Journal of COMMERCIAL BIOTECHNOLOGY

APRIL 2014

VOLUME 20 I NUMBER 2

ISSN: 1462-8732 / eISSN 1478-565X

WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 20 NUMBER 4 APRIL 2014

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Editorial

Building biotechnology in India – Drugs are not the answer

Journal of Commercial Biotechnology (2014) 20(2), 3–4. doi: 10.5912/jcb655
Keywords: India, economic development

I have had the pleasure of participating in national forums on biotechnology development in diverse countries. A common theme I see is that emerging economies wish to develop 'a biotechnology industry like the United States.' I generally temper these ambitions by explaining that the United States does not have a biotechnology industry *per se*, but rather a handful of states have very strong biotechnology concentrations and many other states are still trying to build their domestic biotechnology industries. So the lesson for many emerging economies is to set ambitions at the US-state level rather than the US-national level. Furthermore, I also caution against aiming for drug development. Drug development is extremely expensive and risky—focusing on domestic agricultural or industrial biotechnology opportunities may be a better option.

I was recently in New Delhi, presenting data from the *Scientific American Worldview* project, where I have ranked national biotechnology industries for many years.[1] One may argue that novel drug development should be a target for Indian biotechnology and pharmaceutical companies, but my data suggest otherwise.

When I presented the Indian innovation figures and asked the audience to guess where they ranked. Much to their amazement, India was ranked with the bottom five of the 50+ countries assessed. The issues are myriad — poor patent protection, infrastructure problems, an insufficient quantity (not quality!) of skilled workers, etc.

Compounding this issue, I also refered to my study on pharmaceutical globalization which examined the mobility of pharmaceutical innovation.[2] In reviewing the locations of pharmaceutical patent inventors since 2000, I was surprised to find that it had essentially never moved—The US, Western Europe, and Japan have and still do dominate pharmaceutical invention. This is a sobering finding for any region (a country or even a province/state within one) seeking to improve their drug discovery output. It is notoriously hard to seed new locations.

So, where does that leave India and every other country that doesn't currently have a strong drug discovery industry? Should they simply give up? Clearly that is not a good plan, and it is also not practical because of the strong social, economic and political benefits that come from drug discovery and development. Rather, I think that countries seeking to develop drug discovery capacity should focus first on building foundations for drug discovery, and this is often best done by not working on drugs![3]

One of the problems with providing stimulus to foster novel drug development firms is that, if successful, the talent, products, and profits often move to one of the established drug development hubs. It is akin to trying to build an broadcast entertainment industry outside Hollywood or developing a sports team in a new city—if you do develop talent, much of it will be drawn to the existing hubs.

So, given that successfully developing drugs outside of existing hubs has been shown to be rare, and that any products and talent developed outside of existing hubs is also likely to relocate to existing hubs, what can be done? A better approach is to focus on uniquely domestic needs, which can be later adapted to serve broader problems.

Brazil is a world leader in bioethanol production. This capacity was developed with the initial help of tax subsidies, but it also followed a natural path—sugarcane processing. In Brazil bioethanol is produced by fermentation of bagasse, the pulpy plant mass left behind after sugarcane sugar extraction. Because bagasse was already collected at sugar processing plants, biomass producers simply had to set up shop at the collection points. Furthermore, because bagasse is expensive to ship, it means that the bioethanol companies are likely to stay local.

To come back to the Indian example, it is important to recognize that drugs are but one way to improve health. Another way is to prevent onset of disease. When I was in New Delhi, holidays were providing a respite from smog as farmers upwind from Delhi had temporarily stopped burning crop residues. Investments in industrial or agricultural biotechnology applications to provide alternatives to burning crop residues can improve rural employment while reducing pollution and pollution-borne illnesses. These domestic solutions are unlikely to relocate, and can build a foundation for

further development in other areas, such therapeutic biotechnology.

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Original Article

Fostering technology transfer in industrial biotechnology by academic spin-offs in Europe

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ABSTRACT

Industrial biotechnology is the commercial application of biotechnology using cells or components of cells, like enzymes, for industrial production processes including consumer goods, bioenergy and biomaterials. In the last years this area has gone through a fast technological development resulting in a high number of basic technologies based on research efforts at universities and research institutions. But a technology transfer gap exists between basic research and the commercialisation of the results. This gap can be closed by academic spin-offs which manage the technology transfer from universities and research institutions to industrial companies. After the spin-off process, the technology is further developed within the new venture normally using additional resources from external investors. As soon as the technology reaches a certain grade of maturity, the spin-offs can co-operate with an established company and work for them as a service provider or be acquired. The chosen approach of technology transfer depends on the type of company. Whereas multinational enterprises (MNEs) are very active in making new technologies available both by acquiring spin-offs or engaging them as service providers, small and medium enterprises (SMEs) are focused on partnering with spin-offs, due to limited financial and management resources.

Journal of Commercial Biotechnology (2014) 20(2), 5–10. doi: 10.5912/jcb631

Keywords: industrial biotechnology; bioeconomy; technology transfer; new ventures; academic spin-offs

INTRODUCTION

Biological production technologies are being increasingly applied to produce high value products, such as fine or consumer chemicals, but also bulk chemicals and polymers.[1] The development of these technologies has progressed at an enormous rate and has led to several technological breakthroughs. For example, the genetic engineering of microorganisms has enabled the biotechnological production of new products and, in combination with improvements in process design and reactor technology, it dramatically increases the performance of biotechnological production processes. The applicability of enzymatic catalysis, as another example, was subject to major improvements regarding the reaction environment and process conditions. For instance, the use of non-aqueous solutions increases the substrate spectrum and the application of enzymes from extremophile sources increases the robustness of the processes and the choice of reaction conditions.

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The capability and efficiency of these biotechnological processes often exceeds the existing chemical ones and even enables reactions and production steps that had not been possible with established techniques. In addition, these new processes will comply with modern requirements in eco efficiency including the use of renewable raw materials, mainly agricultural products such as starch and their residues, for industrial purposes. This use of renewable feedstock is widely regarded as the solution to find alternatives for diminishing fossil resources.[2,3] The ecological effect of industrial biotechnology is also due to low operating temperatures of biotechnological processes in contrast to rather energy intensive processes using chemical catalysts and high temperatures required by many chemical reactions.[4] There are numerous examples of successful applications of industrial biotechnology for the generation of innovative and valuable products, including products that cannot be produced using traditional chemical synthesis.

The application of renewable resources will result in economically and environmentally sustainable production processes influencing the economic development of industries, like the chemical industry. This makes industrial biotechnology a key technology for future economic development and offers dynamic growth opportunities for the chemical and related industries.[5,6] Governments in Europe,[7] the United States[8] and other regions recognise the potential of industrial biotechnology and ensure support to remove growth barriers and exploit the application opportunities. This becomes obvious by the many financial incentives given by governmental programmes encouraging investments in this area.[9]

But there are also some barriers to overcome. The chemical industry has optimised chemical synthesis over a long period of time and the production facilities are normally depreciated making the synthesis of existing products using chemical procedures so inexpensive that the development of a biotechnological production process is often not cost efficient.[10] The change of existing chemical processes towards biotechnological processes might require massive new investments so that companies have to manage the high capital requirements to build up new production facilities.[11] Economic advantages due to the implementation of biotechnological processes can only be achieved by lower production costs, since biotechnological products do not achieve higher prices compared to their chemically produced counterparts. A price premium for biotechnological products can be accomplished only in a few segments, such as the food industry.

To achieve this transition from chemical synthesis to biotechnological processes on a cost competitive level compared to chemical synthesis, state-of-the-art technologies have to be employed. Therefore, technological innovation is important for industrial biotechnology which makes the transfer of academic R&D results towards innovative industrial applications a key aspect for the industry.[12] Academic research is typically governmentally funded and conducted in non-profit governmental or semi-governmental institutions (e.g. universities and research institutions, like Max Planck, Helmholtz or Fraunhofer Society). One possibility to commercialise new technologies are entrepreneurial activities by creating new ventures within these institutions.[13-15] These academic spin-offs can bridge the technology transfer gap to use academic R&D results for innovative industrial products and services.[16-18] Due to their lean structure they are more flexible and faster in the commercialisation of new technologies than established companies.[19] The importance of entrepreneurship for universities and research institutions has steadily increased during the last decades.[20] This is accompanied by a change in government policies that encourages universities and research institutions to commercialise their R&D results.[21,22] This means that, besides teaching and research, an additional mission is the support of the economic and social development through the commercialisation of the output of basic research.[20,23,24]

This article investigates the role of technology transfer in industrial biotechnology by creating academic spin-offs. After describing the methodology of the research and describing the role of established companies and spin-offs within the industrial biotechnology sector this article discusses the creation of spin-offs as a method to transfer academic R&D results into industry. The aim is to raise interest for this topic especially within the community of policy makers and traditional companies. Therefore, based on the conclusions in the last chapter concrete recommendations for universities and research institutions, established companies and policy makers are given. It is important to mention that this article has a focus on the situation in Europe and particularly Germany.

METHODOLOGY

The initial literature research was carried out in both academic and practitioner oriented journals as well as publications of relevant institutions (e.g. company presentations, annual reports, press clippings). The main key words, which were searched, were technology transfer, spin-offs, spin-outs, start-ups, new ventures, co-operation, joint development, acquisition, mergers & acquisitions (M&A), service provider and technology provider. Main result was a database with relevant institutions (industrial companies, academic spin-offs, universities and research institutions including TTOs

and venture capital investors including corporate venture capitalists) as well as technology transfer examples including involved parties, background, relevant activities and results.

To understand technology transfer by academic spin-offs interviews with 12 academic spin-offs, 12 universities and research institutions, 22 companies and 15 venture capital investors (of which 4 were corporate venture capitalists) were conducted. The interview partners were selected from the database by 1) ranking them regarding fit to the research scope and 2) interest in and availability for an interview. All potential interview partners with a good fit were asked for an interview and all those who agreed were interviewed. Each interview partner was interviewed by a single interviewer in one sitting of approximately one hour. A reference set of questions was used as a guideline for the interview, thereby leaving enough room for spontaneous answers, which gave a semi-structured nature to the interviews. The questions were structured around different topical groups containing 1) importance and usage of technology transfer from academia, 2) co-operations with academic spin-offs and 3) technology transfer mechanisms and results regarding co-operations with spin-offs.

Before each interview, the interviewer had gathered in-depth information on the company or institution through various sources (e.g. databases, website, press releases), enabling an efficient conduct of the interviews. The analysis of the interview results was based on a comparative analysis to identify specific aspects referring to grounded theory techniques.[25,26] The results of this analysis were used to describe the role of the different company types including spin-offs and especially their involvement in technology transfer.

