subsequently shipped to other countries for final pharmaceutical formulation. After China was implicated as the source, tainted heparin disappeared from the global heparin supply chain. This paper reviews the social and economic factors that were likely responsible for the Chinese incident and whether or not another economically-motivated case of crude heparin adulteration is possible in China.

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Heparin, a naturally-derived, highly sulfated glycosaminoglycan, is an injectable anticoagulant that is widely used to prevent blood clot formation[1]. It is routinely prescribed before most major surgeries, to people who are immobile for long periods and to patients on kidney dialysis[2]. Approximately, 10 to 12 million Americans are treated with heparin each year[3]. The annual worldwide consumption of crude heparin is over 200 tons and sales revenues are in excess of $5.0 billion per year[4, 21].

Pharmaceutical-grade heparin is prepared from mucosal tissues of slaughtered meat animals such as pig intestine or cow lung[5]. Because over half of the world's pigs are in China, it has emerged as the world leader in crude heparin production. In fact, China is the only country in the world that can meet the global demand for the raw materials to produce heparin[6]. At present, China controls more than 60% of the world's crude heparin market. In 2011, Chinese export of heparin exceeded $1.0 billion and by some estimates accounts for up to 33% of the finished heparin sold in the US (Fig. 1)[6, 7].

Although China is the global leader in crude heparin production, final dosage forms of heparin are produced outside of China. To that end, large volumes of crude or partially purified Chinese heparin are exported to foreign manufacturing sites for further purification and processing. Purified heparin (the active pharmaceutical ingredient or API) is subsequently sold to pharmaceutical companies like Baxter International, Inc. (BI) and APP Pharmaceuticals (APP) that formulates and sells final dosage forms. BI and APP each controlled roughly 50% of the US finished heparin market before the incident.

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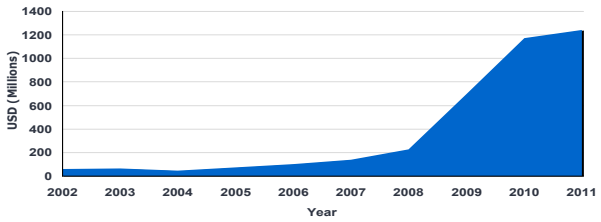

Figure 1: Size of China's crude heparin export market, 2002-2011

CHINESE CRUDE HEPARIN PRODUCTION

Heparin is produced in China via an enormous, complex network of pig farmers, slaughter houses, small, family-run crude heparin extraction companies or "workshops" and larger production companies (heparin consolidators) like Scientific Protein Laboratories-Changzhou (SPL-CZ) and Hepalink that process crude heparin and prepare it for export[8].

Typically, pig intestines from thousands of farmers and slaughter houses are purchased and then processed by the workshops. These workshops are often run and managed by small farmers and are currently exempt from regulatory oversight by the State Food and Drug Administration (SFDA)—the United States Food and Drug Administration (FDA) Chinese counterpart FDA's.

The extraction process involves boiling pig intestines, collecting mucosal membranes and then drying them to create crude heparin extracts. The crude extracts are sold to local or regional Chinese heparin consolidators, where they are combined into larger batches and processed further. These partially-purified heparin preparations are then sold to major Chinese heparin exporters which, in turn, ship them to foreign manufacturing companies that create the final heparin dosage forms used to treat patients[8]. At present, there are about 35 registered heparin producer/exporters in China.

Interestingly, the, farms, slaughterhouses and workshops that supply raw materials and batches of crude heparin to Chinese heparin consolidators and exporters fall outside of SFDA's purview. Consequently, they are not legally required to be operated according to Chinese CGMP. Moreover, according to SFDA CGMP guidelines, there is no requirement for registered Chinese heparin consolidators or exporters (both subject to SFDA inspections and CGMP regulatory oversight) to regularly inspect or audit operations at crude heparin production facilities. Because of this, most Chinese heparin consolidators and exporters choose not to impose strict traceability, accountability and quality manufacturing standards on their crude heparin suppliers to cut costs. Put simply, crude heparin production in China is largely unregulated and represents a "weak link" in the global heparin production supply chain.

ADULTERATED CHINESE HEPARIN

In late 2007 and early 2008 the US FDA and the Centers for Disease Control (CDC) in Atlanta began receiving reports of serious adverse reactions and deaths in patients undergoing dialysis[9]. These reports triggered a series of investigations by the US FDA which linked the adverse events and deaths to heparin products manufactured by Baxter International Inc. This prompted Baxter to recall and remove all of its heparin products from the US market. Once the products were removed from the market and contaminated lots destroyed, reports of heparin-related adverse reaction essentially stopped[10].

Further investigations revealed that adulterated BI heparin products had made their way into the drug supplies of 11 other countries including Australia, Canada, China, Denmark, France, Germany, Italy, Japan, the Netherlands and New Zealand: prompting heparin recalls in those countries[11]. Worldwide, 149 persons died; including 81 deaths in the US.

In early 2008, FDA investigators identified the primary source of the adulterated heparin as Scientific Protein Laboratories-Changzhou (SPL-CZ); Baxter's main supplier of heparin and, at the time, one of China's largest heparin exporters. SPL-CZ is a joint venture of Wisconsin-based Scientific Protein Laboratories, LLC (SPL) and Changzhou, China-based Techpool Bio-Pharm Co Ltd[12]. The SPL-CZ facility opened in 2004 and quickly became the primary source of heparin supplied to Baxter by its parent company Wisconsin-based SPL.

Analyses of Baxter's adulterated heparin products revealed the presence of oversulfated chondroitin sulfate (OSCS); a contaminant that was ultimately linked to the reported adverse reactions and deaths among dialysis patients. OSCS, a heparin-like molecule, is not a byproduct of the heparin production process nor is it a natural product[10, 13]. It is a synthetic material that is produced by chemically modifying chondroitin sulfate, a nutritional supplement that is frequently used to control joint pain.

OSCS can be 100 times less expensive to produce than heparin. Recent estimates suggest that OSCS cost as little as $20/kg to manufacture as compared with a price of roughly $2,000/kg to produce crude heparin[6]. Further, OSCS can mimic many of heparin's chemical and biological properties. Because of this, OSCS was not detected as an adulterant in standard quality assays or by additional analytical tests used by Baxter. The chemical and biological similarities between OSCS and crude heparin suggest that the adulterant was engineered to pass US pharmacopeial and compendial tests and that it was knowingly

and intentionally added to Chinese batches of heparin destined for the US and other countries[12].

Once OSCS was identified as an adulterant, it was quickly detected in heparin lots produced in China by SPL-CZ and also in crude heparin extracts provided to SPL-CZ by several of its consolidators[14]. At that time, SPL-CZ purchased most of its starting materials for further processing from two companies—Changzhou Techpool and Hangzhou-based Ruihua Biomedical Products Co. While Changzhou Techpool and SPL-CZ mostly cooperated with FDA during its investigation Ruihua denied inspectors access to its processing laboratory and declined to provide a list of suppliers of its crude heparin. This suggested that OSCS may have been added to crude heparin extracts before reaching SPL-CZ's processing facilities[14]. To that point, many crude heparin workshops also routinely manufacture large amounts of chondroitin sulfate from animal cartilage (both pig and cow). Consequently, it is possible that the workshops manufactured the OSCS and then added it to the crude extracts sold to SPL-CZ. The amount of OSCS found in adulterated heparin lots ranged from 2% to 50% by dry weight. Because of the scope of the problem, several industry insiders speculated that as much as three tons of OSCS must have been manufactured and used to dilute crude heparin extracts. Substituting OSCS for crude heparin would have generated profits of $1.0 to $3.0 million USD for those individuals or companies responsible for the adulteration[6].

While the world's attention was focused Baxter's heparin supply chain problems, other heparin sellers like Sanofi-Aventis identified OSCS in heparin sold in Germany where 80 German dialysis patients also became ill[15]. Subsequently, FDA identified 11 other Chinese companies (in addition to SPL-CZ) that supplied OSCS-contaminated heparin to 11 other countries besides the US which strongly suggested that the contamination was coming from a source (workshop or consolidator) upstream of SPL-CZ[11].

Yet, despite mounting evidence that implicated China as the source of adulterated heparin, officials from China's State Food and Drug Administration (SFDA)—were reluctant to fully cooperate with the FDA investigation to determine the source of the adulteration[16]. Further, SFDA steadfastly refused to acknowledge that OSCS was responsible for the adverse events and deaths linked to contaminated heparin products. Also, Chinese officials contended that since Baxter had destroyed many of the adulterated heparin lots they could not be analyzed by SFDA to confirm FDA's findings. Finally, Chinese regulators reasoned that because SPL-CZ is subsidiary of US-based SPL then the parent company, not SFDA, should "bear responsibility for the plant and its problems[16]." However, it is important to note that while Chinese government officials were publicly denying any responsibility or culpability for the OSCS adulteration scandal, SFDA inspectors were closely working with US FDA representatives to identify the adulterant source. Public denial of allegations of wrongdoing is Chinese government policy but it does not mean that China is not quietly conducting investigations behind the scence.

WHAT WENT WRONG

While it is still not exactly clear how OSCS found its way into the SPL-CZ heparin supply chain (Fig. 2), there is little doubt that missteps by the FDA, SFDA and Baxter contributed to the problem. First, Baxter began receiving heparin made at SPL-CZ facility in 2004 but failed to conduct its own audit of the facility until 2007, relying instead on earlier audit results obtained by another company[6]. Further, FDA approved SPL-CZ as a supplier for Baxter without conducting a pre-approval inspection partly because the agency confused SPL-CZ with the name of another previously-inspected Chinese manufacturing facility (Changzhou, Pharmaceuticals) in its database[3, 6]. Moreover, when Baxter sent an audit team to inspect the SPL-CZ facility both during and after the incident it was denied access to upstream workshops and heparin consolidators that supplied SPL-CZ with its raw materials.

Second, when FDA finally inspected the SPL-CZ production facility after receiving reports about adulterated heparin that possibly emanated from the facility, its inspectors found a number of manufacturing and quality issues; including unclean heparin production tanks, poor control of raw materials from vendors and a lack of an effective process to remove impurities from lots of processed crude heparin. Similar to Baxter's experience, FDA inspectors, despite repeated requests, were denied complete access to several of SPL-CZ's crude heparin suppliers. While the agency issued a warning letter to SPL-CZ[17], it did not take any further regulatory action or issue import alerts for heparin exported from SPL-CZ and other major Chinese heparin exporters. The agency did, however, place seven upstream heparin producers (and later an additional 22[18]) that were directly linked to OSCS adulteration on import alert lists to prevent importation of additional adulterated lots of heparin into the US[19].

Third, because SPL-CZ was classified in China as a chemical manufacturer it was not required to be registered with the Chinese SFDA (something that is required for all pharmaceutical manufacturers in China)[6]. Therefore, according to Chinese regulations, SFDA did not have the knowledge or authority to oversee

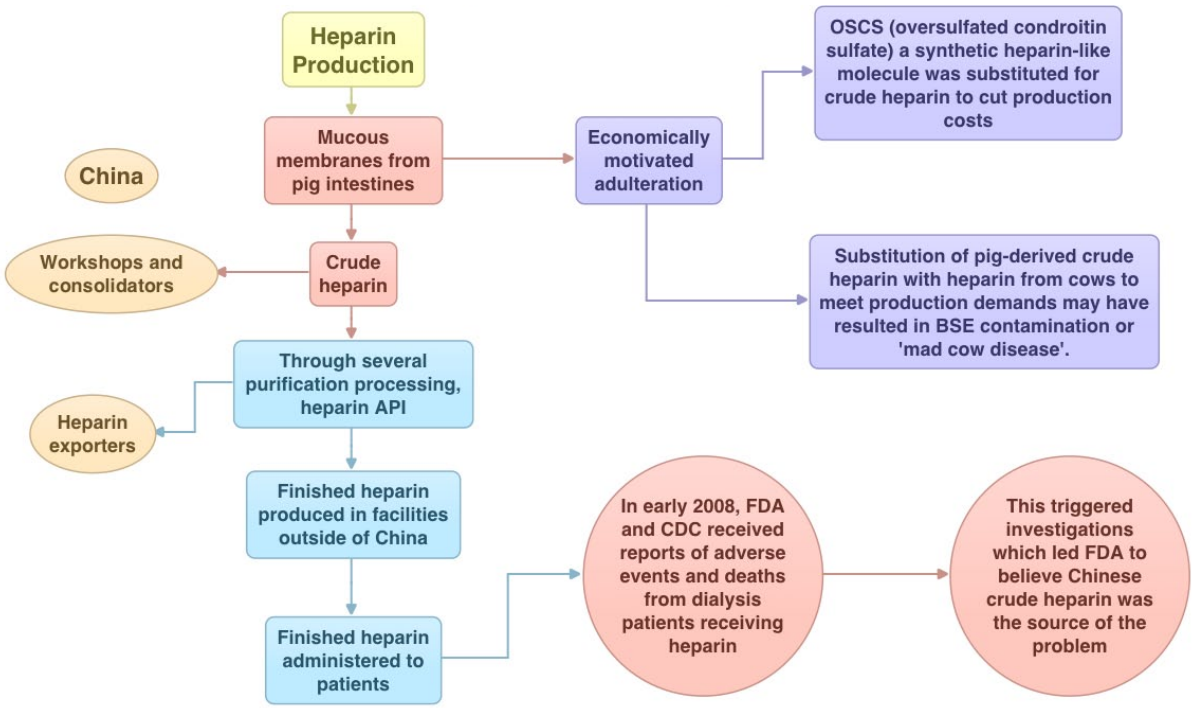

Figure 2: Entry of OSCS into the global supply chain in 2007-2008

manufacturing activities at the SPL-CZ or any of its crude heparin providers. Further, even though Chinese officials acknowledged that OSCS was an adulterant in heparin produced by SPL-CZ, they would not allow FDA inspectors to inspect other heparin producers because they were Chinese not American companies. To that point, a China government official quipped that FDA would be able to inspect Chinese crude heparin producers if SDFA inspectors would be allowed to inspect American heparin manufacturing facilities[16].