ROLES OF THE DIFFERENT COMPANY TYPES

Companies active in the area of industrial biotechnology range from small and medium enterprises (SMEs) to multinational enterprises (MNEs). Based on the definition of the European Union, SMEs have less than 250 employees and less than 50 million Euros annual turnover. Companies with more employees or higher annual turnover are seen as MNEs, because they normally have operations in more than one country. The differentiation into specific company types based on size, i.e. MNEs versus SMEs, and areas of activity, i.e. dedicated to industrial biotechnology versus diversified over a broader range of areas, is necessary to understand the industrial biotechnology sector, as industrial biotechnology is of different importance for these company types (Figure 1).[27] Additionally, these different company

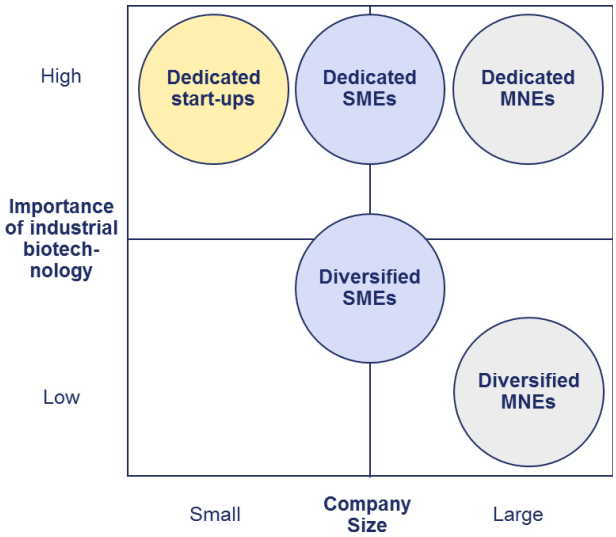

Figure 1: Company types within the field of industrial biotechnology

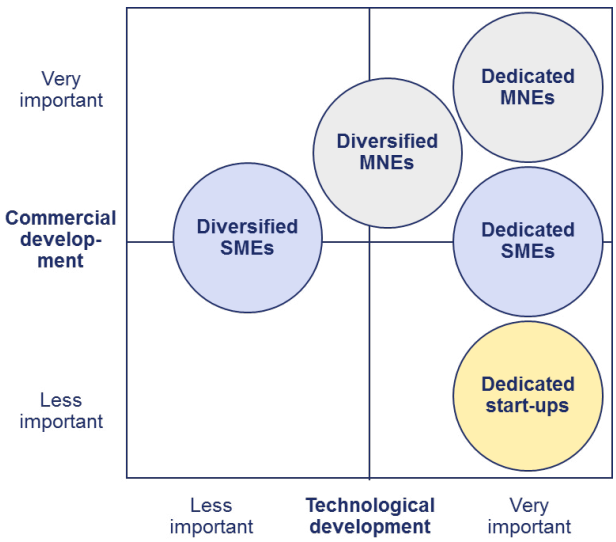

Figure 2: Importance of the different company types for the further development of industrial biotechnology

types have very different roles regarding the technological and commercial development of the industrial biotechnology sector (Figure 2).

Dedicated SMEs focusing on industrial biotechnology were founded mainly in the 1990's (BRAIN) or early 2000's (Codexis). After performing intensive R&D during the first years, they are now focused on the development and market introduction of their own products. This requires a stable revenue situation to finance own R&D projects, development and production facilities, as well as enable market access, e.g. by acquisition of appropriate business units. Dedicated SMEs with their technology focus strongly support the technological

development of industrial biotechnology. Diversified SMEs (e.g. Döhler, Pentapharm) have a longer tradition and focus on established industrial sectors, like the chemical or food industry. Serving already developed markets with highly specialised products, these companies are introducing step by step biotechnology processes and products into their markets to realise growth opportunities despite restricted technological resources. It is expected that diversified SMEs will introduce industrial biotechnology to a wide range of processes and contribute to the commercial development of this segment.

Dedicated MNEs are dominated by companies, which have been active in the area of natural products for decades (e.g. Purac, Lesaffre). Normally, they use optimised biotechnological processes for traditional markets (e.g. starch, yeasts) over many years. Industrial biotechnology is one cornerstone in their technology portfolio and increasingly they are moving towards new biotechnology based products and processes. Other companies in this segment (e.g. AB Enzymes, Novozymes) are more R&D oriented and have industrial biotechnology as core activity. This group contributes significantly to the technological and commercial development of the industrial biotechnology sector. Diversified MNEs are mainly established companies from the chemical industry (e.g. DSM, DuPont), agro industry (e.g. Archer Daniels Midland, Cargill) or food industry (e.g. Danisco, Nestle). Their strength is the broad and integrated technology portfolio which complements industrial biotechnology processes (e.g. purification technologies). They have the technical resources (e.g. engineering) as well as financial resources to commercialise biotechnological technologies and products globally. As biotechnology is only one of many core technologies these companies have a smaller impact on the development of industrial biotechnology than dedicated MNEs.

TECHNOLOGY TRANSFER THROUGH SPIN-OFFS

Dedicated and diversified MNEs have enough in-house resources to realise most of the technology developments in-house. Additional R&D capacity and cost reduction (reducing fixed costs or people on the payroll) is not relevant for working together with external partners, like spin-offs. But these companies have a high interest in additional, external know-how which is not available in-house or too expensive, if it would be built up internally. Expanding in-house capabilities through external expertise is seen as the most important advantage of using external technologies by way of co-operations with service providers. An important task for established companies is to optimally integrate internal and external knowledge within the innovation process, so as to be able to benefit from synergy effects. This strategy has often been used in the past and almost all industrial biotech companies have such co-operations (e.g. R&D co-operations of BASF, DSM, Henkel and others with BRAIN as an example from the chemical industry or co-operations of Shell with Codexis and Total with Gevo in the area of biofuels).

The situation for SMEs is very different, compared to MNEs, as they are more dependent on technology transfer from academic research to develop new products internally or together with partners, due to limited financial and management resources. They see technology transfer from the academic world as an effective method to capture capacity and expertise without investing much money in in-house resources. The preferred option to access new technologies involves R&D co-operations with universities and R&D institutions but also with specialised spin-offs.

It is characteristic for all spin-offs to start with a technology that is immature and requires further development. The proof-of-concept is normally done at laboratory scale. Before larger investments in production, marketing and sales it is necessary to reach the technical proof-of-concept. The need for further development of the technology is directly linked to additional financial requirements and other resources to facilitate the R&D work. Due to restricted resources in their first years, academic spin-offs focus mainly on a service oriented business approach offering their particular know-how to support other companies. The intellectual property (IP) from these co-operations normally belongs to the customer resulting in a limited growth as well as value creation potential. But the business risk is also limited as there are only low capital requirements to realise this business model. The spin-offs avoid the time and cost consuming development of own products, while their customers are able to transfer the spin-offs' technologies into new products.

Nevertheless, the development of own IP and products is necessary for the further growth of new ventures. It can be observed that, over time, the service oriented spin-offs are taking on a more IP/product oriented business approach. This is possible as it is accepted that a significant part of the developed IP within research co-operations belongs to the technology provider. For example, companies like Autodisplay Biotech, C-Lecta and Evocatal are developing biocatalysts for established companies within R&D co-operations whereby a special biocatalyst including all related IP belongs to the customer and new IP regarding further developments of the technology belongs to the spin-off. As a result,

with growing maturity, spin-offs are increasingly able to develop and commercialise own technologies and products.

After building up an attractive technology or product portfolio with correlating IP protection or, if the technological and market proof-of-concept is shown, technology transfer through the acquisition of these spin-offs by MNEs or SMEs is an option. The first step of an acquisition is often an R&D co-operation which gives the established company the opportunity to assess the technology of the spin-off and the fit into the own technology portfolio. In the case of an acquisition, the spin-offs are normally more or less integrated into the buying company so that the complete know-how and IP is fully available for the new owner. There have been numerous examples during the past years, like the acquisition of IEP by Cambrex or the purchase of X-Zyme by Johnson Matthew.

CONCLUSIONS AND RECOMMENDATIONS

It could be shown that academic spin-offs can close the technology transfer gap between academic research and industrial application in the area of industrial biotechnology. Spin-offs make state-of-the-art technological expertise from academic research available for established companies which can use these to leverage their product development and global sales capabilities. Technology transfer from academia to industry creates a win-win situation for all participants leading to a faster dissemination of academic knowledge into practice and resulting in an economic advantage.

The views regarding technology transfer and especially the expected increases in performance of own R&D are similar when comparing the different company types, but the chosen approach of technology transfer depends on the type of company. Whereas MNEs are very active in making new technologies available both by acquiring spin-offs or engaging them as service providers, SMEs are more focused on partnering with spin-offs, due to limited financial and management resources. An important insight is that none of the company types performs all technology developments internally. Working together with external partners, like spin-offs, strengthens internal competencies by combining internal and external know-how. A task for established companies is to optimally integrate internal and external knowledge within the innovation process, to be able to benefit from the positive effects each activity has on the other. The advantage for the established companies is that they can focus more on their core competencies and especially on their markets as external technological competence can be brought into the company.

But creating spin-offs is not yet systematically used for technology transfer from universities and research institutions into the industry. Despite some elements of "entrepreneurial thinking" within the new Horizon 2020 program and some national initiatives within governmental funding programs (e.g. GoBio in Germany) there is still no general awareness about the value of entrepreneurial thinking. Companies should use the advantages of new ventures like more target-oriented R&D work or faster time-to-market to improve the innovation capabilities within their companies. R&D managers in established companies should be more open to actively use new ventures for technology transfer and understand that entrepreneurial behaviour can support technology transfer to improve innovation processes.

Spin-off activities can also be fostered by so called founding angels. With Autodisplay Biotech and Butalco there are success examples in Germany.[28] Founding angels found together with scientists high-tech start-up companies to successfully commercialise the results from academic research. They complement the scientific team members coming mainly from universities and research institutions with business expertise.[29,30] Besides initial funding in the pre-seed phase, founding angels are operationally very much engaged bringing in their expertise from other successful start-up projects. Because of their very early and much more operationally engagement they have more the role of a founder and entrepreneur and less that of an investor. Universities and research institutions should be more open to work together with founding angels because they can support academic institutions in the identification and realisation of interesting start-up opportunities.

As high quality research at universities and research institutions in Europe has not been sufficiently translated into commercial applications, policy makers should more foster this technology transfer mechanism. Policy makers should further support the creation of new ventures for technology transfer through providing incentives for business oriented and experienced people like founding angels or business angels to join new ventures and to successfully help realise technology transfer. These incentives could be tax incentives for the new ventures (e.g. preferred depreciation models for R&D expenses), entrepreneurs and investors (e.g. reduced tax rates on exit profits).

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Original Article

Pharmaceutical R&D productivity: the role of alliances

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ABSTRACT

In recent years, the major research-intensive biopharmaceutical companies (big pharma) have come face to face with a perfect storm of eroding profit margins from blockbuster expiration and generic competition coupled with growing R&D expenses and declining advances in truly novel therapeutics. With long-term research divisions shed in favor of short-term outsourcing options and with public good will at historic lows, industry innovators have sought to reinvent the model of big pharma, its relationship in public-private partnerships, and the role of technology and technology policy in reform. In this paper, we highlight a number of the major alliances reshaping the industry and the role of government, research institutions, and other players in the public-private interface in these endeavors. In particular, this paper looks beyond traditional biotechnology parternships and focuses instead on the developing consortia between biopharmaceutical companies and with clinical research organizations and academic institutions. We examined each alternative model of alliance, identified specific hurdles and potentials for increased productivity.

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Journal of Commercial Biotechnology (2014) 20(2), 12–20. doi: 10.5912/jcb632
Keywords: productivity, alliance, CRO, R&D, big data

INTRODUCTION

The global biopharmaceutical industry is facing unprecedented pressure to produce sufficient numbers of important new drugs that can offer substantial return on rising research and development investment. The costs of research and development are rising and the number of approvals per year is dropping.[1] In the face of this productivity downturn, an understanding of where the industry is, where it is trying to go, and how to survive and thrive is necessary. We begin our analysis by reviewing macro industry trends that fall into the categories of challenges and opportunities to better understand the research and development environment.

CHALLENGES

The increases in cost for research and development have been attributed to the shift in focus to chronic diseases that require larger scope, longer clinical trials as well as the advances in technology raising specificity and complexity in the compound identification process.[2] Though the estimates of the cost of development vary greatly across disease states and projects, costs across all therapeutic areas are increasing at an alarming rate. Another ominous trend is the amount of time required for research and development. On average, it takes 17 years for emerging medical knowledge to become a reality to patients and depending on when patents are filed, market exclusivity periods are shrinking.[3] Compounding these issues is the high attrition rate throughout the drug pipeline. Only 11% of drugs that enter clinical testing are approved.[4] The 11% that do make it to the market have to gross enough revenue to rationalize the investment made in their development as well as the investment made in the 89% of compounds that failed during clinical development. Rising expenses of drug development and increasing time to market leaves very few products that are able to break even on their research and development spending. A blockbuster model, that had served the industry well for generations as a reliable profit-center are becoming more difficult to come by, with the disproportionate expiry of a number of these drugs creating added pressure. Whereas the rise of orphan indications and the mini-blockbuster has been suggested to fill this gap, criticism has grown over the extraordinary prices these drugs command and the growing percentage of approvals (roughly a third) these "orphans" make up.

Utilizing executive interviews and forums of the Blanche and Irwin Lerner Center for the Study of Pharmaceutical Management Issues and the Rutgers Business School Pharmaceutical Industry Alumni Association (Appendix A), we sought to better elucidate the key management strategies being employed to reform pharmaceutical R&D practice and productivity in the face of these challenges. The initial list drawn from executive interview and supported by literature review found these to include acquisitions, strategic partnerships, budget cuts, layoffs, focusing on internal discovery, partnerships with academia, movement of research and development facilities, closing of research and development facilities, and narrowing therapeutic focus.

With access to executives from throughout the biopharmaceutical industry, we next sought to pinpoint current trends in management strategies from this list. Our survey was conducted via an e-mail linked, anonymous, multiple choice and open answer electronic survey. A cluster of three questions pertaining to R&D Practices were included in the survey (Appendix B). Executives that held a variety of positions and had varying levels of experience, from mid-level to senior level, were provided the optional survey. A total of 30 executives completed the survey. Whenever possible, additional input from executives was garnered through open answer on the survey or direct dialogue.

A RENEWED FOCUS ON DIVERSIFYING PARTNERSHIPS

A notable initial commentary voiced by numerous industry executives, in confidence, and supported by a review of the literature, reveals that those strategies pertaining to short-term cost-cutting measures, including outsourcing and staff reductions, and market expansion attempted via merger/acquisitions, failed to address the core issue of productivity plaguing the industry. Often blamed on the past harvest of "low hanging fruit" and an overzealous FDA, it is becoming increasingly clear that a short-term focus on risk reduction and profit maximization coupled with devastating rounds of cuts and realignments, have served only to enhance short term profit at the expense of outside relationships. Our survey of the Rutgers Business School Pharmaceutical Industry

Alumni network and other willing industry professionals from the Lerner Center and beyond appear to have captured this trend. Seventy-three percent of respondents indicated their company was making process changes within the research and development department in the light of external cost pressures (Figure 1). However, the above-mentioned misgivings with short-term cost controls and adverse consequences of cost control on relationship management appear to have trickled into updates in R&D strategy. When polled among the nine strategies to reform R&D practices (acquisitions, strategic partnerships, budget cuts, layoffs, focusing on internal discovery, partnerships with academia, movement of research and development facilities, closing of research and development facilities, and narrowing therapeutic focus) (Figure 2), budget cuts and closing of R&D facilities were noted by only ~15% of respondents and partnership strategies with academic institutions garnering less than 20%.

However, with research divisions gutted or severely curtailed and public goodwill at historic lows, industry innovators have sought to reinvent the model of big pharma, its relationship in public-private partnerships, and the role of technology and technology policy in reform. In our poll of the above-mentioned nine strategies to reform R&D practices (Figure 2), respondents overwhelmingly noted strategic partnerships (>60%) compared to the nearest alternatives, a veritable tie between acquisitions, budget cuts, and layoffs at roughly 40%. In reevaluating the value of this broader R&D ecosystem to externalizing expenses while growing innovation, a number of groundbreaking strategic partnership models have been implemented by the leading players in big pharma and enabled by policy makers over the past decade. In subsequent sections, we will review the literature discussing the implications and opportunities of strategic partnerships, beginning with classic alliances between biotech and pharma and extending to partners valuable in both early stage research as well as late stage development and clinical trial design and execution. Best practices documented within the literature will be described and the recent development of unique consortia highlighted.

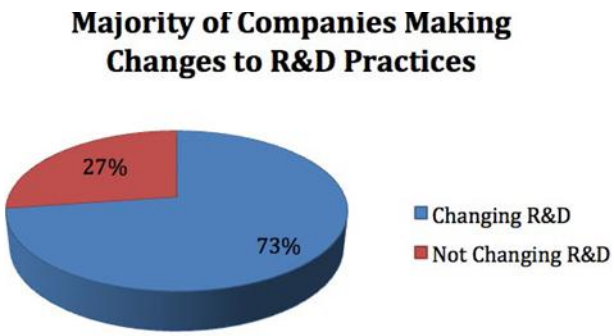

Figure 1: Responses to the prompt, "Has your company made any process changes within the R&D department in light of external cost pressure?"

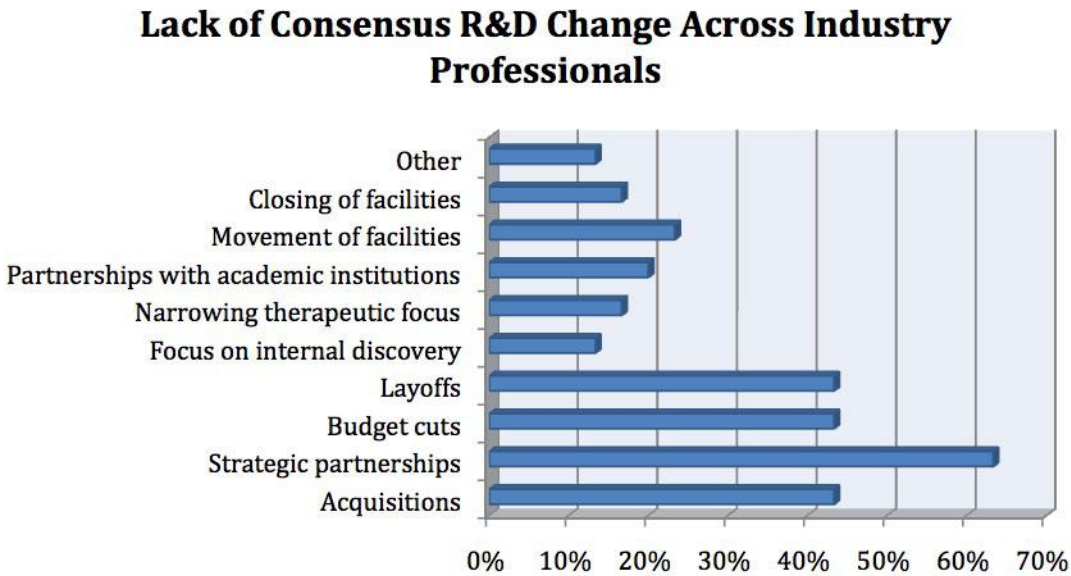

Figure 2: Responses to the prompt, "Has your company done any of the following in an attempt to update their R&D practices? (Select all that apply)"

BIOTECH PARTNERS IN BUSINESS DEVELOPMENT

The pharmaceutical industry has long capitalized on the technology and expertise of biotech companies in early drug development. They have chosen to partner with, license technology, or acquire the companies altogether. Rigorous academic studies have found that collaborative R&D projects involving biotechnology companies in pharmaceutical development have higher probability of success in developing a marketable product.[5,6] Size and experience of the involved companies for product developments are important determinants of success in a collaborative projects as well.[5,7] Companies are choosing to do collaborative research and development twice as frequently as performing in-house development, across industries.[8] This trend represents an opportunity for companies to accomplish more with fewer in-house employees.

STRATEGIC PARTNERING WITH VENTURE CAPITAL

The application of venture capital by the pharmaceutical industry can be labeled as either classic corporate venture capital (CVCs) or strategic limited partner relationships. CVCs tend to be separated from the parent company by somewhat porous "Chinese walls", designed in principal to prevent issues of intellectual property cross-contamination and unintended disclosure of confidential information. Sharing much the same structure and management of independent venture funds, they differ only in their willingness to invest in early stage ventures. For example, a report by David and colleagues found that Novartis CVC demonstrates an enhanced focus on early-stage opportunities compared to a set of independent venture funds.[9] Whereas this has often been cited as examples of improved visibility into emerging biotech and enhanced access to innovation, these arguments are more attuned to classic business development functions. Rather than such informational and networking services, the role of CVCs in big pharma are more attuned to contributing to the health of the early-stage innovation ecosystem, by promoting the growth of innovation ecosystems most aligned with larger development goals.

In addition to internal CVCs, a number of biopharmaceutical companies have chosen to outsource their venture capital efforts, supporting early stage innovation by making strategic alliances with venture capital firms (Appendix C). As a significant limited partner, a biopharmaceutical company or even its associated CVC, can hold sway on deal sourcing, execution, and risk profile. Although some control is lost, these drawbacks are often outweighed by the established nature and risk-sharing advantages of an external firm.[10] As with most outsourcing mechanisms that utilize balance sheet cash, strategic alliances with venture capital allow for greater strategic flexibility than internal infrastructure development. However, this comes at the expense business development participation, toward capability bartering (incubators, data, reagents, development assistance). In addition, a biopharmaceutical company, as one of many limited partners, may inadvertently find themselves in a venture fund alliance alongside an industry rival. Given the overlapping interests in drug class, disease, and sector, this was bound to occur, especially as major biopharmaceutical companies have invested the heaviest in partnerships with those venture funds holding the greatest hope of bringing new drugs of popular or orphan niche classes forward. An example of how this can be handled is given by the case of GlaxoSmithKline (GSK), Johnson & Johnson and Index Ventures (see Appendix C). Of the nine-member Science Advisory Board to be formed, Index will be given five seat, GSK given two seats, and J&J two seats. Under this structure, 50% of funding will come from Index, while 25% contributed by GSK and 25% J&J. Target companies of this fund will need to pursue licensing agreements with Index, as opposed to either GSK or J&J.

Overseas partners

China and India have gained ground in drug development by serving as strategic outsourcing partners of certain research and development functions.[11] Outsourcing overseas, while inexpensive, can lead to frustrations with regulatory standards, quality, and respect of intellectual property. Merck, for instance, outsourced portions of their drug development to WuXi Pharmatech in China, which led to quicker compound discovery, although at the expense of frequent quality issues. The partnership also resulted in a lawsuit against a Chinese scientist who was eventually convicted of stealing and selling two Merck compounds.[12] Such instances further feed the hesitance by Western Biopharma companies that have limited the extent to which such partnerships have been pursued.

Patient groups

Patient groups have always been welcoming of partnerships with big pharma to help fund a variety of projects including disease awareness campaigns, patient information, patient advocacy, and meetings and conferences.[13]

Pharmaceutical giants have used these connections in the past to salvage their public reputation and achieve public outreach objectives. Recently, however, we have seen a shift from pure public outreach to true collaboration between patient groups and pharmaceutical companies in early stages of drug development.