Finally, in the early stages of the investigation, SFDA appeared to be cooperating with FDA and honoring many of the agency's requests. To that end, in 2008, FDA opened offices in China ostensibly to expedite the investigation and to inspect a larger number of Chinese pharmaceutical manufacturers seeking FDA certification. However, as the investigation intensified, SFDA officials continued to deny FDA inspectors access to questionable heparin workshops and consolidators and failed to fully cooperate with the agency. To this day, China acknowledges that OSCS made its way into its heparin supply chain but has not been able to identify the source or entry point of the adulteratant.

Today, there is little doubt among many industry insiders and FDA regulators that OSCS was intentionally added to crude heparin preparations that were exported to the US and other countries[3, 6]. At the time of the incident, there were a number of factors that may have heightened the risk of economically motivated adulteration. For example, OSCS entered the Chinese heparin supply chain in late 2007 after earlier that year a virus known a blue ear disease decimated China's swine industry[3]. Because of this, the price of pigs and pork dramatically increased as did the price of crude heparin (the price of crude heparin doubled between May and November 2007).

Moreover, while not widely reported, the shortage of pig intestines induced some of the less scrupulous Chinese heparin producers to substitute porcine heparin with heparin derived from cows and other ruminant species to meet export demands. The use of cow lungs as a source of heparin was banned in the late 1980s in the US after a large outbreak of bovine spongiform encephalopathy (BSE) or mad cow disease. The possibility of ruminant adulterants in crude heparin manufactured in China led FDA in February, 2012 to issue guidance to heparin producers to screen all heparin APIs imported into the US for BSE[20]. Together, these factors—a shortage of raw ingredients, elevated crude heparin prices and increasing global demand for heparin—led FDA to conclude in a 2012 guidance document that "OSCS contamination of heparin appears to be an example of intentional adulteration, and has also been referred to economically motivated adulteration—i.e., heparin appeared to be intentionally contaminated with OSCS to reduce the cost of production[18]."

HAS ANYTHING CHANGED?

In 2008, shortly after OSCS was identified as the adulterant, about a dozen Chinese citizens were arrested and alleged to be responsible for the adulteration. However, to date no single individual or company has been conclusively identified as a possible source of the OSCS adulteration of crude Chinese heparin. Nevertheless, 19 Chinese heparin producers have ceased operations since 2008; leaving only 35 registered heparin manufacturers (including SPL-CZ) in China. Yet, despite this, in 2011, China's crude heparin exports reached historic levels that were first established in 2006 (Fig. 3)[7]. Also, over the same period, the price of heparin (per kg) has almost quadrupled from approximately $3000 USD in 2008 to over $12,000 in 2011 (Fig. 4)[7]. While the actual production costs of Chinese heparin have not changed much over the past four years, increased regulatory scrutiny by SFDA may have caused the price of heparin to spike. Nevertheless, crude heparin has become an extremely lucrative commodity for Chinese manufacturers.

Rising heparin prices portends well not only for Chinese heparin manufacturers but for China itself. To that point, in 2010 Shenzhen Hepalink Pharmaceutical—one of the few Chinese heparin manufacturers that was inspected in 2008 by FDA during the OSCS incident and deemed to be compliant—listed on the Shenzhen stock exchange. Surprisingly, at the end of the first day of trading, Hepalink had a market capitalization of $7.4 billion; making it the most valuable pharmaceutical, biotechnology or IT company in China's history[21].

Hepalink executives and Chinese shareholders were not the only ones who benefited from Hepalink being listed. So did Goldman Sachs, the American investment bank which in 2007 purchased a 12.5% stake in Hepalink for $4.9 million. Based on Hepalink's offering prospectus, Goldman's stake of 45 million shares was worth more than 200 times its initial investment in Hepalink[21]. Hepalink's stock price soared to 190 RMB per share (the highest in Chinese history) after its initial public offering (IPO). Although Hepalink's current share price is 21.8 RMB per share, Hepalink's founders were deemed to be the richest people in China with personal fortunes in excess of $1.7 billion[21].

Today, Hepalink is China's largest exporter of crude heparin and is the main source of heparin for APP pharmaceuticals (a unit of Fresenius Kabi Pharmaceuticals Holding Inc), which controls roughly 50% of the US market). Currently, Hepalink and four other manufacturers control approximately 80% of the Chinese heparin export business. While Hepalink has lost some of its value since its IPO, three other Chinese heparin manufacturers including Pharmaceutical Biochemical Changshan Hebei Ltd Co., Changzhou Qianhong Biopharma Co.,

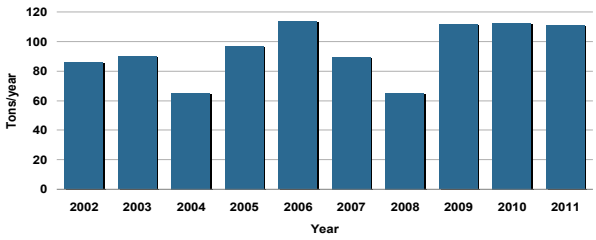

Figure 3: Volume of China's crude heparin exports 2002-2011

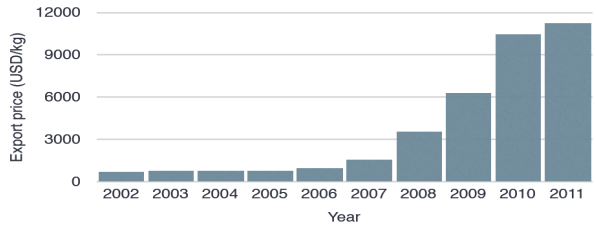

Figure 4: Price of China's crude heparin exports 2002-2011

Ltd. and Dongcheng Biochemicals subsequently have listed as public companies on Chinese stock exchanges. This huge return on investment for foreign investors is likely to cause others to infuse more capital into the Chinese crude heparin industry. At present crude heparin production is one of the most profitable business in China making it more susceptible to economic manipulation and possibly at greater risk of economically motivated product adulteration.

Aside from economic gains, little has fundamentally changed in China from a regulatory perspective to insure the safety of its heparin supply chain. Shortly after the incident in 2008, China agreed to test crude heparin exports using a new, highly sensitive assay (co-developed by FDA and Baxter) to detect OSCS[22]. While there is no way of knowing whether or not Chinese heparin producers are complying with these regulations, to date, there have been no additional reports of OSCS-adulterated heparin from China. This suggests that China is keeping a watchful eye on Chinese heparin production and, that at least, in near term, the possibility of another adulterated heparin crisis is unlikely.

Because the worldwide demand for heparin continues to grow, the US and other countries have agreed to make additional investments in China to help to modernize its regulatory system to prevent future incidents by improving the integrity of the Chinese crude heparin supply chain. Finally, because existing compendial tests failed to detect OSCS in adulterated heparin preparations, European, Japanese and American regulators are collaborating on developing more sophisticated

analytical tests and heparin standards that they hope to harmonize over the next few years.

However, despite these Herculean efforts, in February, 2012 the FDA placed another 14 Chinese heparin producers on an import alert list[18]. This action brings to 22 the number of Chinese suppliers that have been placed on the list to keep their products out the US heparin supply chain. Issuing the import alert allows FDA to seize products from these companies without physical inspection. It is unclear whether or not any of the suppliers on the recently released list currently sells heparin to US-based companies.

WHAT DOES THE FUTURE HOLD

Adulterated heparin joins a growing list of contaminated products that have been exported from China in recent years. Like heparin, these adulterations appeared to be intentional and economically motivated. This is because the country's rapid growth is fueled by intense cost competition, in which manufacturers squeeze out small profits by under pricing their rivals. And, because cost competitiveness is the dominant business strategy in industry after industry in China, the Chinese government has lost the ability to effectively regulate its economy. As one industry analyst put it "unfettered competition combined with a nonexistent or in many cases corrupt government oversight has produced a race to the bottom among Chinese businesses."

Because product adulteration is almost always economically driven, it is difficult to know what analytical tests to develop to detect potential adulterants. Put simply, science will never be able to trump intentional adulteration. By way of an analogy, drug testing of athletes is designed to identify foreign substances that athletes might choose to take. But, just as athletes find ways to circumvent drug testing, so will unscrupulous heparin manufacturers find new adulterants to cut corners and reduce the costs of crude heparin production. Until China is able to more regularly and assiduously inspect and monitor its entire heparin supply chain, its ability to prevent future intentional adulteration may be seriously compromised.

While many foreigners believe that China is undergoing a period of unbridled, expansive economic growth, Chinese citizens have known for quite some time that this growth and prosperity is coming at their own expense. For example, China exports 85% of its crude heparin supply, leaving only 15% for domestic use. Yet, despite OSCS-adulteration of exported crude heparin, astonishingly, there were no official reports of investigations into whether or not OSCS made its way into the domestic Chinese heparin supply. Therefore, it is not unreasonable to assume that contamination of China's domestic heparin supply had occurred. Recently, it was reported that industrial gelatin (extracted from leather scraps) has been routinely substituted for edible gelatin in products ranging from pharmaceutical capsules to food products including jelly. This continues to occur despite government regulations that forbid the practice.

Although SFDA continues to draft new CGMP regulations to ensure improved drug safety and better product quality, enforcing these regulations has been difficult and inconsistent at best. Nevertheless, if the Chinese government fails to impose greater regulatory scrutiny and centralized control over it regional and local pharmaceutical and biologics manufacturing companies the possibility of a future heparin-like incident looms large.

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Original Article

A snapshot of the successful bio-clusters around the world: Lessons for South African biotechnology

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ABSTRACT

Development of clusters in biotechnology has been one of the critical factors in the success of many countries. The aim of this research is to exploit the successful bio-clusters in selected developing countries such as Brazil, Cuba, India and China and to learn some lessons for South African bio-clusters. Research found that government played a critical role in creating successful bio-clusters in these developing countries. 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. With strong government support, these regions could be an important biotechnology hub in the African continent.

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Keywords: clusters; developing countries; South Africa

INTRODUCTION

Biotechnology, a leading industry for the future, incorporates fields as diverse as health care, chemistry, material science, agriculture, and environmental protection. Advances in biotechnology improve the health conditions, food quality as well as environmental issues.

The development of the biotechnology industry has been characterised by a high concentration of firms at a geographical level.[1-3] 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, mainly region specific, provide a platform for effective communication, resources, infrastructure, and expertise and network among governments, research institutions, universities, and industries thereby facilitating the creation of a knowledge-based hub.[4]

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Many studies have yielded similar conclusions on critical factors for successful biotechnology clusters which were 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.[1,5,6]

The aim of this research is to exploit the successful bio-clusters in selected developing countries such as Brazil, Cuba, India and China and to draw some lessons for South African biotechnology development. To achieve this aim, the paper has carried out a literature survey on successful bio-clusters in selected developing countries, examining what is the current biotechnology industry and how the successful cluster works. In addition, research identified the critical factors enabling the growth of bio-clusters.

In this study we will present the bio-clusters in developed countries, then examine the bio-clustering in selected developing countries. The current biotechnology clustering in South Africa will be explained followed by proposed lessons for South Africa.

CLUSTERS OF BIOTECHNOLOGY INDUSTRY

Clusters have been considered potential drivers of economic development and important sources of competitive advantage through enhanced productivity, the pace and direction of innovation, the creation of new businesses and access to new knowledge in the global economy.[7,8] Especially clusters of emerging science-based industries (i.e. biotechnology, medical biosciences, nanotechnology, ICT) are critical factors in shaping economic growth in the 21st century.[9]

Economists have attempted to capture the dynamic linkages within an industrial system between sector clusters which are connected by strong technological and behavioural input/output linkages. More specifically, Rosson[10], Kulkarni[11] and Mills et al.[12] explores some of the benefits of clusters which include raising innovation and productivity, sharing knowledge about best practices, reducing costs by jointly sourcing services, suppliers and infrastructures, facilitating formal and informal knowledge transfer, developing the skilled workforce and transaction efficiency, and encouraging collaboration between institutions. The benefits of clusters and the allure of enhanced business performance have led many government agencies to support clusters as a tool of economic development.[10]

There is no generally accepted definition of clusters. Most frequently used definition of a cluster is defined by Porter as "a geographically proximate group of interconnected companies and associated institutions in a particular field, including product producers, service providers, suppliers, universities, and trade associations". Evidence from literature shows that the development of the biotechnology industry tend to concentrate geographically in a few locations.[2,3,13,14] For example, in both the United States and the United Kingdom, the majority of firms are concentrated in a few states or metropolitan areas. There are strong factors leading to this clustering, including access to university and public research organisations, to venture capital and large markets in major cities. Moreover, Audretsch[15] adds some more factors e.g. specialised knowledge, entrepreneurial culture, high labour mobility and strong networks.

Philips and Ryan[13] highlighted that clustering model may vary in each country, for example, in the United States clustering focuses on commercial outcomes and investment attraction, placing key multinational companies at the centre of their regional clusters. While in Europe, the public sector (universities and R&D institutes) is the main driving force for clustering.

Bioclusters in developed countries

Clustering in biotechnology is important. In both the United States and the United Kingdom, the majority of firms are concentrated in a few locations. Factors leading to this clustering include access to university and public research organizations, access to venture capital and access to large markets in major cities. In the USA strong clusters exist in California (in Los Angeles and San Francisco), Maryland and Washington DC, Massachusetts (Boston), New Jersey (Princeton), New York City, North Carolina (the Triangle Research Park), Pennsylvania and Texas.[16] These agglomerations carry out almost two-thirds of U.S. biotechnology activity. On the contrary, UK clusters are closer to industrial agglomerations and concentrations of graduates. Greater London has the biggest agglomeration, followed by Cambridge and Oxford agglomeration.[16] Both Oxford and Cambridge possessing a world-leading biotech profile through well-known research-intensive universities (the University of Cambridge and Oxford University); leading research hospitals; and a number of important research institutes, such as the Institute for Molecular Medicine and the Wellcome Trust Human Genetics Centre at Oxford, and the Laboratory of Molecular Biology, the Wellcome Trust Sanger Institute (previously known as "the Sanger Centre"), the Babraham Institute and European Bioinformatics Institute at Cambridge.[5]

Oxford and Cambridge have geographical concentrations of firms, including both start ups and more mature companies, and have experienced rapid growth in the number of companies. Both regions have a pool of skilled staff, local venture capitalists and business angel networks, supporting services with legal, patent, recruitment, and property advisers, incubators, science parks, regional biotechnology associations and a strong image and awareness of being a cluster.[5]

During the past decade there has been a huge increase in biotechnology related development activities also in many other places. Table 1 shows the selected biotechnology clusters.