The first example of early R&D collaboration between pharmaceutical companies and patient groups occurred during the development of AIDS treatments. AIDS activists and disease sufferers formed the Clinical Trial group and helped guide clinical trial design at the industry level to meet the needs of the patients.[14] This resulted in products hitting the market that patients felt they were a part of increasing their overall market value. We are also starting to see more patient group involvement in the development of orphan disease treatments. Identifying patients in these small populations can prove difficult so companies like Vertex have chosen to leverage partnerships with Cystic Fibrosis patient groups to raise awareness of current clinical trials and new drugs on the market. In their partnership with Cystic Fibrosis Foundation Therapeutics, Vertex is also receiving funding ($1.5 billion through 2016) for early stage development efforts for the orphan population.[15] With goals aligned, both organizations are sharing the risks associated with clinical development to ultimately reach a small, underserved population.

Contract research organizations

A Contract Research Organization (CRO) represents a unique outlet for innovation. CROs provide a variety of services along the clinical trial process including but not limited to study management, biostatistics, data management, pharmacovigilance, and laboratory processing. Because of organizational structure and specialization, CROs are in a better position to conduct clinical trials concurrently in multiple countries including China, India, Brazil, Russia, Eastern European countries and others where the cost of trials are at a fraction of those in the United States.[16] Recent research highlighted the top five strategic Pharma/CRO partnerships in 2012.[17] Four of these partnerships are between Pfizer and Parexel-ICON, between Sanofi and Covance, Eli Lilly and Paraxel, between Takeda and Covance-Quintiles. It is important to identify why companies are turning to CROs at a high rate and what the key success factors are if this trend is to yield the desired results.

A *Pharmaceutical Technology* survey of industry professionals in 2012 found that 62% of respondents saw an increase in contract research spending from 2011 to 2012 within their organizations.[18] There are a variety of strategic motivations for increasing reliance on CROs. The Pfizer-Parexel-ICON partnership is a five year deal for Pfizer's clinical trials management, Sanofi-Covance partnership is a ten year deal for discovery, toxicology, chemistry, clinical trials, and market access services. Eli Lilly turned to Parexel for help in expanding Lilly's access to the Asia-Pacific drug market. In addition to those functional services, there is a tactical advantage to utilizing CROs. Research has shown that FDA submissions that had high CRO involvement were significantly more complex and they were submitted 30 days closer to the projected submission date.[19] The same study showed improved submission timelines without a significant difference in quality. They were unable to quantify cost differences between internal and external clinical trial management due to the inability or unwillingness of the companies to expose their budgets. This study does, however, provide evidence of a tangible advantage to using CROs.

How can companies structure their partnerships with CROs to maximize their return on investment and reap the advantages cited above? Strategic partnerships and outsourcing innovation require a high level of mutual commitment between parties and enhanced information transfer. Research into successful strategic partnerships indicates that high levels of trust and measurability of results fosters closer relationships between the two parties. One Tufts Center for the Study of Drug Development survey identified the following specific relationship management tools as moderately to highly effective when working with a CRO; negotiation of a relationship management plan with the CRO, co-developing performance metrics, conducting lessons learned reviews with the CRO, and using the CRO's standard operating procedures after sponsor review.[20] Each of these tools requires both trust and information sharing between partners. Pharmaceutical companies will need to understand this and adjust if they want the new alliances being formed with CROs to be effective.

Academic institutions

Multiple companies are moving their research and development sites closer to the world's greatest academic institutions. This is not just a coincidence. With government funded research declining, and biopharmaceutical companies cutting back on in-house research staff, the ideas have to come from somewhere. Industry giants like Pfizer and Sanofi have chosen to focus on academic research institutions for their early stage research efforts to gain access to the investigators, their innovative projects, and the technology already in place.[21] Partnerships with academia have been identified as key linkages in the translational medicine movement. In this section we

will analyze past mistakes and compile best practices for both sides of the agreement to explore.

Goal misalignment has plagued industry-academia partnerships of the past. Academia's desired rewards include publications and grants while industry is hoping for successful regulatory filings from their pipeline. One Stanford University Medical Center developmental biologist described partnerships with pharmaceutical companies as distractions from his work.[22] Another participant in the system went so far as to say that academic scientists view the private sector as, "an ATM for basic research."[22] This goal incongruence comes to light most often in three areas; timelines, confidentiality, and intellectual property. Agreements between industry and academia have gone awry and lead to lengthy and costly legal battles. The agreement Novartis had with Dana-Farber Cancer Institute has lead to a continuing battle over intellectual property with a third entity, Gatekeeper Pharmaceuticals.[23] A case between Stanford University and Roche over rights to a diagnostic HIV test went all the way to the U.S Supreme Court in 2011.[23] Stories like this have not scared industry or academia away from such partnerships. Recent research has identified the top 20 public-private partnerships involving pharmaceutical companies and academic institutions in 2012.[24] The list includes partnership between Sanofi and the University of California at San Francisco for research in diabetes, between Johnson and Johnson and the University of Queensland for research in chronic pain, Novo Nordisk with Oxford University for Rheumatoid Arthritis, Novartis with the University of Pennsylvania for research in personalized T-Cell Therapy, and many others. If these groups hope to avoid disagreements and inefficiencies, both parties need to find ways to align their work and manage their partnerships to make them mutually beneficial and less of a drain on resources.[25]

Both parties, in this case, need to understand each other better to harness the valuable technology that can come out of these partnerships. The first step for a biopharmaceutical company is to pick research institutions or scientists that are already doing research that is closely aligned with their commercial goals. If industry asks an academic researcher to stretch too far from their comfort zone they can find themselves a low priority on the list of tasks. The next step involves front-loading the contracting effort. Confidentiality and intellectual property disputes can be addressed on the front end with explicit contracting language. The issues with timeline adherence are a little more difficult to address as they are grounded in fundamental management differences. Devoted academia project liaisons that understand both sets of interests have been particularly helpful to academia. If these liaisons can keep academic researchers on schedule while respecting their personal motivation there is a large upside. Other industry adjustments include altering academia incentives. The biggest dollar amount is not always the contract winner; sponsored research, publications, and indemnification are necessary to an academic institution's success.[26]

Adjustments from the university side are also helpful in facilitating smooth technology development. Johns Hopkins has started a technology transfer group, which essentially acts as a business concierge.[26] This new, innovative group has lead to five straight years of record breaking performance by their research staff. Pharmaceutical companies should seek out universities or private institutions with infrastructure catered to industry needs and relevant experience to increase the probability of success.

One noteworthy example of industry attempting to adjust to the specific needs of a partnership with academia is seen in Pfizer's Centers for Therapeutic Innovation (CTI). The model hinges on co-location of academic and industry researchers, sharing proprietary technology, and equitable intellectual property and ownership rights.[27] Proposals for research in this program receive a pre-approval from Pfizer before the larger final proposal is drafted by a team of both industry and academia. Safeguards are put in place to ensure that terminated research projects have safety-net salary built in for researchers to limit the risk the academic institution must take on. In addition, Pfizer guarantees one-month turnaround on manuscript reviews to ensure non-proprietary information can be published in a timely manner.[28] Pfizer's willingness to understand and adjust to the specific interests of academia has led to enhanced relationships and project output.

"BIG DATA" AND THE EMERGENCE OF INDUSTRY-LED DATA CONSORTIA

Even before the landmark passage of the Affordable Care Act, a new era in open information in integrated healthcare was well underway. The digitization and standardization of medical records by big pharma and other organizations has brought with it the demand for transparency and searchability by the healthcare sector as a whole. Described as "big data", for its sheer volume, complexity, diversity and timeliness, a variety of stakeholders have begun to analyze big data to obtain insights. Software and hardware improvements are overcoming many of the traditional obstacles to compiling, storing, and sharing information securely. These advances have extended to patient privacy, allowing for more convenient means to sanitize data.[29]

Meanwhile, policy-makers have sought legislation that balance patient privacy with the social utility of big data as a collaborative mechanism. For example, the 2009 Open Government Directive and the Department of Health and Human Services (HHS) under the Health data Initiative (HDI) have begun to liberate data from various agencies including the Centers for Medicare and Medicaid Services (CMS), the Food and Drug Administration (FDA), and the Centers for Disease Control (CDC). In another example, as part of the 2009 American Recovery and Reinvestment Act, the Health Information Technology for Economic and Clinical Health (HITECH) Act, seeks to incentivize payment for providers to use EMRs. In yet a third example, the federal government is sponsoring big-data initiatives at the state level. HHS has allocated $550 million in funding for the State Health Information Exchange Cooperative Agreement Program, for the creation of information exchanges.

More recently, a consortium of pharmaceutical companies, *CROs, and various research institutions* have come together under a project entitled "DataSphere", to create a repository of data sets from cancer trials conducted by drug companies, academic labs, and other organizations. Started through the CEO Roundtable on Cancer, a nonprofit convened in 2001 by then president, George H. W. Bush, the DataSphere initiative has been launched with two data sets contributed by Sanofi. Companies, research institutions, and universities are expected to contribute additional data. Whereas such strategies have been long-encouraged by all parties involved, efforts have previously been hampered by patient privacy, data security, international law, corporate policies, and system incompatibility. Utilizing advanced data-security and anonymity technologies, the platform promises to pool multiple studies associated with the same diagnosis. The network will be hosted by the Synapse technology platform sponsored by Sage Bionetworks. Notably, this platform already serves the Cancer Genomics Hub, a large-scale data repository and user portal for the National Cancer Institute. It is hoped that sponsors can design more cost-effective trials and thereby reduce drug development costs by as much as 10%.[30,31]

A yet more comprehensive strategy has taken shape out of a regular meeting of the industry's leading research chiefs. TransCelerate BioPharma Inc., a nonprofit established by 10 major pharmaceutical companies, aims at accelerating the development of new drugs, beginning with improving the efficiency of clinical trials. The founding companies include Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Co., Genentech (a part of Roche), GlaxoSmithKline, Johnson & Johnson, Pfizer, , and Sanofi. Each company's R&D head sits on TransCelerate's board of directors. In the spring of 2013, six new companies joined TransCelerate, including Astellas Pharma Inc., notably the first member of TransCelerate headquartered in Japan, Biogen Idec, Braeburn Pharmaceuticals, EMD Serono, Inc. (a subsidiary of Merck KGaA), Forest Research Institute (a subsidiary of Forest Laboratories, Inc.) and Onyx Pharmaceuticals. With clinical study execution the most immediate area of focus and standardization, five major topics have been selected for further funding and advancement. These include development of risk-based site monitoring approach and standards, development of a shared user interface for investigator site portals, mutual recognition of study site qualification and training, development of clinical data standards, and establishment of a comparator drug supply model. [31,32]

Although one of the most ambitious, Transcelerate is by no means the first of such consortia. In 2012, Merck and Eli Lilly and Co. joined with Janssen Research & Development LLC in the establishment of a global cross-pharmaceutical Investigator Databank designed to improve efficiencies of industry-sponsored clinical trials. Similar to above consortia, the new Investigator Databank will serve as a repository for key information about clinical trial sites, such as infrastructure and Good Clinical Practice (GCP) training records. It is hoped that such synergy will reduce duplication of time-consuming administrative work involved in the identification of appropriate clinical trial sites.

CONCLUSION

Biopharmaceutical research and development is in a state of flux due to internal and external pressures and is facing an unprecedented lapse in productivity. Both financial and social pressure to make the drug development process, including clinical research, more efficient has prompted a growing wave of consortia initiatives among pharmaceutical companies, government agencies, research institutions, and academic medical centers. At its core, technological improvements in standardization and protection of patient privacy, backed by support of policymakers, has brought big data to the forefront in collaborative initiatives. In this review of current trends and potential strategy updates we hope to have increased awareness of challenges and potential solutions. Each alternative has specific hurdles but also significant potential for increased productivity. We will be watching closely to see how the industry responds and what proves successful in the long term.

ACKNOWLEDGEMENTS

We thank the Rutgers Business School Almni Association (RBSAA) and the Blanche and Irwin Lerner Center for the Study of Pharmaceutical Management Issues for their contribution to the survey effort.

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APPENDIX A: SURVEY RESPONDENTS

Blanche and Irwin Lerner Center for the Study of Pharmaceutical Management Issues

The Lerner Center is an endowed center established in 2004 at the Rutgers Business School with an objective to promote and facilitate research in economic and management issues in the Bio-Pharmaceutical industry. The Center is overseen by an 11 member external of Board of Advisors. Members of the board are senior leaders (CEOs, Senior VPs, former CEO, Group President etc) in the bio-pharmaceutical industry. The Center provides Executive Education to the industry executives – both on campus at the Rutgers Business School and customized training on companies' sites. It also hosts a high profile healthcare conference each year with speakers from the government and academia. About 200 executives from the bio-pharmaceutical industry attend the conference. The Center maintains data base of bio-pharmaceutical executives those attended any of the events organized by the Center. Currently, it exceeds over 1,200 in number.

The Center also maintains several data bases acquired from the IMS Health. These data bases are available to the faculty, PhD students and other researchers at Rutgers and elsewhere for conducting their research.

Rutgers Business School Alumni Association

Rutgers Business School is recognized as one of the top MBA programs for Health Care, Pharmaceuticals, and Biotechnology in the world. Rutgers Business School has been able to capitalize on both the location of the school within the pharmaceutical hub of New Jersey and partnerships with leading pharmaceutical companies to build and establish a pioneering pharmaceutical management MBA concentration. The well established pharmaceutical management program has produced alumni, over 250, who have gone on to contribute to major pharmaceutical companies around the world. Many of them are now senior executives in the industry. The alumni networks of both the pharmaceutical management program and the larger school database were leveraged to complete the survey provided.

APPENDIX B: EXECUTIVE SURVEY

Central Questions: What are the changes pharmaceutical companies are making to reduce R&D spending and increase quality product approvals? What are the best practices within the industry? What can the pharmaceutical industry learn from other trailblazing process-oriented industries?

1. Has your company made any process changes within the R&D department in light of external cost pressure?
   Yes
   No
2. Has your company done any of the following in an attempt to update their R&D practices (check all that apply or rank)?
   a. Investing in smaller Biotechs
   b. Strategic partnerships with a competitor
   c. Budget cuts

d. Layoffs
e. Focus on internal molecule discovery
f. Partnership with academic institutions
g. Movement of facilities
h. Closing of facilities
i. Narrowing therapeutic focus

3. Do you have any specific examples of a particularly successful update to your R&D processes or practices.
(Free text entry)

APPENDIX C

Biopharmaceutical Industry Venture Fund Alliances, 2013		
Biopharma / Associated Venture Group	**Venture Fund**	**Million (USD)**
GlaxoSmithKline (GSK) and GSK's Venture arm, SR One	Canada Life Sciences Innovation Fund	$50
Merck & Co.	Lumira Capital	$101
Merck & Co.	Teralys Capital	$50
Eli Lilly	TVM Capital, Teralys Capital, BDC Venture Capital, Fondaction, Advantus Capital Management	$150
Daiichi Sankyo	Kearney Venture Partners	$180
GlaxoSmithKline (GSK), Johnson & Johnson	Index Ventures	$200
GlaxoSmithKline (GSK)	Sanderling Ventures	$250
Novartis, Amgen Ventures	Atlas Ventures	$265
Merck Research Laboratories (MRL) + Merck Research Ventures Fund	Flagship Ventures	$270
GlaxoSmithKline (GSK)	Avalon Ventures	$495

Original Article

Deciding between biobetter versus biosimilar development options based on net present value calculations

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ABSTRACT

The growing share of biopharmaceuticals is paralleled by an increasing interest in biogenerics, as blockbuster biologics are approaching their patent expiries. Companies need to make decisions whether to invest in biosimilars or in biobetters with enhanced properties, the latter enabling favorable differentiation vis-à-vis the original product on the one hand and biosimilars on the other hand. Net present value (NPV) modelling was applied to compare the financial value of two categories of biobetters with the value of biosimilars, proving superiority of truly innovative biobetters. Regardless of the high economic attractiveness of such products, engaging in such projects might not be appropriate for every company and recommendations are provided which options should be preferred depending on a company's scientific and technical capabilities and business model.

Journal of Commercial Biotechnology (2014) 20(2), 21–31. doi: 10.5912/jcb636
Keywords: biobetter, NPV modelling, portfolio management

INTRODUCTION

History and current status of biosimilars

The class of biologic drugs is increasingly gaining importance for the pharmaceutical and biotech industry. It is therefore obvious that there is a significant interest in developing and approving generic versions of such products after their patents expire.[1] Based on the significantly higher complexity of these products compared to small molecules, regulatory agencies request more than a pharmacokinetic study to demonstrate the safety and efficacy of such drugs. Special attention has to be given to the issue of immunogenicity of biologic drugs that is still not fully understood.[2] The European Medicines Agency (EMA) has published guidelines for different classes of biologic drugs that request phase III-like studies in all cases.[3] Another significant difference of biosimilars compared to small molecule generics is that, because of the higher molecular complexity of the earlier, the full identity of two biosimilar products can usually not be proven. This is why, by now, the term biosimilar is used instead of biogeneric.[4]

Over the past 15 years, many companies have been attracted by the new biosimilars business opportunity. In fact, both companies with generic and with innovative business focus are working in this sector today.[5] However, the significant investments have so far not paid off. The first approved biosimilars in Europe, i.e., the insulines, human growth hormone, and erythropoietin, are struggling to gain market share. The only advantage of biosimilar products compared to their innovative predecessors is their lower price. The high development costs and high cost of goods of biosimilars limit, however, the potential for price reductions. Opposite to small molecule originators it is now commonly believed that biologic originators will be able to keep 70-90 % of the total market.[6] These factors, combined with the need to promote biosimilars through a dedicated sales force,

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increase the investment per project and the risk of financial failure significantly.[7]

New hope: biobetters, talk of the town

Some years ago the term biobetter was introduced to describe a new type of projects that gain more popularity ever since. The term biobetter refers to a biological product that "is similar to an already approved biologic product, but is superior in one or more product characteristics".[8] Frequently targeted product improvements include longer half-life,[9] reduced immunogenicity,[10] higher potency,[11] and more convenient administration.[12] Currently, regulatory agencies have not yet issued guidelines for this new product category, but it can be expected that for biobetters a full development program will be required, at least when molecular changes have been introduced. When offering a meaningful advantage such products would have the potential to differentiate themselves not only from biosimilars but also from the original, potentially leading to significantly higher sales volumes compared to the latter. Indeed, most of the companies engaged in biosimilars as well as newly founded venture capital-backed biotech companies such as, e.g., Itero Biopharmaceuticals Inc., Femta Pharmaceuticals Inc., Glycotope GmbH, and PolyTherics Ltd., are currently developing biobetters.

Analytics for managers to select the most attractive projects

With the emerging concept of biobetters in addition to biosimilars, the number of potential projects is virtually unlimited, given the various approaches to create a biobetter. This article intends to provide guidance to decision makers how, for a given organization, value-creating projects with strategic fit can be selected. In a first step, the possible options of creating biobetters are categorized, and it is analyzed to which classes of biologics they may apply. In a second step, the concept of portfolio management will be applied, indicating the expected financial value for different classes of biologics. This will be done in light of the strategic options the originator companies have to defend their franchises.

Scope and limitations of the investigation

The regulatory and economic environment for the development and commercialization of biosimilars and biobetters differs significantly in various regions of the world. The regulatory environment is certainly the most stringent and demanding in the US, Europe and some other developed countries, which leads to high development cost. In certain developing countries requirements are significantly lower for the local supply. The present investigation focuses on developed countries because the sales levels of biologics are highest in these territories (compare Table 1), and the analysis of the diverse regulatory environments in different emerging markets would go beyond the scope of this article.

DIFFERENT CLASSES OF BIOLOGICS AND TECHNICAL OPTIONS TO CREATE BIOBETTERS

The 10 bestselling biologic products in 2012 belong to two distinct categories, i.e., monoclonal antibodies and proteins. The present analysis focuses on these two classes of products because their economic potential is most attractive.

Three potential approaches for the development of biobetters will be discussed:

- Improvement of pharmacokinetic properties through pegylation / glycosidation
- Enhanced drug formulation
- Improvement of the benefit/risk ratio through deimmunization or through an increase of efficacy

These technical approaches give rise to two categories of biobetters that differ with respect to their benefits:

- Product modifications that reduce the application interval and/or improve compliance, such products are called "biobetterFORM" in this analysis
- Molecular modifications that improve the safety and/or efficacy of the drug, such products are called "biobetterADD"

The most widely used approach to improve protein drugs is to improve their pharmacokinetic properties. Initiatives to prolong the half lives of protein drugs have been pursued ever since this class of products entered the market. For example, pegylation describes the process of a covalent attachment of polyethylene glycol polymer chains to other molecules including proteins. Pegylation leads to product enhancements such as improved solubility, increased molecular stability, extended plasma half life, and reduced dosing frequency. Since the introduction of the first pegylated product, Adagen® by Enzon Pharmaceuticals in 1990, a total of 12 pegylated drugs

Table 1: The ten best-selling biotechnology drugs in the year 2012[13]

Name	Lead Company	Type of Molecule	Approved Indication(s)	World-Wide Sales (US$ million)
Humira (adalimumab)	AbbVie	mAb	Rheumatoid arthritis (RA), juvenile rheumatoid arthritis, Crohn's disease, psoriatic arthritis (PA), psoriasis, ankylosing spondylitis, ulcerative colitis (UC), Behçet syndrome	9,266
Enbrel (etanercept)	Amgen	Protein	RA, psoriasis, ankylosing spondylitis, PA, juvenile rheumatoid arthritis	7,967
Rituxan (rituximab)	Roche	mAb	RA, chronic lymphocytic leukemia/small cell lymphocytic lymphoma, non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies associated vasculitis, indolent non-Hodgkin's lymphoma, diffuse large B-cell lymphoma	7,049
Remicade (infliximab)	J&J	mAb	RA, Crohn's disease, psoriasis, UC, ankylosing spondylitis, Behçet syndrome, PA	6,564
Herceptin (trastuzumab)	Roche	mAb	Breast cancer, gastric cancer	6,188
Avastin (bevacizumab)	Roche	mAb	Colorectal cancer, non-small cell lung cancer, renal cell cancer, brain cancer (malignant glioma; anaplastic astrocytoma, glioblastoma multiforme)	6,059
Neulasta (pegfilgrastim)	Amgen	Protein	Neutropenia/leukopenia	4,092
Lucentis (ranibizumab)	Roche	mAb	Wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion	4,003
Avonex (interferon beta-1a)	Biogen IDEC	Protein	Multiple sclerosis	2,913
Rebif (interferon beta-1a)	Merck Serono	Protein	Multiple sclerosis	2,408

have been approved by the FDA.[14] The sales of the two most successful pegylated products, Pegasys® (pegylated interferone alpha for the treatment of hepatitis C), and Neulasta® (pegylated GCSF for chemotherapy induced neutropenia) exceeded US$ 5 bn in 2011[15,16]. The pegylation of these two products led to a significant prolongation of their plasma half lives. As a consequence, Neulasta® requires only one application per chemotherapy cycle, while Neupogen® must be applied daily until a normalization of Granulocyte levels is achieved (which usually takes around 14 days after conventional chemotherapy).