Phillips and Ryan[13] examined seven Canadian biotechnology-based clusters. The Montreal cluster is the largest biotechnology cluster. It benefits extensively from provincial government programs and national research labs. Recent surveys identified 351 players in the area, comprising, 130 in human health, 26 in human nutrition, 12 in agricultural biotechnology; and seven environmental companies; 171 service and supporting enterprises; one government lab; and four related universities.

Waxell and Malmberg[17] examined the clustering in Uppsala, Sweden. Uppsala region has been receiving increasing worldwide recognition during the past five

Table 1: Selected biotechnology clusters

North America	Central & South America	United Kingdom / Ireland	Continental Europe
Seattle, USA San Francisco, USA Los Angeles, USA San Diego, USA Saskatoon, Canada *Minneapolis/St. Paul/Rochester USA Austin, USA Toronto, Canada Montreal, Canada Boston, USA New York/New Jersey, USA Philadelphia, USA Baltimore/Washington, DC, USA Research Triangle NC, USA	West Havana, Cuba Belo Horizonte/Rio de Janeiro, Brazil Sao Paulo, Brazil	Glasgow-Edinburgh, Scotland Manchester-Liverpool, England London, England Cambridge-SE England Dublin, Republic of Ireland	Brussels, Belgium Medicon Valley, Denmark/ Sweden Stockholm/Uppsala, Sweden Helsinki, Finland Paris, France Biovalley, France/Germany/ Switzerland BioAlps, France/Switzerland Sophia-Antipolis, France BioRhine, Germany BioTech Munich, Germany BioCon Valley, Germany
Middle East	**Africa**	**Asia**	**Oceania**
Israel	Cape Town, South Africa	Beijing, China Shanghai, China Shenzhen, China Hong Kong, China Tokyo-Kanto, Japan Kansai, Japan Hokkaido, Japan Taipei, Taiwan Hsinchu, Taiwan Singapore Dengkil, Malaysia New Delhi, India Hyderabad, India Bengaluru, India	Brisbane, Australia Sydney, Australia Melbourne, Australia Dunedin, New Zealand

Source: Global biotechnology clusters map,[18] accessed 04 July 2009

years as a strong and dynamic cluster in the field of biotechnology. It is a well-established fact that the contemporary growth and dynamism of an industrial cluster is the result of historical processes. One of the key factors of biotechnology clusters across the globe is a close relationship between industry and academia. The Uppsala biotechnology cluster is no exception as the development of this cluster is clearly related to the historical and current interplay between industry and academia.

There is a significant concentration of biotechnology activities in Uppsala. Around 80 biotech firms together employ around 5000 people, the system taken as a whole can be estimated to employ around 8000 people in Uppsala.[17]

Bioclusters in developing countries

In developing countries such as Brazil, Cuba, India and China have been successful in developing biotechnology industries by setting up clusters and assisting companies with financial, technical and other resources. Below we draw a picture of the development of clustering in Brazil, Cuba, India and China.

Brazil: The Minas Gerais biotechnology cluster

There are around 181 private life science companies identified in Brazil[4,19] with the majority active in the agricultural biotechnology sector, followed by health, natural resources and environmental sectors.[4]

Table 2 shows the geographical distribution of life sciences companies are clustered by state and regions in

Table 2: Distribution of life science companies by state and region in Brazil

Region	State	Life Science companies
North	Amazonas	2
Northeast	Pernanbuco	6
	Piauí	1
	Alagoas	1
	Bahia	1
Mid-west	Distrito Federal	3
	Goiás	2
	MatoGrosso	2
	MatoGrosso do Sul	1
Southeast	Minas Gerais	66
	São Paulo	66
	Rio de Janeiro	11
South	Rio Grande do Sul	12
	Paraná	5
	Santa Catarina	2
Brazil	Total	181

Source: Santos,[19] 2008

Brazil. The Southeast region is home to 79% of all life science companies.

Brazil is promoting the biotechnology sector to stimulate industrial development. The Federal Government continuously improves its policy concerning foreign capital investment (FDI), creating constructive regulations for goods and services, fiscal benefits to attract the companies and facilitating imports of equipment.[20]

Belo Horizonte (the capital of Minas Gerais), São Paulo, and Rio de Janeiro are the three leading biotechnology clusters. Success of the Minas Gerais cluster has mainly depended on the public institutions including the University of Minas Gerais, which has reputation for its science and technology and hosts more than 160 biotech experts. Such institutions also restructure the lack of specialised inputs and equipments required for the industry by allowing firms to use their facilities.[49] Biominas Foundation, located in Belo Horizonte, has assisted 33 biotechnology companies generate business opportunities since its inception in 1990, and its "Incubator of Companies program" has introduced 21 start-ups to the market since 1997. The Biominas Foundation is actively lobbying for the biotechnology industry, and its officers have created close ties to the government and the venture capital community.[21] In the Minas Gerais cluster, biotechnology investments are heavily funded by government, but recently there has been an increase in private VC companies, such as Votorantim Ventures Capital, FIR Capital and Rio Bravo.[49]

Cuba: West Havana biotechnology cluster

Cuba has prioritized investment in health biotechnology since the early 1980s and have developed both human resources and innovative infrastructure. An integral part of Cuban health biotechnology is a focus on local health needs and the close ties between the public health sector and the Science and Technology (S&T) system.[22] The Centre for Genetic Engineering and Biotechnology (CIGB) is the flagship organization for biotechnology research in Cuba and was founded in 1986, to promote biotechnology innovation. Over a six year period (1990-1996), the Cuban Government invested around US$1 billion to give rise to what is currently known as "The Western Havana Bio-Cluster".[23,24] It includes ten core centres, like the Centre for Genetic Engineering and Biotechnology (CIGB), Centre for Molecular Immunology (CIM), and Finlay Institute, as well as some 50 related research, production and marketing facilities. Western Havana Bio-Cluster is linked to a number of hospitals, medical universities and other partners.[22]

Once described as "Cuba's billion dollar gamble", the government supported programme achieved 100 R&D facilities and pharmaceutical centres, over 150 international patents for new drugs and treatments, and employment of more than 30,000 workers in the field of scientific development. Despite a strong venture capital funding model, Cuban biotechnology industry has grown rapidly. Cuba's expertise in this industry has already provided the basis for many international partnerships especially, in the creation of joint companies abroad, where Cuban institutions contribute towards technology, know-how and technical assistance.[4]

India: Bengaluru biotechnology cluster

India is among the first few countries in the developing world to have recognized the importance of biotechnology as a tool for advancing growth in the agriculture and health sectors.[25] The milestones of the evolution of biotechnology industry in India began in 1978, in Bengaluru, when the country's first biotechnology company Biocon was established for producing industrial enzymes and later venturing into biotherapeutics.[4] The Government provided a major thrust to the sector with the establishment of the National Biotechnology

Table 3: Biotechnology clusters in India

States	Cities	% Share in 2007-08	% Share in 2008-09
Maharashtra	Mumbai and Pune	35.19	32.78
Karnataka	Bengaluru	21.61	20.89
Andhra Pradesh	Hyderabad	17.82	18.03
NCR	NCR	14.14	14.77
Gujarat	Ahmadabad	4.60	6.23
Other states		6.65	7.31
Total		100	100

Source: Biospectrum[30,31]; 2008, 2009

Board (NBTB) in 1982 as the body to identify priority areas and evolve a long-term plan for the development of biotechnology. Later, in 1986, NBTB was upgraded to a fully fledged government department called the Department of Biotechnology (DBT).[25] This paved the way for furthering the growth and development of biotechnology in the country through creating a scientific workforce, a large infrastructure network, and strong support to R&D in life sciences and fiscal incentives include relaxed price controls for drugs, subsidies on capital limits, and tax holidays for R&D spending.[4,26]

The state governments recognized the economic potential of the emerging sectors.[27] The leading states include Maharashtra, Karnataka, Andhra Pradesh, National Capital Region (NCR), and Gujarat.[4] These states have revealed state-specific biotechnology policies and have established biotechnology parks and clusters around strong academic and publicly-funded R&D institutions. These clusters are also found in the proximity of leading pharmaceutical/IT firms to attract investment in this industry.[27] The biotechnology clusters consist of the following subsectors; Bio-pharmaceuticals (vaccines, therapeutic drugs, animal biological), Bio-services (data management, clinical trials, site management bioequivalence and bioavailability studies, toxicology studies, knowledge process outsourcing), Bio-agriculture (Bt cotton), Bio-industrial (industrial enzymes) and Bioinformatics. Larger numbers of biotechnology companies are involved in bio-pharmaceuticals, followed by bio-services and bio-agriculture. Bio-industrial companies are still a minority in the Indian market.[28] At present there are more than 380 biotechnology companies in India, providing employment for over 20,000 scientists.[29]

Table 3 shows the biotechnology focused states and cities in India with the percentage of revenue shares. Actual revenues are 2.2 billion USD dollars (2007-2008); 2.6 billion USD dollars (2008-2009); 3.1 billion USD dollars (2009-2010); 4.0 billion USD dollars (2010-2011).[29-32]

Bengaluru is known as "the Silicon Valley of India" because of the number of Information Technology companies located in the area. In order to diversify from IT, the Karnataka state government was active in promoting Bengaluru as a knowledge hub for biotechnology that links private and public science. The state government enhanced the biotechnology region by[33];

1. establishing a "Vision Group on Biotechnology" and
2. funding a biotechnology institute in Bengaluru's technology park and linking it to a number of public science institutions,
3. granting tax concessions for importing inputs and capital goods,
4. creating a biotechnology fund to be co-financed by private venture capital.

Thus, the Karnataka state government planned to develop a policy-driven biotechnology clusters following the success of the more spontaneous Bengaluru IT cluster.[33] Today, Bengaluru is the largest biotechnology city-cluster in India, which houses 191 biotechnology companies alone.[34]

China: Shangai biotechnology cluster

The Chinese Government has been a key investor in the biotechnology industry. In 2006, the Government adopted the Medium and Long-Term National Plan for Science and Technology (S&T)—2006-2020, which aims to make China a leading S&T power and innovation economy. The plan identifies biotechnology, alongside seven other frontier technologies, as a priority for funding.[4] According to the China National Centre for Biotechnology Development (CNCBD), there are around 20 biotechnology parks throughout China, with most companies focusing on human therapeutics and agriculture.[4] The largest groupings of biotechnology companies are in Shanghai and Beijing.

Despite the promotion of research and development by the state, the main competitive edge of Shanghai's growing biotechnology industry lies in low cost development and production expertise.[33] According to Miller et al.[33]; 158 firms, 31 R&D institutions and 22 higher education and subsidiary institutions were active in biotechnology in Shanghai. As expected with Shanghai's manufacturing legacy, over three-quarters of all biotechnology firms in Shanghai were in the manufacturing sector. R&D expenditure patterns also point toward

a production focus. Sixty-eight percent of Shanghai's R&D expenditure is concentrated on product/process development, 26% applied research, and 6% basic research.

However, Shanghai continues to face challenges of inadequate protection of intellectual property, lack of venture capital investment, and the tightening supply of highly qualified knowledge workers.[33]

South Africa: Technology innovation agency

South African government introduced the National Biotechnology Strategy (NBS) which is a key policy driver to build a biotechnology hub in South Africa in 2001. Government allocated R450 million (around US$58 million) in public funding for biotechnology development for the years 2004-2007.[35,36] The aim of this strategy was to stimulate the development of biotechnology skills, capacities and tools in South Africa.[37] One of the important result of this 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.[38,39] BRICs served as vehicles for facilitating and supporting biotechnology innovation and commercialisation. Three regional biotechnology innovation centres were created. These are Cape Biotech Initiative in Western Cape, the East Coast Biotechnology Consortium (EcoBio, operating under the trade name of LIFElab) in Kwazulu Natal and Biotechnology Partnership for Africa's Development (BioPAD) in Gauteng province. The BRICs have difference focus areas: Cape Biotech and LIFElab focus on human health biotechnology research and development while BioPAD on several areas, including biotechnology research and development in agriculture, mining, and environmental applications.

According to National Biotechnology Audit,[40] 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. Characteristics of biotechnology companies in South Africa can be seen in below (see Table 4).

Based on the number of biotechnology companies based in Gauteng and Western Cape, 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.

ANALYSES OF CRITICAL FACTORS TO DEVELOP BIO-CLUSTERS IN SOUTH AFRICA

Many studies have shown the critical factors needed to develop the biotechnology sector. Most of the researchers in these studies have come to largely similar conclusions, emphasizing the role of a strong science base, a skilled workforce, supportive infrastructure and the availability of services and financing, as well as policy support etc.[1,14] Although many industries benefit from the factors listed above, they apply especially well to biotechnology. Biotechnology is a science-driven, which means that clustering often arises in close proximity to key knowledge centres which conduct high-level research, e.g. universities, public research institutes, R&D centres and hospitals. Because this knowledge is very often tacit and tied to individual researchers or research groups, effective utilisation requires close interaction between actors and multilevel partnerships.[1]

In the following sections we examine the ten critical factors that encourage the development of biotechnology in South Africa (Table 5). These factors can be grouped into three sets[5];

1. Exploitation of the research base (covering a strong science base and entrepreneurial culture),
2. Company development (covering the ability to attract key staff, supportive physical and transport infrastructure, availability of finance, business support services and large companies, and a skilled workforce), and
3. Government support (effective networks, and government support).

Exploitation of the research base

Strong science base

The geographical concentration of biotechnology is also known as the concentration of scientific knowledge.

* BRICs (Lifelab, Biopad, Cape biotech) no longer exist and are now a component of the 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, Lifelab, Biopad, Cape biotech, Plantbio, Tshumisano, Innovation fund and Amts (Advanced Manufacturing Technology Strategy).