Alternative strategies to prolong the half life of proteins are

- attachment to human serum albumin[17]
- attachment of hyaluronic acid[18]
- attachment of sugar molecules[19]

These methods have in common that the original protein is modified to create a new molecule with improved properties.

The majority of biologic drugs is administered either via the intravenous, intramuscular, or subcutaneous route. More convenient drug delivery might not only improve compliance but also lead to a more predictable release profile and thereby to a higher acceptance by physicians.

Examples for alternative drug delivery approaches are:

- pulmonary delivery[20]
- transdermal delivery[21]

Insulin was the first protein being investigated intensively for the pulmonary route of application. Of the several inhaled insulin devices that are in different

stages of development, the Exubera® formulation (Pfizer) was the first to achieve regulatory approval both in the US and EU,[22] proving technical feasibility of pulmonary delivery. Commercially, Exubera® never lived up to its expectations and was finally taken off the market.[23]

Transdermal delivery of proteins avoids the disadvantages of invasive parenteral administration. Since proteins are large hydrophilic molecules they cannot passively permeate through the skin. Enhancement techniques such as iontophoresis,[24] microneedles,[25] and others[21] are overcoming the skin barrier in different ways. These approaches do not require molecular modification of the biologic drug; only a suitable formulation and potentially a device are to be developed.

Alternatively, the original protein can be modified in order to reduce side effects and/or improve efficacy. Depending on the therapeutic context, biologics have proven to be surprisingly immunogenic. This is also the case for humanized or fully human monoclonal antibodies.[10] Different factors can contribute to clinically relevant immunogenicity, for example, molecular aggregation or the presence of epitopes in the molecule that attract a T-cell response. Various approaches have been developed to reduce the immunogenicity of protein drugs through reformulation[26] or protein engineering.[27]

For mABs, increasing the efficacy in a clinically meaningful way is an attractive option but not easy to accomplish. An impressive example for this approach is the second generation Anti-Her2 drug called Kadcyla® that was developed at Roche and recently approved by the FDA for 2nd line treatment of HER2-positive breast cancer relapsing after previous Herceptin-containing regimes. Kadcyla® is an antibody- drug conjugate consisting of the monoclonal antibody trastuzumab (Herceptin®) linked to the cytotoxic agent emtansine. Trastuzumab inhibits cellular growth by binding to HER2/ neu surface receptors, whereas emtansine is internalized and finally destroys the tumor cells by binding to tubulin.[28] In the Kadcyla® example the introduction of a cytotoxic mechanism has led to an impressive survival benefit of 5.8 months compared to standard therapy.[29] Another outstanding example for a biobetterADD is GA 101, also developed at Roche to enhance the activity of the CD 20 antibody Rituxan. Improved activity compared to the original molecule could be achieved by an optimization of the glycosidation pattern. The superiority of GA 101 was recently confirmed in a Phase III trial in which GA 101 had shown significantly higher efficacy than Rituxan in first line CLL (chronic lymphatic lymphoma) and might potentially lead to a paradigm change in the treatment of CLL.[30]

METHODS

Given the various options of developing biobetters, the present analysis focuses on the question under which conditions financial value creation can be expected. In addition, insights shall be generated how to make decisions with respect to biobetters on the one hand and biosimilars on the other hand.

In a previous analysis, net present value (NPV) modeling was applied to evaluate the financial attractiveness and business risk of different categories of biosimilars.[29] In the current analysis, the same methodological approach is applied to biobetterFORM and biobetterADD. In order to establish quantitative decision criteria for biobetterFORM versus biobetterADD, NPV analyses for both categories were conducted and compared to the analysis for biosimilars. It was investigated under which conditions a minimum acceptable NPV can be expected. General consensus is assumed that the minimum acceptable expected (risk-adjusted) NPV at project kick-off is around US$ 10 million. The applied NPV algorithm reflects the risk of development failure at each development milestone, while cost and revenue uncertainty was investigated 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. The applied NPV model was described in detail previously.[31]

Table 2 summarizes the development assumptions that represent average values for biosimilars on the one hand, (compare 7), and the two categories of biobetters on the other hand. Regarding the probabilities of development success (PoS), it is assumed that a biobetterADD would be comparable to an average New Biological Entity (NBE), therefore the probabilities were taken from benchmark statistics for monoclonal antibodies[32] which represent, to our knowledge, the most recent publicly available source indicative of NBEs. PoS for biobetterFORM refer to the same benchmarks with the exception of the PoS for Phases II and III. For Phase II the PoS is increased from 37 to 80 % and for Phase III from 65 to 75 %, taking into account that the product's basic mechanism of action had already been established by the originator, leading to a significantly lower development risk. Timeline and cost assumptions were derived from information published by the Tufts Institute.[33] Sales, General and administration (S,G&A) costs were assumed to be 20% of sales, as reflected by data published in annual reports of companies marketing specialty products. Cost of goods sold (CoGs) are assumed to be around 30%. Efforts were made to establish plausible differences between the cost assumptions for the three project

Table 2: Assumptions applied for the valuation were taken from ref[29]. Alternative scenarios were also evaluated (see Tables 2 and 3)

	Biosimilar			BiobetterFORM			BiobetterADD		
eNPV: US$ 10 million	Probability of Success	Duration (years)	Cost (US$ m)	Probability of Success	Duration (years)	Cost (US$ m)	Probability of Success	Duration (years)	Cost (US$ m)
Process R&D	90%	2,5	12	90%	2,5	15	90%	3	15
Preclin Dev	85%		8	75%		8	75%		10
Formulation Dev	95%	1	5	90%	2,0	5	90%	2,0	5
Scale-up	95%		10	95%		10	95%		10
Phase I	90%	1	8	77%	1	8	77%	1	8
Phase II	100%	-		80%	1,5	10	37%	2	20
Phase III	75%	3	55	75%	3	55	65%	3	110
Registration	80%	1,5	2	95%	1,5	2	95%	1,5	2
Overall Probability of Launch	37%			25%			10%		
COGS (%of Sales)	30%			30%			30%		
Peak Sales (US$m)	**180**			**270**			**690**		

categories, driven by the focus and number of clinical trials. Overall, the figures represent base case assumptions. The impact of the ranges of uncertainty on value was investigated in the sensitivity analyses.

The NPV model includes all project related cash flows from the start of preclinical development (year 1) up to year 20. Cash flows are inflated by 2% per year. The discount rate is 8%, and the tax rate is 40%. Peak sales are achieved in year 5 on the market and are maintained for 2 years. Thereafter, a sales decline of 5% for the biobetterADD, 7,5% for the biobetterFORM, and 10% for the biosimilar is assumed. The sales decline reflects the impact of emerging new treatment options, which is expected to be less pronounced for a biobetter compared to a biosimilar, and to be lowest for the most innovative version. Cash flows beyond year 20 are modeled as terminal value, assuming a continuous decline at a yearly rate of 10%.

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$10 million could be achieved. As indicated above, an expected NPV of US$ 10 million at project start was considered a minimum requirement to justify a "go" decision in the present analysis.

RESULTS

On Tables 3 and 4, scenario 1 reflects the base case assumptions for biobetterFORM and biobetterADD, respectively, as indicated in Table 2. Taking into account these assumptions, required peak sales were determined to yield an expected NPV of US$ 10 million at development start. It turned out that, for BiobetterFORM, peak sales of US$ 270 million would be sufficient to achieve that goal, US$ 90 million above the sales level required for biosimilars.[30] This is mostly driven by the higher development risk and longer development time of biobetterFORM compared to biosimilars (overall PoS 25% versus 37%, development time 11,5 versus 9 years, respectively). In contrast, the profile of a biobetterADD more closely compares to the profile of New Biological Entities (NBEs), with peak sales of US$ 690 million being required for an expected NPV of US$ 10 million at project start, and a development time of around 12,5 years. Since regulatory agencies will not require a biobetterADD to closely resemble the innovator molecule regarding, e.g., pharmacokinetic profile, efficacy and safety, biobetterADDs are considered comparable to NBEs and may therefore benefit from their higher probability of approval compared to biosimilars.

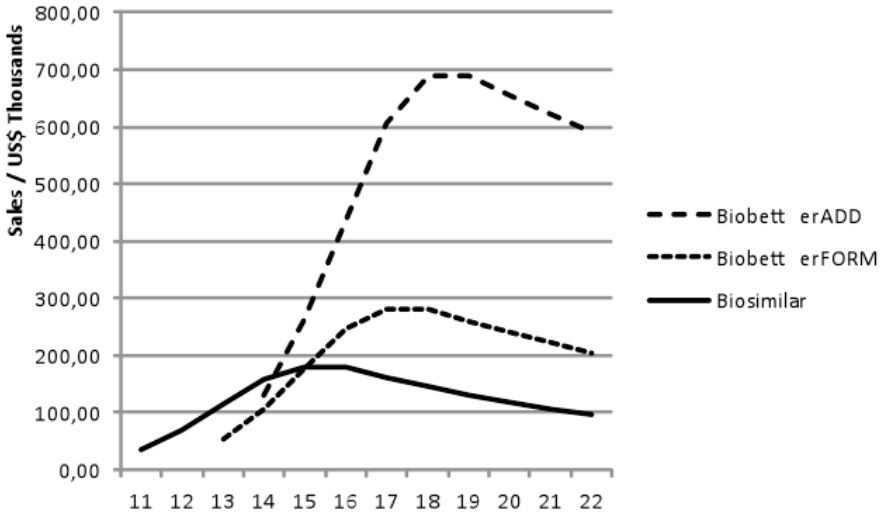

Figure 1: Expected life cycle curves for BiobetterADD and BobetterFORM, in comparison to a biosimilar. In the base case it is assumed that, after 6 years of marketing, sales will be impacted by innovative treatment alternatives. However, the impact will likely vary depending on the degree of innovativeness of the respective product category: the decline of sales is expected to be 10%, 7.5% and 5% for biosimilars, BiobetterFORM, and BiobetterADD, respectively.

In Scenarios 2 and 3 the influence of higher discount rates was investigated. While in the base case scenario a discount rate of 8% is applied, which appears appropriate for established pharmaceutical companies, higher discount rates are used in smaller corporations (10%) and biotech companies (15%) based on their higher cost of capital. At a rate of 15%, however, both biobetterFORM and biobetterADD run into negative NPVs (below US$ -10 million), at a rate of 10% NPVs are virtually zero. For a BiobetterADD, forecasted peak sales would actually have to be at a level of US$ 2,3 billion to achieve the target NPV of US$10 million (Scenario 4, Table 4).