Table 4: Core and biotechnology active companies in South Africa

Characteristics	Core Biotechnology Companies	Active Biotechnology Companies
Number of companies	38	78
Location (Provinces)	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-offs	Companies 16 (From universities 44% From government 31%)	Companies 25 (From universities 28% From government 36%)
Foreign Owned	Companies 5	Companies 12
No of employees (2006)	765	72,844
Products	559	1542
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%	-

Notes: BRICs: Biotechnology Regional Innovation Centres, IF: Innovation Fund
Source: DST[40], 2008

Universities, public research organisations, R&D institutions and research hospitals are the key players to favour the advancement of knowledge and expertise, and provide a workforce for local firms.[1]

There are 23 universities in South Africa and nine of them are located in Western Cape and Gauteng regions. In Western Cape region there are four universities (University of Cape Town, Stellenbosch University, University of Western Cape and Cape Peninsula University of Technology) and in the Gauteng region there are five universities (University of Witwatersrand, University of Johannesburg, University of Pretoria, University of South Africa and Tshwane University of Technology). Pouris[41] shows that only six South African universities are included in the top 1% of the world's institutions, based on citations in the international scientific literature, namely, the Universities of Cape Town, Stellenbosch, Pretoria, Witwatersrand, Kwazulu-Natal and the Free State. Lubango and Pouris[42] investigated the inventive activity of South African universities and found that the Universities of Pretoria, Stellenbosch, Cape Town, Witwatersrand and the North-West are the most patent active universities (i.e. those generating more than 16 patents over the past 10 years).

Seven universities from two regions (out of top ten) were also ranked by the National Research Foundation as having the highest percentage of rated researchers in South Africa (see Table 6). The National Research Foundation (NRF) is South Africa's national agency for promoting and supporting research across fields.[43] NRF considers that the evaluation and rating system provides independent and objective information on the quality of an individual's research and South Africa's research capacity in different fields, reinforces the importance of internationally competitive research, stimulates competition between researchers, and can be used by the universities to position themselves as research-intensive institutions.[44]

Entrepreneurial culture

In the development of regional biotechnology industries, small-to-medium size enterprises (SMEs) are the driving force with start-up companies which bring biotechnology products and processes to the market. Biotechnology start-up companies and projects in established SMEs require champions with a sound knowledge of the relevant science and a familiarity with business principles relating to product innovation, market development and venture capital.[45] Above all else, one of the important factors needed to develop a biotechnology industry in a region is to have an entrepreneurial culture, in other words, a strong entrepreneurial ability is required in an industry. This refers to the fact that scientists should look not only at the scientific side of research but also at the commercial exploitation of their results.[46]

To exploit the potential of the biotechnology industry in South Africa, there should be entrepreneurial scientists who should have both research and management

Table 5: Critical factors encouraging the development of biotechnology

Group I: Exploitation of the research base	
Strong science base	Leading research organisations: university departments, hospitals/ medical schools and charities, Critical mass of researchers, World leading scientist(s)
Entrepreneurial culture	Commercial awareness and entrepreneurship in universities and research institutes, Role models and recognition of entrepreneurs, Second generation entrepreneurs
Group II: Company development	
Growing company base	Thriving spin-out and start up companies, More mature "role model" companies
Ability to attract key staff	Critical mass of employment opportunities, Image/Reputation as biotechnology cluster, Attractive place to live
Premises and infrastructure	Incubators available close to research organisations, Premises with wet labs and flexible leasing arrangements, Space to expand, Good transport links: Motorways, Rail, International airport
Availability of finance	Venture capitalists, Business angels
Business support services and large companies	Specialist business, legal, patent, recruitment, property advisors, Large companies in related sectors (healthcare, chemical, agrifood)
Skilled workforce	Skilled workforce, Training courses at all levels
Group III: Government support	
Effective networking	Shared aspiration to be a cluster, Regional trade associations, Shared equipment and infrastructure, Frequent collaborations
Supportive policy environment (national, regional and local)	National and sectoral innovation support policies, Proportionate fiscal and regulatory framework, Support from RDAs and other economic development agencies, Sympathetic planning authorities

Source: Sainsbury[5] 1999

skills and also an understanding of scientific, regulatory and ethical issues. Entrepreneurs who can develop the industry and build bridges between the science of biotechnology and the commercialisation thereof are needed in South Africa. By developing new competencies through education, biotechnology entrepreneurship can promote new biotechnology creations.[47] In South Africa only a few institutions and private companies have recently created bio-entrepreneurship programmes. In Gauteng and the Western Cape these programmes are mainly run by public institutions.

These programmes, in chronological order are:

1. Biotechnology in the Workplace-FABI, University of Pretoria (Gauteng region).
2. The Certificate in Bio-entrepreneurship – University of Pretoria (Gauteng region). This programme started in 2008.
3. The Cape Biotech Bio-entrepreneurship programme (Western Cape region). This programme started in 2008 and was the first bio-entrepreneurship programme in the Western Cape region.
4. In 2010, XCell Bioconsulting, a private company, in association with the University of Cape Town, Graduate School of Business offer the first online and Executive Education Bio-Entrepreneurship course for science graduates in Africa. Graduate candidates have a choice of three specialised programmes.
5. The Certificate in Bio-entrepreneurship presented by the Technology Innovation

Table 6: Top ten universities in South Africa in terms of the percentage of their research staff with valid NRF rating (2008)

Institution	Rated Researchers	Research Professionals	Percentage Rated
University of Cape Town	291	937	31.1%
Stellenbosch University	247	867	28.5%
University of Pretoria	241	1638	14.7%
University of the Witwatersrand	177	979	18.1%
University of KwaZulu Natal	155	1476	10.5%
North-West University	102	927	11.0%
University of South Africa	78	1313	5.9%
University of the Free State	78	756	10.3%
University of Johannesburg	71	853	8.3%
University of the Western Cape	57	518	11.0%

Source: NRF[43] (2011)

Agency (Gauteng and Western Cape region) commenced in 2011. Candidates who have a certificate in bio-entrepreneurship or business may join the Advanced Bio-entrepreneurship programme. Candidates are expected to present a business plan for possible selection for a week-long Summer School, held in Switzerland.

6. In 2012, a technology commercialisation course for under-graduates was developed by an initiative administered jointly by the University of Western Cape, University of Cape Town and Cape Peninsula University of Technology.
7. The Gauteng Accelerator Programme - Biosciences (GAP - Biosciences) in collaboration with Emory University in Atlanta, Georgia (Gauteng region). GA is a nine-month programme that includes educational programmes and a business plan competition, designed to accelerate the establishment of biosciences-based companies.

Company development

Growing company base

Bio-clusters require successful start-ups as well as more mature biotechnology companies that can act as role models for others.[5] To have critical mass attracts other large companies, investors, suppliers, ad skilled people in clusters. In South Africa, biotechnology spin-offs from universities and public research organisations are lacking as can be seen in Table 4. They are still in their embryonic stage. University researchers are currently not interested in creating companies; rather they license their research at an early stage. Most researchers may lack entrepreneurial skills, which may affect the need for spin-off creation.

Ability to attract key staff

Biotechnology companies must be able to attract top management and scientific researchers from overseas and from larger companies in order to become a mature industry. Clusters are one of the important ways to attract staff by providing an intellectual and business-led environment and also offering employment opportunities for partners and career development. The quality of life, a friendly environment, areas of natural beauty and vibrant international cities also play a role in individual decisions about where to locate.[5] There is a big difference in terms of friendly environment between Gauteng and the Western Cape regions. Cape Town is attractive and friendly, and internationally well-known, but is not a business hub while Johannesburg and Pretoria have more problems with crime issues but more business focus.

Premises and infrastructure

Biotechnology companies require specialist premises with leasing arrangements which are flexible enough to meet their changing needs.[5] The Biotechnology Parks and Incubation Centres provide an excellent model for both the promotion of biotechnology start-up companies and Public Private Partnerships. But the problem

is that there are no specifically biotechnology parks in South Africa. In Gauteng, Innovation Hub was created as an internationally accredited Science Park in 2005 but there is not much activity in the biotechnology industry. In Western Cape region, South Africa's first health innovation hub, Cape Health Technology Park (CHTP), has recently been approved by the government.

Availability of finance

Biotechnology companies are often financially dependent on the financial community for long periods of time. Companies and investors value being located close to each other in clusters.[5] However, even in comparison with other developing countries, e.g. China, India, Brazil, South Africa is falling behind in this level of finance. Financing for biotechnology in South Africa is government-led, with the BRICs (part of the TIA now) at the forefront. Other sources of government funds most frequently accessed are the Innovation Fund (now part of the TIA) which funds research across a wide range of sectors; the Industrial Development Corporation (IDC), a national development financing institution supporting competitive industries; and the Support Programme for Industrial Innovation (SPII), an initiative of the Department of Trade and Industry (the DTI), which was designed to promote technology development in the manufacturing industries.[36]

Private financing for biotechnology is very limited in South Africa and only biotechnology VC firm, Bioventures, is recently dormant. the Bioventures raised a fund of R80 million ($10.3 million) in 2001 from the South African IDC and the International Finance Corporation (Washington, DC).[36,39] The problem in South Africa is the lack of finance available for seed and start-up companies.[48] The lack of a VC in biotechnology, a limited investors who understand the biotechnology sector, risk aversion and the bigger returns on investment available from competing industries, such as construction or information technology, have all been cited as reasons for the funding gap.[48]

Government funds for the biotechnology industry are limited, and South Africa's investment community in biotechnology is immature. Without a change in this funding picture, the government efforts in stimulating biotechnology activity will be in the near future threatened.[36]

Business support services and large companies

Proximity to specialist business services, such as patent agents, biotechnology consultants, lawyers, recruitment and property advisors form an important benefit for companies in clusters. Proximity to large companies in industries relating to biotechnology (e.g. pharmaceutical, agri-food and chemical) is an important driver to cluster development in a number of ways, such as providing management expertise, partnering opportunities and customers to biotechnology companies.[5] South Africa has a well established pharmaceutical industry. One limitation of this industry though is that the South African companies tend to be largely generic players. The big global pharmaceutical companies all have a presence in South Africa but their offices tend to focus on sales and marketing rather than R&D.[48] The absence of a research-based pharmaceutical industry and the small size of the biotechnology sector also affects graduates in biotechnology. There are very limited apprenticeship opportunities for graduates, and as a result, many of them are employed in other sectors or look overseas for biotech and pharmaceutical experience.[36]

Skilled workforce

According to a National Biotechnology Survey carried out in 2003, many companies had experienced shortages in human resources, listing a lack of skilled scientists at various levels, particularly MScs and PhDs, as well as quality-control staff, production engineers with pharmaceutical experience, bioinformaticists and protein chemists, among others. However, in recent years, a very different picture exists, where many professional scientists are seeking employment opportunities in academia and the sector.

Government support for cluster development

Effective networking

In the Gauteng and Western Cape area, Cape Biotech had previously provided opportunities for companies, researchers, and others to meet and exchange views and information and undertake a range of activities to promote biotechnology in the area. However, with the recent re-structuring of TIA and subsequent budget cuts few of these activities are arranged.

Supportive policy environment (national, regional and local)

Public policy cannot create clusters, they must be business driven. National, regional and local government do, however, create the conditions which encourage their formation and growth. National government is responsible for setting the macro-economic conditions which support innovation and ensure that regulations are necessary and proportionate.[5]

LESSONS AND CONCLUDING REMARKS

The biotechnology industry is gaining priority in many countries as a key engine for their long-term economic growth. This is also the case in South Africa.

Compared to Brazil, Cuba, India and China; the biotechnology industry is in its embryonic stage in South Africa. In all countries the government played a vital role in creating successful bio-clusters. Brazil has a strong science base with an incubation programme and venture capital. Cuba has large financial resources with infrastructure and government support and an integrated health biotechnology and public health sector. India has strong government support systems, cost effective manufacturing capabilities and at a regional level, the financial capacity to develop a bio-cluster in close proximity to the IT industry. This creates a critical mass of employment opportunities in the region. The government of China has created biotechnology parks and promotes R&D in the biotechnology industry. However the main competitive edge for most Chinese companies is low cost development and production expertise.

Cluster development requires action and co-ordination between government departments, decentralized administrations, regional economic development agencies, universities, public research organizations, Public private partnerships, R&D centres, research hospitals, companies and others. Governance and networking at a local level are indeed the real added value for cluster success.[6] Small biotechnology clusters e.g. those in South Africa can succeed if the conditions are favourable. These are a strong local science base, strong national support and the ability of local actors. This support can take many forms, for instance substituting private services for lacking public services, supporting research, building up a working education and research system, creating a constructive legal and economic environment for new start-up companies, and working to stop "brain drain."[1]

In conclusion, the biotechnology landscape in South Africa is as follows;

1. The biotechnology sector in South Africa is still small in comparison to the sectors in India, China, Brazil and Cuba.
2. Entrepreneurial skills are required to improve the biotechnology sector.
3. Both regions, Gauteng and Western Cape, have reputable higher institutions in scientific fields.
4. There are currently no biotechnology parks in South Africa.
5. In terms of attracting key staff, Cape Town has more advantage than Johannesburg and Pretoria as it is an internationally well-known city.
6. Access to the finance is still the main challenge for biotechnology companies.
7. One of the main advantages of the Southern African region is that it has potential as an innovation hub in Africa. 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 could become biotechnology hubs for the Africa continent if they receive strong local and national government support.

Given this evolution we propose following policy recommendations;

1. Government should focus on creating a biotechnology parks.
2. To create a favourable environment, government should attract foreign investors and create more specific biotechnology venture capitals.
3. Government should create more mobility between entrepreneurs for knowledge spillovers.
4. Government should encourage the companies to focus R&D rather than sales and marketing.
5. Academics should be better incentivised to commercialise products developed in the laboratory.

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From the Boardroom

Improving IPO market still not an exit path

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The two biopharma companies that went public on October 10, 2012 did something that caught the attention of industry watchers. They completed successful initial public offerings at the top of their expected ranges. Not only that, but both increased the size of their offerings because of demand, and both proceeded to trade at premiums after their debut. That sparked excitement about the prospects for a more robust IPO market for biopharmaceutical companies and speculation in the trade press about which venture investors would be replenishing their coffers with big profits from newly exited investments.

Intercept Pharmaceuticals raised $75 million in its IPO after increasing the size of the offering to 5 million shares from its planned 4.3 million. It came at $15 a share, the top of its range. By the end of October, its shares traded up more than 20 percent. The company is in late-stage clinical testing of its first-in-class treatment for primary biliary cirrhosis, a rare chronic autoimmune liver disease that can ultimately lead to liver failure. Kythera Biopharmaceuticals raised $70.4 million after increasing the size of its offering by 10 percent. The company is in late-stage clinical testing of its experimental injectable drug that reduces submental fat, otherwise known as a "double chin."