CoGs strongly influence the value of pharmaceutical products. Therefore, CoGs are a relevant uncertainty for biobetterFORM at development start. The reason is that biobetterFORM may only enjoy a moderate price premium compared to biosimilars, ranging around 15%. The sensitivity analyses in Scenarios 4-6 (Table 3) indicate that an increase of CoGs from 30% to 43% results in an expected NPV of US$ -15 million, which could potentially be compensated by an increase in peak sales from US$ 270 million to US$ 775 million in order to get back to the targeted NPV level of this analysis. In order to achieve improvements in a product's pharmacokinetic profile or application mode, increased CoGs are not uncommon which need to stay in balance with realistic sales expectations. For biobetterADDs, product prices are assumed to reflect the more innovative product properties; therefore, CoGs beyond 30% are considered unlikely. There may rather be room for a value increase through lower CoGs, as indicated in Scenario 6 (Table 4).

The impact of higher development costs was also investigated. If a second Phase 3 where required for a biobetterFORM (Scenarios 7 and 8, Table 3), development costs could increase by US$ 55 million. This would reduce the project's expected value by US$ 7 million. In order to compensate for this effect, peak sales would have to be forecasted at a level of US$ 320 million. In order to have a similar impact on expected NPV, cost for a biobetterADD would have to increase by US$ 75 million. This could occur if one additional Phase II and III trial, respectively, or one additional large Phase III trial, were required. The value impact of the additional expense would be compensated by an increase in expected peak sales to US$ 811 million (Scenarios 7 and 8, Table 4).

The sensitivity to overall development risk was also investigated. For example, the development risk for a BiobetterADD could be exceptionally low if an innovative route of administration did not (only) lead to improved convenience, but also to significantly enhanced efficacy. In certain cases, e.g. neurodegenerative diseases, constant plasma levels brought along by a sustained release formulation could induce a quantum leap in benefit. Such a case could be reflected by Scenario 9 (Table 4), with an increase of PoS from 10% to 25%. This would increase the value of the project from US$ 10 million to US$ 61 million. Also a biobetterFORM could potentially benefit from a reduced development risk if a Phase II had virtually no risk to fail based on information generated in Phase I and the knowledge generated by the innovator. This may increase overall PoS from

Table 3: BiobetterFORM: Major value determinants for the base case scenario (1). A peak sales level of US$ 270 million (and total life cycle sales according to the graph indicated in Figure 1) would be required to achieve an expected NPV of US$ 10 million. Scenarios 2-14 demonstrate the sensitivity of the base case NPV to variations of individual parameters that are within common margins of market, development, and financial uncertainties.

Scenario	Development Time (years)	Development Cost (US$ million)	PoS	Peak Sales (US$ million)	Yearly Sales Decline after Year 6	Discount Rate	CoGs (% of Sales)	SG&A Cost as % of Overall Slaes	Risk-adj. NPV (US$ million)	NON Risk-adj. NPV (US$ million)
1	11,5	113	25%	270	7,5%	8%	30%	20%	10	101
2	11,5	113	25%	270	7,5%	10%	30%	20%	0	59
3	11,5	113	25%	270	7,5%	15%	30%	20%	-10	8
4	11,5	113	25%	270	7,5%	8%	17%	20%	35	159
S	11,5	113	25%	270	7,5%	8%	43%	20%	-15	3
8	11,5	113	25%	775	7,5%	8%	43%	20%	10	100
7	11,5	168	25%	270	7,5%	8%	30%	20%	3	80
8	11,5	168	25%	320	7,5%	8%	30%	20%	10	108
9	11,5	113	31%	270	7,5%	8%	30%	20%	18	101
10	11,5	113	25%	270	7,5%	8%	30%	30%	-10	21
11	11,5	113	25%	575	7,5%	8%	30%	30%	10	101
12	11,5	113	25%	242	5%	8%	30%	20%	10	100
13	11,5	113	25%	200	0%	8%	30%	20%	10	101
14	11,5	113	25%	480	20%	8%	30%	20%	10	101

Table 4: BiobetterADD: Similar to Table 2, Table 3 indicates the major value determinants for the base case scenario (1). A peak sales level of US$ 690 million (and total life cycle sales according to the graph indicated in Figure 1) would be required for a BiobetterADD to achieve an expected NPV of US$ 10 million. Scenarios 2-14 demonstrate the sensitivity of the base case NPV to variations of individual parameters.

Scenario	Development Time (years)	Development Cost (US$ million)	PoS	Peak Sales (US$ million)	Yearly Sales Decline after Year 6	Discount Rate	CoGs (% of Sales)	SG&A Cost as % of Overall Slaes	Risk-adj. NPV (US$ million)	NON Risk-adj. NPV (US$ million)
1	12,5	180	10%	690	5%	8%	30%	20%	10	316
2	12,5	180	10%	690	5%	10%	30%	20%	-1	193
3	12,5	160	10%	690	5%	15%	30%	20%	-12	50
4	12,5	160	10%	2260	5%	15%	30%	20%	10	271
5	12,5	180	10%	515	5%	8%	30%	20%	0	218
6	12,5	180	10%	690	5%	8%	17%	20%	35	566
7	12,5	255	10%	690	5%	8%	30%	20%	3	288
6	12,5	255	10%	811	5%	6%	30%	20%	10	356
9	12,5	180	25%	690	5%	8%	30%	20%	61	316
I0	12,5	180	10%	690	5%	8%	30%	30%	-9	133
11	12,5	180	10%	1305	5%	8%	30%	30%	10	316
12	12,5	160	10%	588	0%	6%	30%	20%	10	315
13	12,5	180	10%	810	10%	8%	30%	20%	10	316
14	12,5	180	10%	1203	20%	8%	30%	20%	10	316

25% to 31%, increasing the expected NPV from US$ 10 million to US$ 18 million.

In highly competitive markets, overall SG&A cost may exceed the 20% reference to overall sales. The impact on value is comparable to the effect of CoGs. For a biobetterADD, an increase of SG&A to 30% of sales would reduce the expected NPV to US$ -9 million. Peak sales estimates would have to be as high as US$ 1,3 billion to get back to the target NPV of US$ 10 million (see Scenarios 10 and 11, Table 4). The effect of high SG&A cost would be comparable, in relative terms, for biobetterFORM (Scenarios 9 and 10, Table 3): increasing SG&A to 30% of sales reduces the NPV to US$ -10 million, peak sales estimates of US$ 600 million instead of US$ 280 million would compensate for this effect.

The late phases of the product life cycle are generally difficult to predict. In particular, it is uncertain to what extent innovative treatment paradigms will affect the sales of product classes with a longstanding history. The last three scenarios of the sensitivity analysis focus on this issue. For example, if there were no sales decline for a biobetterADD over a prolonged time period (Scenario 12, Table 4), expected peak sales could stay below US$ 600 million to yield the target NPV. If, however, the sales decline would aggravate to 10% or 20% per year, expected peak sales would have to achieve US$ 810 million or US$ 1,2 billion, respectively, to compensate for the losses in the later years. Applied to biobetterADD, a prolonged period without sales decline would reduce the peak sales level required to achieve the target NPV down to around US$ 200 million, while a strong competitive impact leading to 20% decline per year increases required peak sales to US$ 480 million.

The results suggest that the market size of the pioneer, a strong competitive profile vis-a-vis the pioneer/biosimilars, low to moderate biobetter and/or innovator competition, and only moderate CoGs and/or favorable pricing opions represent the strongest driver for value creation. However, the two categories of biobetters are impacted differently by these factors.

DISCUSSION AND RECOMMENDATION

The critical success factors for the development of biosimilars have been described earlier.[7] Besides establishing the required infrastructure for a cost-effective commercial production and the sales force for detailing the product, it is of utmost importance to be the first or second market entrant, because the market share of generics is depending on the number of competitors and the order of market entry (34, 35; see also discussion in 7).

A true biobetter, exhibiting a superior benefit/risk profile compared to the originator, is an alternative with the option to create more financial value compared to biosimilars. There is a significant chance that the higher investment for biobetters would be balanced favorably by higher sales compared to the respective biosimilars. In particular, an extended label may enable market and value expansion by increasing the patient pool and by maintaining a favorable price. In addition, new patents guarantee exclusivity for many years and a significantly improved standard of care will minimize the impact of potential competition from biosimilars. Therefore, biobetters are highly attractive projects

However, the biobetter strategy demands particular skills from the organization that go beyond process development. Analyzing potential options for the improvement of the originator product early on, combined with access to the required technologies to execute the ideas, requires strong capabilities in discovery research and development. Innovation capabilities resulting in products such as, e.g., Kadcyla® and GA 101 developed at Roche, might only be available at very few research based companies and not at the standard generic companies that are attracted by the biosimilars market. As a case in point, Roche has established a noteworthy strategy for defending its HER2-franchise by elevating the therapy standard in breast cancer in two steps.[36] In step one, the antibody Perjeta® (pertuzumab, a HER2 dimerization inhibitor that works complementary to Herceptin®) was developed for 1st line therapy in combination with Herceptin®. Combination therapy increases progression-free survival by more than 6 months compared to Herceptin® alone. It can therefore be assumed that, by the time of launch of Herceptin® biosimilars, combination therapy will have become treatment standard, giving Roche the opportunity to generate significant profits with Perjeta® on the one hand and still benefit from Herceptin® on the other hand, while pricing can be adapted flexibly to the future biosimilars environment. Purchasing the overall treatment package from one provider could then become the preferred option for oncology centers, reducing the commercial opportunity for Herceptin® biosimilars. In step two, Kadcyla® has been developed successfully for 2nd line therapy for patients relapsing after previous Herceptin®-containing regimens, again yielding an outstanding survival benefit.[37] This further expands the HER2-franchise and opens the option of positioning Kadcyla® in 1st line therapy. In fact, Roche is currently investigating a combination of Kadcyla® and Perjeta® in 1st line treatment in the ongoing MARIANNE study[37] which, if showing superiority of the combination over current standard therapy, could significantly reduce the role of trastuzumab in breast cancer therapy in the future. Overall, Roche's strategy

outlines that originator companies may successfully defend their commercial position vis-à-vis biosimilars by outperforming competition with innovative biobetters, leading to more volatile commercial scenarios for biosimilars today compared to previous years. In conclusion, any company considering biosimilar (and biobetter) approaches needs to be aware that most likely the innovator company will evaluate all potential options to protect and potentially expand the existing franchise by investigating second generation products with improved properties.

Regarding development requirements, biobetterFORM projects are in between biosimilars on the one hand and biobetterADDs on the other hand. The investments for biobetterFORMs are not significantly higher than for biosimilars. To create enough differentiation over biosimilars, however, an advantage for patients and payers has to be demonstrated. This could, for example, be achieved by an improved benefit/risk ratio through a more sustained Pk profile. In such cases, preferring a biobetterFORM approach over a biosimilar approach might make sense because it would lead to a differentiated product. Such product opportunities are particularly valuable in therapeutic areas where a substitution therapy requires long-term therapy and continuous drug exposure, such as, e.g. factor VIII deficiency or other genetic disorders like Gaucher disease.

In summary, each company engaged in the biologics or biosimilars business needs to establish a systematic evaluation process in which new product opportunities are reviewed on a regular basis and the different approaches ranging from biosimilars over biobetterFORM to biobetterADD are compared and prioritized. The final decision should be based on a realistic attitude towards the capabilities and the competitive strength of the own organization. For companies with a generic background the decision will likely be between pure biosimilars and biobetterFORMs. In contrast, for originator companies and for companies with significant research capabilities in the required areas biobetterADDs might be the most appropriate alternative.