The solid debuts of the two IPOs provide additional encouragement to biotech investors, building on strong performances by earlier biopharma IPOs in 2012. This group of companies at the end of October was up an average of 19.9 percent. That compares to a 7.2 percent increase of the Dow Jones Industrial Average and a 14.3 percent gain for the Nasdaq Composite Index.

But the suggestion that this improving IPO activity will lead biotech venture investors to lucrative exits seems to be a bit premature and detached from the reality of these deals. The maxim oft repeated by venture investors has never been truer: IPOs are financing events, not liquidity events.

Crack open the regulatory filings for recent IPOs and a clear pattern emerges. Venture-backed biotechs that are going public are doing so with substantial participation from their venture investors as well as other insiders. In fact, when Burrill & Company sifted through filings from the past three years, it found this trend is increasing. biopharmaceutical companies that went public in 2012, on average, did so with venture investors and other insiders purchasing 31.5 percent of the initial public offering. That compares to 28.1 percent for the IPOs in the same sector in 2011 and 26.7 percent in 2010. It is also in line with what others have found. In fact, an earlier study of deals in 2011 by Needham & Co. found in just four years time, the portion of IPO shares being purchased by existing investors nearly doubled to 28 percent, rising from 14.5 percent.

Again, these are financing events, not liquidity events.

That reality is made even starker by the fact that the valuations of these IPOs are often coming at a modest increase in valuation relative to the last round of venture funding, offering little opportunity for venture investors to capture big returns without substantial moves in the aftermarket for these stocks. While the increase in valuations between the previous venture round and the IPO has been improving, they have done so only modestly. A May 2012 analysis by reporters at *Start-Up* found that 2012 deals boasted step-ups of 1.6 times the previous venture round. That is an improvement over the 1.2 times step-up averaged in 2011, but below the levels seen in 2009, when biopharmaceutical companies went public with an average step-up of 2.6 times earlier valuations.

Mergers and acquisitions have become the preferred exits for venture investors, not only because of the expediency these transactions provide, but because the valuations are generally far more favorable. The average

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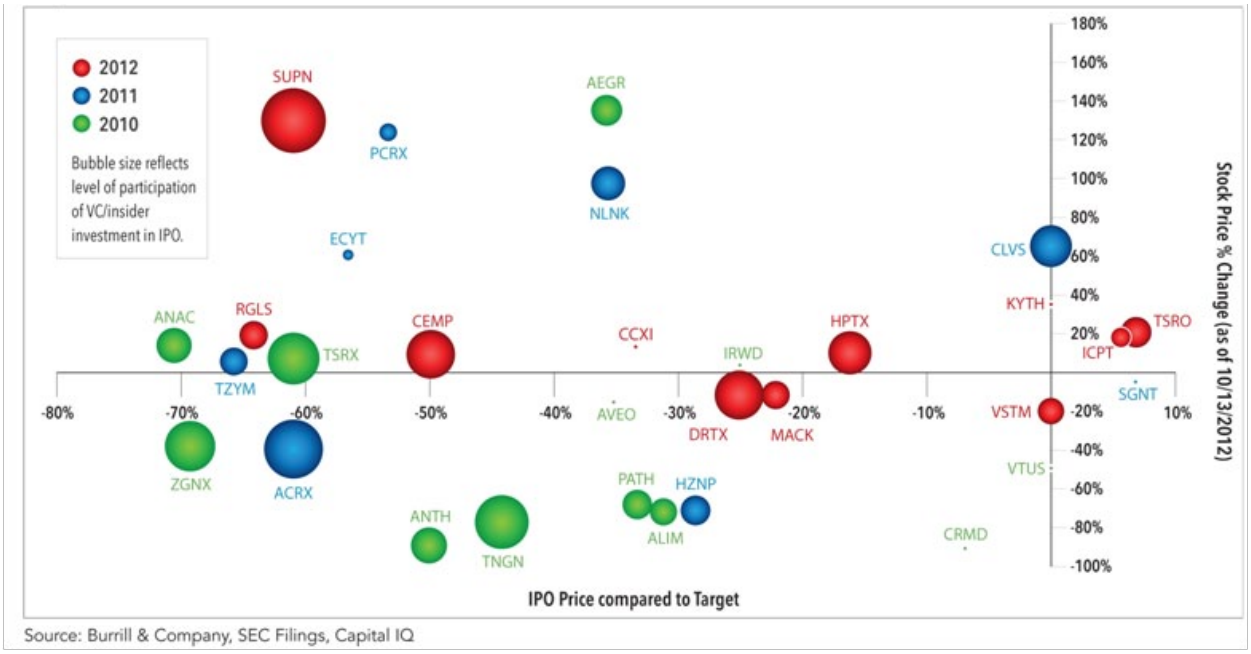

Source: Burrill & Company, SEC Filings, Capital IQ

Figure 1: Biopharmaceutical IPOs, 2010 to 2012

step-up in valuations from previous venture rounds in M&A transactions has grown steadily over the past three years. In 2012, the average step-up reached 3.7 times previous venture rounds, more than twice what companies going public commanded as step-ups in the same period.

There is good news on the IPO front, however. Public market investors and companies appear to be closing a gulf in the perceived value of the companies. In 2012, biopharmaceutical companies that went public did so at an average of 25 percent below the midpoint of their expected ranges. That may not sound good, but it does represent a steady improvement over the past two years. In 2010, biopharmaceutical companies that completed initial public offerings did so at 39.4 percent below the midpoint of their expected ranges.

The participation of venture investors in many cases has become essential for public market investors who otherwise might be unwilling to buy biopharmaceutical IPO shares. For the venture investor, these offerings may not only provide an attractive valuation at which to purchase additional shares, but also a path to liquidity since they will be able to sell stock once any lock-ups expire.

It is interesting to note that the level of participation of existing investors in biopharmaceutical IPOs does not appear to function as an indicator of whether deals get completed within their target ranges, how deeply they needed to cut their prices in order to complete public deals, or how they perform in the aftermarket.

Where there is a correlation is between the aftermarket performance of these issues and the extent to which they cut their initial offering prices relative to their expected ranges. Shares in IPOs that priced at 50 percent or more below their range since 2010, as of the end of October 2012, were up 19 percent. For those IPOs that came in less than 50 percent below their expected range, or at or above it, those issues are down 4.5 percent. That means leaving something on the table for public market investors helps generate enthusiasm in new issues and their aftermarket trading.

What is troubling in all of this is that not only are venture investors not replenishing their war chests through IPOs, they are emptying them because public market investors are unwilling to take on the role of funding the public debuts of these companies without the participation of the venture investors. That means IPOs are failing to generate the returns venture investors need to reinvest in promising new innovative companies. It is also directing large sums of capital from investors who have traditionally funded early-stage companies into later stage deals where investors see less risk and a faster path to desired returns. There is some hope as IPO performance improves and investor interest broadens, this situation will change, but it is unlikely any such changes will be dramatic enough to alter the dynamics today. IPOs are for funding and M&As are for exits.

Legal & Regulatory Update

Use of medicines for carved out indications in Europe — Time for a change in approach?

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ABSTRACT

All stake-holders in the pharmaceutical industry recognise that valuable new medicines can be obtained from investing in the research and development of new uses for existing drugs. The present system of awarding second medical use patents to originators which develop new and inventive medicines from known drugs does not provide sufficient incentive to this part of the industry. Moreover the status of second medical use patents is so uncertain that generics do not know where they stand. A solution which provides proper protection to second medical use patents is required to bring certainty and fairness to all involved in the industry to the ultimate benefit of patients.

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Throughout medical history there have been numerous examples of new uses for known drugs providing substantial advances in the treatment of patients. Some notable examples include:

- Rapamycin was first used as an anti-fungal agent but was subsequently discovered to be a powerful immunosuppressant;
- Allopurinol was first used in the treatment of gout but was subsequently found to be effective as an anti-neoplastic agent;
- Zoledronic acid was first used in the treatment of tumour-induced hypercalcemia and later found to be effective against osteoporosis; and
- Finasteride was first used in the treatment of prostate disorders but was subsequently discovered to be effective in the treatment of alopecia.

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The cost and time for developing a new indication for a known drug is substantial. It can be comparable to developing a new drug. In particular, the fact that a drug has been developed for an earlier indication does not negate the need for expensive Phase III clinical trials to be carried out before marketing approval can be obtained for the new indication. Such trials account for a significant proportion of the total costs of bringing a drug to market. The development of the drug for the earlier indication does however mean that the safety profile of the drug has already been established. As such, a patient participating in a trial for a further medical use of a known drug is subject to a lower risk of unwanted side effects than a patient participating in a trial for an entirely new drug.

SECOND MEDICAL USE PATENTS

Until the 1980s it was not possible in many parts of the world to obtain patents for new indications for known drugs. In Europe, recognising that this prohibition was a major disincentive to the development of known drugs for new indications with consequential disadvantages for patients, the Enlarged Board of Appeal of the EPO

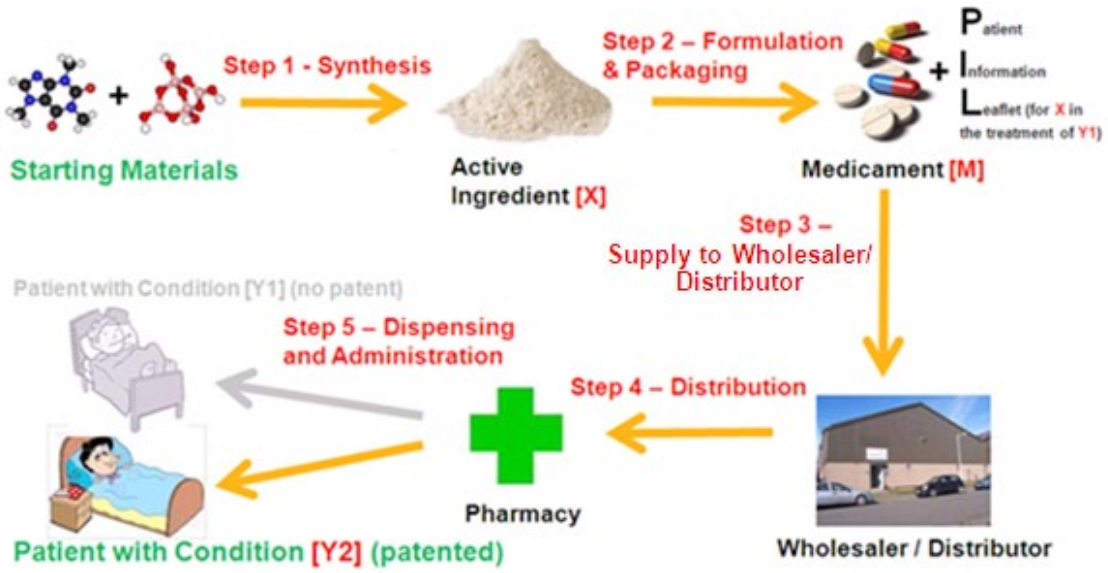

Figure 1: A typical supply chain for a generic medicine

in Eisai[1] held that it was permissible for second medical use patents to be granted provided the claims were in the so-called "Swiss form".[2] In the years that followed, Eisai was applied by national courts and adopted by national Patent Offices around Europe. The European legislature subsequently adopted the approach of the judiciary by enacting provisions in EPC 2000 that allow the patenting of inventions relating to second medical uses.[3]

POTENTIAL PROBLEMS WITH SECOND MEDICAL USE PATENTS

A problem with allowing patents for second medical uses of known drugs was that if a generic manufacturer were obliged to fully adopt the label of the originator's medicine in order to obtain marketing approval, then it led unavoidably to liability for patent infringement on account of having included the patented indication in its label. This could have led to an inappropriate extension of the originator's exclusivity. It may be helpful to illustrate this point with an example: Assume an originator invented a new drug, zyphophen in 1990. In the same year it filed a patent application for this new drug and in the specification of the patent disclosed that zyphophen was useful in the treatment of hair loss. The patent for zyphophen and the use of zyphophen in the treatment of hair loss would expire in 2010, twenty years after the filing date. Thus as of 2010 generics companies ought to be able to sell medicines containing zyphophen for the treatment of hair loss and other non-patented indications. Assume that, subsequent to the discovery of zyphophen, the originator continued research and development work on zyphophen and, in 1995, discovered that zyphophen was useful in the treatment of heartburn. Following the case-law/EPC 2000, provided the utility of zyphophen in the treatment of heartburn was not obvious, the originator ought to be able to obtain a patent for the treatment of heartburn using zyphophen. If this patent for the treatment of heartburn using zyphophen is filed in 1995, then it would not expire until 2015. The label for the originator's medicine would include both hair loss and heartburn and, if the generic were forced to adopt the originator's label in full, it would effectively be prohibited from selling zyphophen at all until 2015 because the label would state that the medicine could be used in condition heartburn, in infringement of the originator's second medical use patent. This would in-effect give the originator five years of exclusivity for zyphophen in the treatment of hair loss to which it was not entitled.

1 G05/83 – Eisai; decision of the Enlarged Board of Appeal of the EPO regarding second medical use claims (5 December 1984)

2 "Use of drug X in the manufacture/preparation of a medicament for the treatment of condition Y"

3 Article 54(5) EPC 2000

CARVE-OUT AND "SKINNY LABELS"

This potential unfairness was addressed by the European legislature in Directive 2004/27/EC[4] which amended the Community code relating to medicinal products for human use and allowed patented indications to be "carved out" of labels. All stake-holders agree that such a measure was necessary to enable generics companies to bring a medicine to market for those indications which were not patent protected. However, whilst this was a necessary step it was not a sufficient step and the current framework has generated unfairness and legal uncertainty for both patentees and manufacturers of generic drugs.

SUPPLY CHAINS AND PRESCRIPTION PRACTICES

Although the supply chain for a medicine from synthesis of active ingredient to administration to patients varies considerably from medicine to medicine and country to country, the figure below may serve as a useful illustration of a supply chain for a generic medicine. In the figure below, it is assumed that active ingredient X was the subject of a compound patent which has now expired and that the compound patent disclosed that X could be used in the treatment of medical condition Y1. However some time later a patent is granted for the use of X in condition Y2. The generics company obtains (as it is entitled to) a label for the use of X to treat Y1.

In most countries doctors prescribe a drug without reference to the indication for which it is prescribed. As a result the pharmacist dispensing the medicine at step 5 of the figure above, will not know the indication for which the drug is being dispensed and is likely to, and will often be required to, dispense the cheapest medicine which will fulfil the prescription, irrespective of whether the indication for which the patient is to be treated is on the label. As a result of this, even when a generics company has "carved out" the patented indication (Y2) for the drug, there is no guarantee that this drug will not ultimately be used "cross-label" in the treatment of the patented indication.

LEGAL ANALYSIS AND FURTHER ISSUES ARISING

As a result of the above, patents protecting new indications may prove to be less effective than intended. Additionally there is much legal uncertainty as to which steps in the supply chain would amount to an act of infringement (whether direct or indirect infringement) or the procurement of infringement of a second medical use patent. Should a Swiss form claim be construed literally and acontextually in which case step 2 (formulation and packaging) would be the relevant act of infringement or should the claim be construed by reference to the inventive concept, in which case attention would focus on step 5 (dispensing and administration)? The law in relation to second medical use patents was reviewed in *Ranbaxy v Astra Zeneca*[5] and in his judgment Kitchin J. emphasised that the skilled person would appreciate that Swiss form claims are an artificial construct of patent law, which may point towards step 5. The situation is further complicated by the fact that Swiss form claims are no longer available in many jurisdictions including the European Patent Office in light of interpretation of EPC 2000 as requiring claims to take the form of "Medicine X for use in the treatment of disease Y".

In *Actavis v Merck*[6] Jacob LJ. observed, obiter, that "*manufacturers, particularly for prescription medicines..., have to provide detailed instructions and information about the use(s) and dosage(s) of their products. So in practice you can tell whether someone has used X for the manufacture of a medicament for the treatment of Y. He will have to say that his product is for the treatment of Y on his [Patient Information Leaflet].*" Many commentators, however, consider that this statement is not limiting and that the use of a medicine for a "carved out" indication could still infringe in circumstances where those in the supply chain know, or ought reasonably to know, that the medicine was being used for a "carved out" indication. However much uncertainty remains.

As such, there is little motivation for pharmaceutical companies to invest in research and development of new uses for known drugs in circumstances where an insufficient period of market exclusivity remains for recovering investments. The current system also acts to the detriment of generic pharmaceutical companies as there is no legal certainty as to whether they will be held liable e.g. for contributory patent infringement in circumstances where they have "carved out" the patented use of the drug.

Due to the inadequacy/uncertainty of the current system, pharmaceutical companies are allocating more resources on the research and development of new compounds rather than investigating potential new uses of known drugs with proven safety and efficacy records.

4 Amending Directive 2001/83 of the Community Code relating to medicinal products for human use

5 Decision of Kitchin J. of 22 July [2011] FSR 44

6 Decision of the English Court of Appeal of 21 May [2008] EWCA Civ 444

Instead of unnecessarily exposing patients to new safety risks, the system should encourage pharmaceutical companies to devote more resources to the investigation and development of new uses for known drugs by providing appropriate protection for second medical use inventions. Such a system would operate to the benefit of all stakeholders in the industry since it is generally accepted that maximising the potential of all known drugs reduces the overall burden on the healthcare system by e.g. leading to a reduction of hospital stays, visits to GPs, a reduction in morbidity, and so on.

A POSSIBLE SOLUTION

It is likely that a fair solution to all parties cannot solely be achieved by revising pharmaceutical patent law and that it is necessary for there to be changes made to the way that medicines are prescribed, dispensed and reimbursed. For example, it is possible to conceive of a fair solution whereby a pharmacist is alerted to the indication for which a medicine is to be dispensed and will only be obliged to dispense the originator's medicine where the indication is for the new patented medical use. This would give the originator the exclusivity for the new indication whilst giving the generics companies legal certainty. Such a system ought not to compromise the physician's freedom to treat a patient according to the best of his or her skill and not place an undue burden on pharmacists or others involved in the supply of and payment for medicines.

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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
- patent & trade mark litigation
- data protection
- EU & competition law
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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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UK: RECENT COURT DECISIONS RELATING TO ARTICLES 3(A) AND 3(B) OF THE SPC REGULATION AND THE APPLICATION OF CASE C-322/10 MEDEVA

Case C-322/10 Medeva precluded the grant of a supplementary protection certificate "relating to active ingredients which are not specified in the wording of the claims of the basic patent relied on in support of the application for such a certificate." Since then there have been several further decisions in various EU Member States seeking also to apply Case C-322/10 Medeva and the various other decisions of the Court of Justice of the EU (CJEU) given at around the same time as to Articles 3(a) and 3(b) of the SPC Regulation.

Thus earlier in 2012 there were two decisions in the English Courts in which the active ingredient was held not to be specified in the wording of the claim in the sense required by the Regulation, namely *Novartis v Medimunne* (10 February 2012)—a monoclonal antibody case—and *Medeva v Comptroller* General of Patents (3 May 2012)—a vaccine case. In *Medeva v Comptroller* General of Patents, a vaccine case, where the claim was directed to an active ingredient providing immunity against pertussis, the Court of Appeal, which had originally referred Case C-322/10 *Medeva* to the CJEU, rejected the application for an a SPC occasioned by the grant of a Marketing Authorisation for a combination vaccine of which this was a component, observing that:

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[33] … the issue for the national court is to determine which active ingredients are specified in the wording of the claims. The ambit of "specified" may range from express naming, through description, necessary implication to reasonable interpretation. Where on that scale the dividing line is to be drawn will necessitate further references in due course in the light of the facts of the cases in which the issue arises. The problem for Medeva in this case is that wherever the dividing line is to be drawn the active ingredients relating to vaccines against diphtheria, tetanus, meningitis and polio are excluded.

However, on 20 September 2012, the English Patents Court encountered a case in which the question was less clear-cut and decided to make what is believed to be the first new reference to the CJEU seeking clarification as to what in this context "specified" (or in some of other decisions "identified" in the English versions) actually means. The English Court also decided that another issue raised in the decision in Case C-322/10 *Medeva*, relating to Article 3(c) of the Regulation, and which has, separately, been referred to the CJEU by the Dutch courts, was one that it should also refer to the CJEU.

These references to the CJEU arose in *Actavis v Sanofi Pharma Bristol-Myers Squibb* SNC [2012] EWHC 2545 (Pat). Here Sanofi had secured an SPC with EP (UK) No 0 454 511 as the basic patent for the single product irbesartan, which SPC expired on 14 August 2012. It had also secured a second SPC with the same basic patent, with an expiry date of 14 October 2013, but for a combination of irbesartan and hydrochlorothiazide, the validity of which SPC Actavis challenged. The combination product which had led to the application for the second SPC was indicated for the treatment of hypertension. There were claims in the basic patent not only to irbesartan (and other related compounds) but also to pharmaceutical compositions containing irbesartan (or other related compounds), in association with various actives described generically by reference to function, one of which was to a diuretic. Hydrochlorothiazide is a commonly used diuretic and so the issue was whether or not such claim could be said to specify or identify such combination; if it did not the SPC was invalid as the requirement under Article 3(a) that "the product is protected by a basic patent in force" would not be fulfilled. The English court thus referred to the CJEU the question:

"What are the criteria for deciding whether 'the product is protected by a basic patent in force' in Article 3(a) of the Regulation?"

Courts in other countries, considering parallel national designations of the same patent, had come to differing views on the issue. Thus the Paris Court of First Instance (10 August 2012 – Case RG 12/55806) had refused to grant an interim injunction because it questioned the validity of the SPC whereas the Dusseldorf District Court (15 August 2012 – Case 4a O 109/12) and the Hague District Court (14 September 2012 – Case 425814 / KG ZA 12-905) had taken the view that it was liley that the SPC was valid and had granted such interim injunctions. But beyond referring the question to the CJEU the English court also made its own proposal as to how it should be answered, having observed that it was evident from the decision in Case C-322/10 *Medeva* that it was a necessary, but not a sufficient, condition, that the combination infringe the patent claim. It suggested that the further requirement was that:

[76] … the product must infringe because it contains an active ingredient, or a combination of active ingredients, which embodies the inventive advance (or technical contribution) of the basic patent. Where the product is a combination of active ingredients, the combination, as distinct from one of them, must embody the inventive advance of the basic patent. Thus in a case such as the present, where the inventive advance of the Patent consists generally of the compounds of formula I, including specifically irbesartan, a medicinal product whose active ingredient is irbesartan is protected by the Patent within the meaning of Article 3(a) because it embodies the inventive advance of the Patent. A medicinal product whose active ingredients are irbesartan and a diuretic such as [hydrochlorothiazide] in combination is not protected by the Patent within the meaning of Article 3(a) because the combination, as distinct from irbesartan, does not embody the inventive advance of the Patent. …

It went on to justify this suggested approach by explaining that:

[76] … This is not a question of the wording of the claims of the basic patent, which as discussed above can be manipulated by the patent attorney who drafts it, but of its substance. …. if a later inventor were to obtain a patent for an invention consisting of a combination of irbesartan and substance X which surprisingly had a synergistic effect in treating hypertension, then a medicinal product whose active ingredients were irbesartan and X would be protected by that patent since it would embody the inventive advance of that patent. ... this interpretation of Article 3(a) would accord with the object of the Regulation, which is

to encourage invention in the field of medicinal products by compensating inventors for the delay in exploiting their inventions due to the need to obtain regulatory approval, and not to confer unjustified monopolies.

As to the second question, relating to Article 3(c) of the Regulation, the English court observed that the Dutch Patent Office had adopted the opposite interpretation of the CJEU's ruling in Case C-322 *Medeva* to that adopted by the UK Intellectual Property Office in holding that Article 3(c) precluded the grant of more than one SPC per basic patent. In Case AWB 10/4769 *Georgetown University v Octrooicentrum Nederland* the Hague District Court (11 July 2012) had held that the correct interpretation of Article 3(c) was unclear and decided to refer a question to the CJEU provisionally worded as follows:

"Does [the Regulation], more specifically Article 3(c), in the situation in which multiple products are protected by (the claims) of a basic patent, preclude the proprietor of the basic patent being issued a certificate for each of the products protected?"

As the same issue arose in the *Actavis* case before it, the English court decided to refer this question as well, provisionally worded in the same terms as the Dutch court had done. The English court observed however that the issue did not arise if Article 3(a) were interpreted in the way it had proposed. Thus if "the product is protected by a basic patent" within Article 3(a) because the active ingredient (or combination of active ingredients) embodies the inventive advance of the patent, then one SPC may be granted in respect of that product and that patent. If, however, the patent protects two products, because it discloses and claims two inventively distinct active ingredients (or combinations of active ingredients), then one SPC may be granted in respect of each product, and hence two SPCs in respect of that patent.

As we head towards this further iteration in the CJEU as to the meaning of Article 3(a) of the Regulation we have, in the meantime, yet to see how national patent offices and courts seek to apply the potentially even more momentous decision of the CJEU in Case C-120/11 *Neurim* of 19 July 2012 in which the CJEU held:

1. Articles 3 and 4 of [the SPC Regulation] must be interpreted as meaning that, in a case such as that in the main proceedings, the mere existence of an earlier marketing authorisation obtained for a veterinary medicinal product does not preclude the grant of a supplementary protection certificate for a different application of the same product for which a marketing authorisation has been granted, provided that the application is within the limits of the protection conferred by the basic patent relied upon for the purposes of the application for the supplementary protection certificate.

3. The answers to the above questions would not be different if, in a situation such as that in the main proceedings where the same active ingredient is present in two medicinal products having obtained successive marketing authorisations, the second marketing authorisation required a full application in accordance with Article 8(3) of Directive 2001/83/EC … on the Community code relating to medicinal products for human use, or if the product covered by the first marketing authorisation of the corresponding medicinal product is within the scope of protection of a different patent which belongs to a different registered proprietor from the SPC applicant.

This decision involved a somewhat extreme fact pattern, in that the CJEU thereby told the national court that the UK Intellectual Property Office had been wrong to have held that Article 3(d) of the Regulation (precluding the grant of an SPC in those cases in which the Marketing Authorisation referred to under Article 3(b) was not the first one to place the product on the national market as a medicinal product), meant that an earlier Marketing Authorisation for melatonin as a veterinary medicinal product precluded the grant of an SPC in respect of a basic patent which would not have been infringed by the veterinary product, following the grant of a Marketing Authorisation for this as a human medicinal product. Use of the "in a case such as that in the main proceedings" wording could give the CJEU scope to limit its decision to similar extreme situations, but the reasoning as set out in the decision, and the wording of its conclusions on their face, suggests that the principle as formulated by the CJEU in Case C-120/11 *Neurim* is of general application. If so, this then opens up the prospect of being able to secure a separate SPC in respect of a newly authorised indication for a previously authorised product, always assuming that the basic patent for the new SPC would not have been infringed by the previously authorised product. This is a question that can ultimately only be answered by the CJEU itself, but until this happens we can expect to see patent offices and courts in different Member States exploring it over the coming several

months, in much the same way as they have, for the past several months, been exploring the fall-out from the CJEU's decision in Case C-322 *Medeva* in a way which has culminated in the recent reference to the CJEU in *Actavis*.

FRANCE: SUCCESSFUL NON-INFRINGEMENT DECLARATORY ACTION IN PHARMACEUTICAL PATENT LAW

Even though French patent law does specifically provide for non-infringement declaratory actions, this procedural route is only implemented as an exception in litigation strategies, making for very scarce case law.

A recent decision from the Court of First Instance in Paris (Ratiopharm GmbH et al v. Sanofi Aventis, RG 09/14154, 3rd Chamber 3rd Section, 06 April 2012) is one rare decision illustrating a successful non-infringement declaratory action in the pharmaceutical field.

The claimants in the action were Ratiopharm GmbH, the holder of a marketing authorization for a generic clopidogrel product (antiplatelet medicine marketed under the trademark Plavix by Sanofi Aventis and indicated for certain cardiovascular conditions); Merckle GmbH, the manufacturer of this generic product; and Teva Santé, successor in title of Laboratoires Ratiopharm and exploiting the product in France.

This generic product contains clopidogrel as the sole active ingredient. The related patient leaflet as well as the summary of the product characteristics ("SPC") state that for certain treatment, the medicine is to be administered in combination with acetylsalicylic acid (commonly known as aspirin).

Sanofi Aventis is the holder of European Patent EP 0 881 901, whose main claim 1, following limitation proceedings before the French patent office, is the following product claim:

> *"Pharmaceutical composition containing a combination of active principles wherein the active principles are clopidogrel and aspirin, both constituent being present in a free state or in the form of a pharmaceutically acceptable salt, the active principles being formulated in dosage units containing from 0.1 to 500 mg of said active principle per dosage unit, and the amounts of clopidogrel and of aspirin being expressed in equivalents of clopidogrel and aspirin in free state".*

The claimants sought a declaratory judgment for non-infringement of EP 0 881 901. They asserted that the claims should be construed so as to be restricted to a single galenic form (single tablet) comprising both active ingredients, namely clopidogrel and aspirin. They proposed to interpret the claims on the basis of the common general meaning of the words, as well as patent rules. They further argued that, even though the patent discloses two embodiments, the patentee elected to protect only one, namely the single tablet. The claimants also raised an auxiliary invalidity counterclaim.

The defendant raised an infringement counterclaim, asserting that the offer for sale of the generic product amounts to contributory infringement. They argued that the patient leaflet and the SPC recommend the combination of clopidogrel with aspirin, and asserted that the patent covers two embodiments: a single composition comprising both active ingredients, and a set of two compositions (one with clopidogrel and one with aspirin) as supported by the patent specification.

After recalling the principle of claim interpretation under Article 69 EPC and its protocol for interpretation, the Court proceeded with a detailed analysis of the patent specification. It noted that the description indeed discloses a separate administration of the compounds clopidogrel and aspirin, but that this embodiment was distinct over that claimed. The reference in the specification to this embodiment, which is not covered by any claim, does not make it part of the patent scope. The Court concluded: "If, for the skilled person, a composition comprising two active ingredients does not necessarily mean that they are contained in a single galenic form, then in the present case, the drafting of EP patent 901 rules out that its protection be extended to two galenic forms since claim 1 is not directed to two galenic forms and neither suggests this". The Judge further ruled "the Court shall not analyse the patent in view of the scope which the right holder would have liked it to have, only the contents of the patent matter. The Court further notes that, on the contrary, Sanofi Aventis may be had an interest in connection with validity to have it limited to a single galenic form". The Court concluded that claim 1 is restricted to a single galenic form comprising clopidogrel and aspirin. The marketing of Clopidogrel Ratiopharm, together with the patient leaflet referencing administration in combination with aspirin, does therefore not infringe. Based upon this finding, the Court did not proceed with ruling on the counterclaims.

ITALY: THE APPLICATION OF THE PRINCIPLE SET FORTH BY THE EUROPEAN COURT OF JUSTICE IN *MEDEVA* (C 322/10) BY THE COURT OF ROME

In a decision on 25 November 2011, confirmed on 6 February 2012, the Court of Rome held that it is not possible to enforce an SPC granted for a combination product which was not claimed by the basic patent, thereby referring to the European Court of Justice decision in *Medeva* (C 322/10).

Background

These decisions have been issued in preliminary injunction proceedings pending between the originator Novartis and the generic company Mylan.

Novartis was the owner of European patent EP 0 443 983 (hereinafter "EP '983") and among others of two Italian SPCs based thereon:

- SPC No. C-UB1997P000590, which expired on 13 May 2011 and was extended until 13 November 2011 in accordance with Art. 13(3) Reg. (EC) No. 469/2009, claiming *"Tareg (valsartan)"* (hereinafter "SPC '590"); and
- SPC No. C-UB1999P000648, expiring on 25 September 2012 (hereinafter "SPC '648"), claiming *"Cotareg – valsartan, idroclorotiazide"*.

Mylan obtained the marketing authorisations for the generic product *valsartan* as well as *valsartan and hydrochlorothiazide* and intended to launch these on the Italian market on 15 November 2011.

As a result, Mylan started proceedings on the merits for revocation of SPC '648 asserting that it is invalid:

i) pursuant to Art 3 a) of EC Regulation No. 469 of 9 May 2009 (hereinafter "SPC Regulation") since the combination (*valsartan and idroclorotiazide*) is not "protected" by the basic patent EP '983;
ii) pursuant to Art 3 c) of SPC Regulation since another SPC on *valsartan* (SPC '590) had already been granted based on the same EP '983 patent.

In response, on 17 October 2011 Novartis filed an application for a preliminary injunction with the Court of Rome against Mylan enforcing SPC '648 and SPC '590.

By a decision dated 11 November 2011 the Court, disregarding Mylan's thesis, granted the injunction ordering that Mylan was prevented from any form of manufacture, commercialisation, advertising, distribution, storage and offer for sale (including the request of inclusion in the so-called "transparency list") of the Mylan generic medicinal products containing as active ingredient the combination of *valsartan and hydrochlorothiazide*. Further, the Court ordered drugs potentially already distributed be recalled and that the Italian Health authority (AIFA) and other pharmaceutical databases be informed of this preliminary injunction.

In particular, in examining the likelihood of validity of the enforced Novartis' SPC (the so-called "*fumus boni iuris*" necessary to obtain an interim measures), the Court applied the infringement test in Art 3(a) of the SPC Regulation and stated that Art 3(c) was not violated since the products claimed by the Novartis' SPCs at issue (*valsartan* by SPC '590 and the combination of *valsartan and hydrochlorothiazide* by SPC '648) were different.

The Judge indicated he reached such a conclusion *"unless the Court of Justice will issue a contrary decision interpreting the Regulation no. 469/2009 and in particular Article 3 lett. a) and c)"*. The Judge thereby was referring to the decision of the European Court of Justice (hereinafter "ECJ") expected for 24 November 2011, which would decide on the interpretation of the above said rules of the SPC Regulation in the cases Medeva C-322/10 and Georgetown C-422/10.

Mylan appealed against the interim order and following the issue of the ECJ decisions sought an application to stay the preliminary injunction pending appeal.

By his order issued on 25 November 2011, the President of the IP Division of the Court of Rome considered that the ECJ decisions, in particular Medeva, affirmed that Art 3(a) of the Regulation should be interpreted *"as precluding the competent industrial property office of a Member State from granting a supplementary protection certificate relating to active ingredients which are not specified in the wording of the claims of the basic patent relied on in support of the application for such a certificate"* and consequently ordered the provisional suspension of the preliminary injunction decision.

Finally, the Panel of Judges also adopted such interpretation and granted the appeal by a decision dated 6 February 2012.

Conclusions

This ruling is important since it is the first Italian decision in which the principles set by the recent Medeva ECJ decision have been applied.

Furthermore, this decision is interesting because it concerns an SPC claiming the combination of *valsartan and hydrochlorothiazide*. As a matter of fact, in the majority of the other European Countries (e.g. UK, Germany, France, Denmark, Sweden, Austria, Switzerland), Novartis applied only for an SPC on *valsartan* alone on the basis of EP '983.

In this regard, the decision of the President of the Court of First Instance in Paris, with a similar subject matter to the Italian one[1], clearly stated that *"in France, the patent owned by Novartis on the valsartan active principle [EP '983] does not allow to grant an SPC on the combination of valsartan and hydroclorotiazide, as this second active ingredient is not claimed in the patent in question"*.

In Italy, however, where the Patent Office (UIBM) does not carry out any examination on the validity requirements of an SPC prior to granting it, Novartis had also been able to obtain a SPC on a combination, which was not specifically claimed by the basic patent.

The Italian decision may have left some doubt as to the possibility of enforcing the SPC on valsartan against generic products containing *valsartan* in combination with another active ingredient (as *hydroclorotiazide*) since it did not consider this specific issue. Nevertheless, thanks to the decision of ECJ on 9 February 2012 in *Novartis v Actavis* C-442/11, this last doubt should be dispelled.

TRANSPARENCY REGARDING AUTHORISED MEDICINES: EUROPEAN MEDICINES AGENCY AND NATIONAL MEDICINES REGULATORS ANNOUNCE NEW JOINT APPROACH TO THE IDENTIFICATION OF COMMERCIALLY CONFIDENTIAL INFORMATION AND PROTECTED PERSONAL DATA

Transparency of regulatory procedures is a much-discussed and developing topic. Until fairly recently, it was often hard for third parties to obtain even basic information concerning medicinal products from some medicines regulators, even after the product had been authorised. It is a very different picture today, with the increasing trend for public bodies to respond to requests for information from the public, backed up by the introduction of Freedom of Information legislation which restricts the situations in which a public body can deny access to information requested. The European Medicines Agency (EMA) and many national medicines regulators ("National Competent Authorities"—NCAs) have been making great efforts to gradually expand the amount of information on authorised medicines available upon request. Increasing transparency has been high on the EMA's agenda (and likewise a priority for many of the NCAs) for some time. Most information submitted to regulators continues to be treated as confidential during the authorisation process, although even here steps are being made to increase transparency, with the EMA recently starting to publish (from March 2012) details of the international non-proprietary name (INN) and therapeutic area (and for innovative medicines also information on the type of salt, ester or derivative of the active substance) in relation to all (validated) applications entering the approval process. This initiative follows publication of recommendations on transparency of ongoing evaluations adopted by the EMA and Heads of Medicines Agencies (HMA) in November 2010; a few Member States already make such information available.

Regulators already issue a (European) Public Assessment Report ((E)PAR) once a medicine has been authorised, summarising the dossier content and the evaluation of the product during the authorisation process while excluding "information of a commercially confidential nature". In addition, freedom of information laws on public access to documents can be relied on at Member State level to request further information on dossier content and assessment, and for the European institutions (including the EMA) the rules contained in Regulation (EC) No.1049/2001 regarding public access to documents apply. Since the introduction of freedom of information policies and legislation, regulators have faced a large increase in the number of requests for release of information contained in the assessment reports and authorisation dossier, as clinical trial data and other content can be of great interest to patients, healthcare practitioners, patient/consumer groups and competitors alike. It has taken some time to work out how the freedom of information rules should be applied in this context, in particular how the exceptions to the general rule favouring release of information may be applied to protect certain of the content (some of which is considered confidential, at least by applicants) from release. An attempt by the EMA to refuse access to clinical study reports and trial protocols for two anti-obesity drugs was referred to the European Ombudsman, following a complaint from the Danish researchers who had requested access in order to carry out an independent analysis. In mid-2010, the Ombudsman found that the EMA's refusal to grant access on the grounds that disclosure would undermine the drug producers' commercial interests

was a case of "maladministration" and that the EMA should either disclose the material or produce convincing arguments as to why access could not be given, since disclosure would not in fact, in the Ombudsman's view, undermine commercial interests. The EMA finally accepted this position and granted the access requested.

In the face of an ever increasing number of requests for access to clinical and safety data or other information concerning authorisations granted, and once some experience of dealing with them had been gained, it soon became obvious that it was in the interest of all parties for the regulators to adopt a common approach to which parts of the dossier can be released and which should remain confidential. Since almost all authorisation procedures now involve several, if not all, EU Member States, then it is only sensible that for any given procedure/product, the same information should be available upon request from any Member State involved in that procedure. To provide clarity and to address some of the discrepancies that had arisen in the interpretations given to their release of information obligations by the different NCAs, this new "HMA/EMA Guidance Document on the identification of commercially confidential information and personal data within the structure of the marketing authorisation application—release of information after the granting of a marketing authorisation" has been finalised through the HMA forum, together with the EMA. It covers the release of information on authorised human (not veterinary) medicinal products, and specifies that dossiers on orphan drug designations, paediatric investigation plans and withdrawn / rejected applications are also not within the scope (but guidance may be produced in future). The guidance applies within the framework of publication/access to document policies already in place e.g. EMA policy on access to documents and "HMA/EMEA recommendations on transparency—recommendations on the handling of requests for access to Periodic Safety Update Reports". A second document, "Principles to be applied for the implementation of the HMA/EMA Guidance on the identification of CCI and PPD in MA applications" should be read in conjunction with the Guidance.

The Guidance document divides dossier information into four different categories: Commercially Confidential Information (CCI), "Can Be Released" (CBR) information, "Case By Case" (CBC) information (which may be suitable for release but needs to be considered on a case-by-case basis prior to possible release) and Protected Personal Data (PPD).

- CCI means (for the purposes of the Guidance) "any information which is not in the public domain or publicly available and where disclosure may undermine the economic interest or competitive position of the owner of the information"
- PPD means personal data that has to be protected and therefore cannot be released or should be redacted before release. "Personal data" means any information relating to an identified or identifiable natural person (the definition in EU Directive 95/46/EC on the protection of individuals with regard to the processing of PD applies)
- CBC suggests the need for a case-by-case review prior to possible release
- CBR means this section can generally be released but always after a preliminary review

The Guidance document contains a table dividing up the information contained in the application into categories according to the Common Technical Document (CTD) format and assigning a release category (CCI/CBR/CBC/PPD) to each, together with further explanation where necessary. The basic approach is to limit the scope of the information which can be regarded as CCI—broadly speaking, information about quality and manufacturing of a medicine, as well as information about facilities / equipment and some contractual arrangements between companies remains confidential (and is therefore not released, or redacted in any disclosed material). The Guidance notes that "Efforts can be made to inform or consult the Marketing Authorisation Holder prior to responding to a request of access to documents. This will depend on national legal frameworks".

For a number of sections of information (information on quality and manufacturing, description of types of test methods (unless they meet specific pharmacopoeial monographs), characterisation of the active substance) the approach taken is that detailed information is CCI but general information should be disclosed. Pharmaceutical development information (including detailed data concerning active substance, formulation and manufacturing and test procedures and validation) is classed as CCI while the final qualitative formulation (composition) is not. Detailed information on the synthesis or manufacture of the active substance is CCI, while structural informations not. Qualitative and quantitative information on impurities and degradation products is regarded as CCI unless disclosure is necessary for public health reasons. Information on inspections is not treated as CCI although specific details (e.g. regarding facilities and equipment) are. For biotechnology products, a general description of the active ingredient including the type of molecule and its general structural features or

the type of producer cell is not considered CCI, neither is general information on the fermentation and purification process or general statements on the establishment of the master cell bank or working cell bank and their stability. Information on non-clinical and clinical development and subsequent assessment by the regulator is not *per se* considered CCI (including information relating to environmental risk assessments and summaries of risk management plans), although in "exceptional and substantiated cases, particularly where innovative study designs and/or innovative analytical methods have been used, consideration will be given to the need for redaction".

Regarding "personal data", the starting point is that very little information in the application dossier should be regarded as PPD. Personal data related to experts or designated personnel (e.g. QPs, clinical experts and investigators) is classed as CBR and applicants are advised not to include non-essential information such as personal contact details, nor should they include personal details of other staff (although such details will be treated as PPD if necessary). If personal data related to patients included in clinical trial study reports are part of the dossier then they will be treated as PPD, but it is noted that legislation requires patient information to be included in non-identifiable form in the application. Likewise personal data related to pharmacovigilance information on individual patients is classed as PPD and where necessary identifying information will be redacted before release. When access to periodic safety update reports is requested, access to information which could reasonably be traced back to individual persons is not granted; at a minimum the patient's date of birth (reporting) country and patient identification code must be deleted to ensure anonymisation and a case-by-case assessment is needed to decide whether any further information must be removed.

The document is helpful to applicants to the extent that there is now more clarity on what information may or may not be released once a product is authorised. During the consultation process, industry was broadly in favour of release of clinical data but raised specific concerns with regard to the disclosure of non-clinical data. Some of the concerns raised remain open for further review (e.g. concern raised over potential conflict with publication in medical journals following publication of clinical data). In other cases industry has been advised to pay careful attention to the disclosure rules and take responsibility for the content of their dossiers accordingly (e.g. concern raised that disclosed information may be abused by companies and regulators where equivalent IP protection to that in the EU does not apply, to which the regulators replied that "As a general policy, in order to facilitate international collaboration, EU regulators would like to promote greater reliance on assessments performed by EU regulators. Publication or access to this information will facilitate this … [so] companies should consider carefully how they present data in this section"). However, at the end of the day the Guidance is just guidance—the final decision on disclosure lies with the regulators who "have to follow their national/European legislation in terms of access to documents and on the protection of personal data … Also, in cases of an overriding public health reason, regulatory authorities may disclose information normally classified as CCI … if their legislation so provides".

As an indication of how transparency efforts on the part of regulators may continue to evolve, the document on principles to be applied notes that "in order to reinforce transparency and public confidence in the European Medicines Regulatory System, NCAs are intending to develop strengthened efforts to release (either on request or proactively) growing amounts of clinical data" and notes that one possible way forward to help deal with the administrative burden on regulators in dealing with these requests might be to develop a new CTD format or similar tool to allow for the preparation of a non-confidential version of application dossiers. When it comes to transparency, there is clearly no reverse gear.

THE NETHERLANDS: REMOVAL OF PATENTED INDICATIONS FROM THE SmPC AND PIL: IS THE DUTCH MEDICINES EVALUATION BOARD (MEB) ALLOWED TO REQUIRE THE INCLUSION OF A STANDARD PHRASE IN THE PIL THAT THE MEDICINAL PRODUCT HAS ALSO BEEN AUTHORISED FOR OTHER INDICATIONS WHICH ARE NOT MENTIONED?

This issue particularly arises in cases of generic market entry, when the branded medicinal product has multiple therapeutic indications and patents for the branded medicinal product as such and for at least a first therapeutic indication have expired, but where patent protection for one or more therapeutic indications continues.

In such case, marketing authorisation holders (MAHs) of generic medicinal products are allowed to leave out such a patented indication from the SmPC and the PIL, in order to prevent potential patent infringement.

Further, the Dutch MEB requires the MAH to insert the following standard phrase in the PIL:

> [product name] *comprises as active ingredient* [name of the active substance]*, which is also authorised for other disorders that are not mentioned in this patient information leaflet. Ask your doctor or pharmacist if you have further questions.*

Recently, two decisions relating to the same case have been published on this topic. The first was published by the District Court of Arnhem last March, although the decision was already rendered in February 2011. The second decision concerns the appeal against this Arnhem decision with the Council of State (the Dutch administrative Supreme Court), which was rendered and published in March 2012.

The key question in this case was whether the Dutch MEB is allowed to require a MAH of a generic product, for which a therapeutic indication is still protected by patent rights and for which that therapeutic indication is removed from the SmPC and the PIL, to insert the standard phrase (see above) in the PIL.

The case concerned a dispute between Sanofi-Aventis and the MEB, involving also the generic MAHs Sandoz, Mylan and Focus Pharma as interested parties. Sanofi-Aventis is the MAH of various registrations concerning Prezal® (*lansoprazole*, a proton-pump inhibitor). The SmPC of Prezal® comprised as a therapeutic indication the use thereof, combined with two appropriate antibiotics, for the eradication of *Helicobacter pylori* (a micro-organism), for patients with peptic ulcers with the goal of preventing recurrence of *ulcus ventriculi* and *ulcus duodeni*. This indication was protected by Takeda's second medical use patent 0 382 489. The patent—amongst others—protected the use of lansoprazole for the manufacture of a drug for the prevention or treatment of infectious diseases caused by the micro-organism belonging to *Helicobacter pylori*. In the Netherlands, this patent was exclusively licensed to Sanofi-Aventis.

In 2005, the MEB decided to grant marketing authorisations to Sandoz, Mylan and Focus Pharma regarding generic lansoprazole variants of Prezal®. Takeda's patent was still in force, and Sanofi-Aventis had communicated to the MEB that it had objections against inclusion of the—briefly put—*Helicobacter pylori* indication in the generic SmPCs and PILs. The MEB thus decided that this indication should be removed from the generic SmPCs and PILs. Moreover, the MEB obliged the generic MAHs to insert the above standard phrase in the PIL in the interest of public health.

Sanofi-Aventis objected to this decision, *inter alia* arguing that the standard phrase in the PILs would invite "*off-label use*", more particularly use of the generic lansoprazole medicinal products for the patented indication. However, the MEB did not agree[1], and, rejecting the objection, held that the standard phrase was inserted for the benefit of public health.

In an administrative appeal to the District Court of Arnhem, Sanofi-Aventis reiterated its objections to the inclusion of the standard phrase in the PILs of the generic lansoprazole products, arguing that there was no legal basis for such inclusion, and more particularly that:

- it is in conflict with Article 60 of Directive 2001/83 *("Member States may not prohibit or impede the placing on the market of medicinal products within their territory on grounds connected with labeling or the package leaflet where these comply with the requirements of this Title.")*;
- it renders risks for public health;
- it leads to inconsistency between the SmPC and the PIL;
- it induces patent infringement.

The District Court of Arnhem, however, rejected Sanofi-Aventis' objections. Amongst other reasons, it held that a proper legal basis for omission of the standard phrase existed, referring to Article 59 (1, d, viii) of Medicines Directive 2004/27/EC[2]. *("The package leaflet shall be drawn up in accordance with the summary of the product characteristics; it shall include [..] specific recommendation to consult the doctor or the pharmacist, as appropriate, for any clarification on the use of the product").*

At the time of the District Court's decision, this Directive should already have been transposed into Dutch national law, but this had not happened yet. This explains why reference is made to this provision in the Directive, but not to Article 71 (2, f, 8) of the Dutch Medicines Act.

The District Court held that the standard phrase concerned a *specific recommendation*, as in this provision, because it was given due to the removal of the *Helicobacter pylori* indication from the PIL, and as it had the aim of informing patients about the use of the generic lansoprazole products from the viewpoint of the protection of public health.

In addition, implicitly referring to Article 59 (3) of the Medicines Directive 2001/83/EC, the District Court held that the standard phrase in the PIL can be regarded as *"the results of consultations with target patient groups"*, which ensures that it is intelligible, clear and easy to use.

In respect of Sanofi-Aventis' assertion that the standard text in the PIL would induce patent infringement,

the District Court held—without a lengthy motivation – that it does not share this view.

Further, with regards Sanofi-Aventis' position that the standard phrase would lead to inconsistency between the SmPC and the PIL, the District Court held that this was a logical consequence of Sanofi-Aventis' own decision to object to the inclusion of the *Helicobacter pylori* indication in the PILs of the generic MAHs.

Sanofi-Aventis lodged appeal against this decision with the Council of State, which rendered a decision on 14 March 2012. The Council of State did not assess the standard phrase as, contrary to the District Court, it decided that Sanofi-Aventis did not have a legal interest in the assessment of its objections. It argued Sanofi-Aventis had not made sufficiently plausible a causal link between the decline in sales and the insertion of the standard phrase in the PILs of the generic lansoprazole products. For this reason, the appeal was therefore held inadmissible.

Therefore, as matters currently stand in the Netherlands, removal of particular indications from the SmPC and the PIL due to patent protection of those indications, can and will be "compensated", from a public health perspective, through the MEB with the standard phrase "[product name] *comprises as active ingredient [name of the active substance], which is also authorised for other disorders that are not mentioned in this patient information leaflet. Ask your doctor or pharmacist if you have further questions.*" This practice became the MEB's official policy on 1 December 2009. It may be added, that this policy also indicates that the SmPCs and PILs which are available via the MEB must be complete, i.e. must comprise all indications of the reference product, but that in the versions used by the generics, patented indications can be removed. In such cases, in addition to the above standard phrase in the PIL, the MEB requires:

- that all safety-information pertaining to the removed indication must remain included in these versions of the SmPC and the PIL;
- that in these versions of the PIL the following reference must be made to the website of the Dutch MEB (in Dutch): *"Detailed information about this medicinal product is available on the website of the MEB: www.geneesmiddeleninformatiebank.nl".*

NEW ETHICAL RULES ON ADVERTISING OF VACCINES IN SWEDEN

On July 1, 2011, the Ethical Rules for the Pharmaceutical Industry (the "Ethical Rules") were tightened in regards to campaigns for vaccinations. The purpose of this tightening was to ensure that campaigns for vaccination focus on encouraging the public to be vaccinated against infectious diseases and not for it to choose a specific brand's vaccine over another. Vaccination campaigns approved no later than June 30, 2011 and initiated at the latest by December 31, 2011 were, however, allowed to continue to run until April 30, 2012. Consequently, today the new tightened Ethical Rules apply to all of the trade organisations LIF's (the Swedish Association of the Pharmaceutical Industry), IML's (the Swedish Association of Innovative Smaller Life Science Companies) and FGL's (the Swedish Association of Generic Drugs) members' vaccination campaigns.

Background

The Swedish Medicinal Products Act states that marketing of prescription drugs to the public is prohibited. The exception to this rule relates to campaigns against vaccination for infectious diseases, which are allowed.

The standard for the sort of vaccination campaigns allowed is laid out in the Ethical Rules which have been the main document specifying the Pharmaceutical Industry's responsibility regarding drug information since 1969 when the rules were originally adopted. The Ethical Rules need to be observed by LIF's, IML's and FGL's member companies, which include pharmaceutical companies representing a vast majority of the total sales of pharmaceuticals in Sweden. The Ethical Rules require, inter alia, a member company to include balanced, factual and current information about their drug's quality, effects and appropriate use when marketing and providing information about the product.

In May 2008, the industry introduced its own preview of drug information, performed by the IGM (the Swedish Pharmaceutical Industry Information Examiner). The IGM is appointed by LIF's Board of Directors. The introduction of a preview of drug information has resulted in, inter alia, campaigns for vaccination in advertisements, on the radio and on television now having to be previewed and pre-approved by the IGM prior to launch in order to ensure that they are in accordance with Swedish legislation and the Ethical Rules. Furthermore, all vaccination campaigns must include confirmation that the campaign is pre-approved.

What is new?

- Product name, product logo, or such other distinctive features or the drug's generic name are not allowed to appear in vaccination campaigns.
- However, vaccination campaigns are not considered to be marketing a specific pharmaceutical drug (thereby being in violation of the new tightened Ethical Rules) where at the time of the campaign only one (or a few) approved drug(s) against the infectious disease referred to in the campaign is (are) on the market and the public may as a result be able to determine the exact product name.
- Pre-approved vaccination campaigns are not allowed to be disseminated by directly distributed information material, regardless of whether addressed or unaddressed.

Companies not members of LIF, IML and FGL

The Ethical Rules for the Pharmaceutical Industry are only applicable to the member companies of LIF, IML and FGL. However, they are considered industry practice and companies that are not members of the said organisations usually agree to comply with the Ethical Rules.

NOTES

1. Decision of 6 July 2006.
2. Obviously, Directive 2001/83/EC, as amended by Directive 2004/27/EC, is meant.

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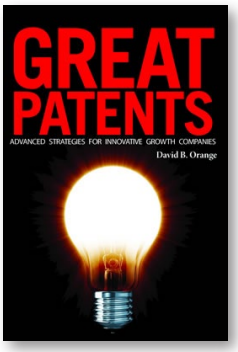

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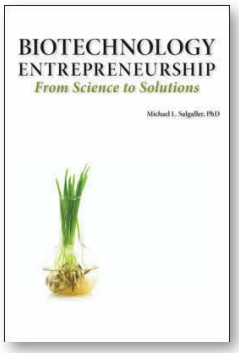

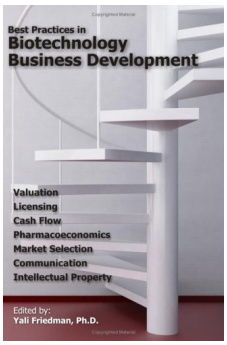

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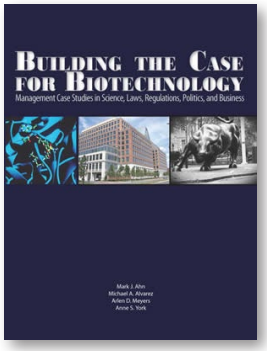

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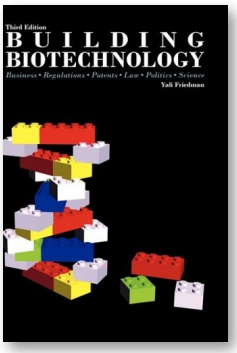

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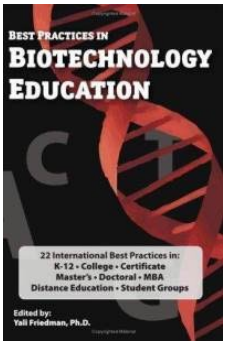

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