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Original Article

Market orientation, alliance orientation, and business performance in the biotechnology industry

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ABSTRACT

The purpose of this study was to test the unexplored relationship between market orientation (MO), alliance orientation (AO), and business performance (PERF) in the medical/healthcare subsector of the Canadian biotechnology industry. The study surveyed Canadian biotechnology executives via mail and web-based questionnaires. It was found that the relationship between MO and PERF was positive and significant and the relationship between AO and PERF was positive and significant. It was also found that the relationship between MO and AO was positive and significant, supporting the existence of a mediation relationship. Specifically, MO's influence on PERF was found to be fully mediated by AO. This suggests that Canadian medical/healthcare biotechnology companies that were highly market-oriented were also highly alliance-oriented, and highly alliance-oriented companies were top performing companies. This study outlines the apparent sequential relationship between market-oriented behavioural commitments, alliance-oriented activities, and business performance outcomes among Canadian biotechnology companies. Furthermore, it has business development and the commercialization process implications for biotechnology managers.

Journal of Commercial Biotechnology (2014) 20(2), 32–40. doi: 10.5912/jcb645
Keywords: market orientation; alliance orientation; business performance; management; marketing

INTRODUCTION

Canada is a leader in biotechnology, ranking in the top five countries globally.[1-3] The largest subsector of the global biotechnology market is medical/healthcare, accounting for more than 67 percent of total market value.[4] In the biotechnology market, effectiveness is predicated on having a strong and complete management team with competencies in all functional areas including marketing.[5] Costa, Fontes, and Heitor state that marketing is an imperative managerial competency for successful biotechnology commercialization.[6] Additionally, biotechnology ventures with high market knowledge are more likely to be acquisition candidates, obtain licensing deals, and accumulate capital infusions.[7] Top managers of biotechnology companies identified having a focus in marketing strategy and the establishment of strategic alliances as critical industry success factors.[8] There is a strong demand for biotechnology managers and entrepreneurs with marketing and

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alliance-building competencies, as these traits enable organizational success.[9] Due to the biotechnology industry's competitive intensity with regard to the attainment of capital and survival, managers need to be successful in identifying target markets and sharing knowledge with strategic alliance partners, as these competencies have been proven to perpetuate organizational success.[10]

Although strategic marketing capabilities are said to be an imperative in the commercialization process, the body of research related to marketing in the biotechnology industry is limited. It is widely accepted that MO is fundamental to the marketing concept and measures an organization's commitment to marketing and marketing strategy.[11-21] Narver and Slater[20] theorize that MO is a construct comprised of behavioural components including customer orientation, competitor orientation, and interfunctional coordination. "The theory of market orientation suggests that the three behavioral components are equally important" in determining an organization's commitment to marketing and marketing strategy (p26).[20]

Strategic alliances are inter-organizational agreements aimed at collectively achieving individual organizational goals and gaining competitive advantages.[22-24] In the biotechnology industry, strategic alliances are highly prevalent, as these cooperative efforts enable global expansion and minimize risk for alliance partners.[25,26]

Strategic alliances in the North American biotechnology industry have been extensively studied in academic research.[27-34] AO is a construct designed to comprehensively measure strategic alliance practices, including the employment of alliance strategies in organizations. More specifically, it measures a company's ability to scan for new alliance partners, coordinate alliance strategies, and learn from alliance experiences.[35]

The purpose of this study was to examine the influence of MO and AO on business performance in the medical/healthcare subsector of the Canadian biotechnology industry.

LITERATURE REVIEW

The MO and performance relationship has been studied across various industries (biotechnology, construction/surveyor, exporters, forestry, hotel, internet advertisers, manufacturing, mass-merchandisers, multi-industry, and services) and in many countries (Australia, Canada, China, Ghana, India, Israel, Saudi Arabia, United Kingdom, and United States).[11,12,15,17,20,21,36,37-50]

MO has been repeatedly shown to have a positive, and direct or moderating role in its relationship with performance in diverse settings[11,12,15,17,20,21,36-39,41-47,49-51] Cano, Carrillat, and Jaramillo[52] and Kirca, Jayachandran, and Bearden,[53] provide evidence for the robustness of MO's influence on performance. The majority of studies used data from the manufacturing industry or a multitude of sectors, [39,54] while only a small number of studies have explored MO and performance in the biotechnology industry.[12,55,56]

Appiah-Adu and Ranchhod[12] employed the Narver and Slater[20] instrument to measure MO and performance among UK biotechnology companies. Appiah-Adu and Ranchhod[12] hypothesized that MO would be positively related to new product success, growth in market share, profit margins, and overall performance. Their findings supported three of four hypotheses, specifically MO's positive relationship with growth in market share, profit margins, and overall performance.[12] No statistically significant relationship was found between MO and new product success.[12] Appiah-Adu and Ranchhod[12] concluded that the unsupported hypothesis was a result of the peculiarities of the biotechnology industry.

De Luca, Verona, and Vicari[55] measured MO and performance in the Italian biotechnology industry. De Luca, Verona, and Vicari[55] hypothesized that customer orientation, competitor orientation, and interfunctional coordination would be positively related to their newly developed performance construct. Results supported their third hypothesis, indicating interfunctional coordination was positively and directly related to performance.[55] It was found that customer orientation and competitor orientation were not positively and directly related to performance, leading to the rejection of the first and second hypotheses.

Renko, Carsrud, and Brannback[56] explored the relationship between MO and performance among US and Scandinavian biotechnology companies. Overall, MO was found to be an antecedent to capital invested in biotechnology companies, ultimately supporting their hypothesis. However, when examined separately, the significance of the MO and performance relationship was only present among Scandinavian companies. This suggests that differences, related to the strength of the relationship between MO and performance, may exist across various national borders.

Hypothesis 1: Market orientation will have positive effect on business performance in the medical/healthcare subsector of the Canadian biotechnology industry

Strategic alliances in the North American biotechnology industry have been extensively studied in academic research.[27-34] Furthermore, Baum, Calabrese, and Silverman,[27] Baum and Silverman,[28] and Silverman and Baum[32] have examined the role of strategic alliances in all subsectors of the Canadian biotechnology industry.

Baum, Calabrese, and Silverman[27] found that new biotechnology companies' performance increased with the size and efficiency of the alliance networks.[27] Particularly, biotechnology companies that obtained early alliances with pharmaceutical companies experienced more patenting, a proliferation of revenue, an increase in the number of research and development (R&D) and non-R&D employees, and growth in R&D spending.[27] Baum and Silverman[28] investigated differing types of strategic alliances and their relationship with financing and overall performance in the Canadian biotechnology industry.

Baum and Silverman[28] found that new biotechnology ventures financially benefited most from downstream (partnerships with firms closer to the market) and horizontal (partnerships or agreements with rival biotechnology companies) alliances as opposed to upstream (agreements between biotechnology companies and universities, research institutes, government labs, hospitals, or industry associations) alliances. Baum and Silverman[28] suggest that biotechnology companies with alliances closer to the market (downstream or horizontal) raise more capital and perform well because it demonstrates legitimacy and commercial viability to venture capitalists.

In their study of Canadian biotechnology firms, Silverman and Baum[32] found that horizontal alliances, particularly those with rivaled biotechnology firms, can impede exit rates and success. Specifically, forming horizontal alliances with rivaled companies that have greater access to the market and have more efficient networks can have negative implications for the partnering firm.[32]

In various settings involving biotechnology companies, individual strategic alliance elements (e.g. alliance size) have been empirically shown to have positive and direct relationships with performance.[27-30,33]

There is collective evidence showcasing how effective strategic alliance management is an antecedent to performance, yet no known study has measured it comprehensively and examined its effect on business performance in the biotechnology industry.[27-30,33] Therefore, the use of the Kandermir, Yaprak, and Cavusgil's[35] AO instrument for this study was appropriate, as it was designed to comprehensively measure a company's commitment to strategic alliance management. The prior review of literature regarding strategic alliances and performance led to the formulation of the second hypothesis.

Hypothesis 2: Alliance orientation will have a positive effect on business performance in the medical/healthcare subsector of the Canadian biotechnology industry

Marketing and strategic alliance management competencies have been cited as biotechnology industry success factors.[8,9] MO has been shown to increase the likelihood of commercial success in the biotechnology industry[12,55,56] and effective strategic alliance management has been proven to increase biotechnology companies' performance.[27-30,33] Therefore, if biotechnology companies' marketing (measured by MO) and strategic alliance management competencies (measured by AO) are strong and positive, performance is also likely to be favourable. Empirically, MO and other constructs (e.g. organizational entrepreneurship, corporate entrepreneurship, organizational flexibility, export market knowledge, quality and service, cultural affinity, and channel support) have been identified as unique and additive predictors of performance.[57-59] Combining MO and AO to examine their additive effect on business performance is novel, as it is presumably an unstudied research area. The third hypothesis was developed based on evidence highlighting the importance of MO and strategic alliance management in the biotechnology industry, as well as findings from studies examining the additive effects of MO and other constructs with performance.

Hypothesis 3: Market and alliance orientation will have a positive and additive effect on business performance

METHODS

Data source

A questionnaire was mailed to 453 Canadian medical/healthcare biotechnology companies. In order to ensure the inclusion of the 115 medical/healthcare biotechnology companies located in the Province of Quebec, with the cooperation of the Université du Québec à Montréal (UQAM), the original questionnaire was translated from English to French. A web-based option was provided as an additional completion option. Senior executives of Canadian biotechnology companies were selected as key informants due to their comprehensive knowledge of marketing, alliance strategy, business performance, and an overall understanding of their companies. Biotechnology executives (CEOs, Presidents, Vice Presidents, or Managing Directors) were identified using the Canadian Life Sciences Database and Industry Canada's Company Database.

Data collection began in May and ended in August of 2012. At the end of data collection a total of 87 responses and 53 return-to-sender packages were received. Six of the 87 responses explicitly stated that the focus of the biotechnology company was not, nor did it have the potential to become, medical/healthcare focused. These

six were then removed, reducing the responses and sample size to 81 and 447 respectively. Upon receiving the return-to-sender packages, online searches were conducted in order to determine the status of the companies. From the searches it was found that the companies had merged, been acquired, filed for bankruptcy, suspended trading, moved, or dissolved. These 53 companies were subsequently removed from the sample, further reducing its size to 394. Therefore, the response rate of the project was 20.6% (81/394). Comparatively, the number of responses received was favourable to similar studies of MO in the biotechnology industry.[12,55,56] Specifically, Appiah-Adu and Ranchhod,[12] De Luca, Verona, and Vicari,[55] and Renko, Carsrud, and Brannback[56] obtained 62 (58.49%), 50 (30.67%), and 85 (44.27%) responses, respectively.

According to Armstrong and Overton,[60] subjects that respond later, as opposed to earlier, more closely resemble non-responders. Therefore, in the absence of non-responder questionnaires, key constructs can be compared among early and late responses to determine the existence of a nonresponse bias.[60] Leveraging the works of Armstrong and Overton,[60] independent sample t-tests were conducted to compare the group of companies classified as early responders and the group of companies classified as late responders, based on their group mean scores of MO, AO, and PERF. No statistically significant differences were found in the analyses, suggesting that early and late responders did not differ. Seeing as early and late responders did not significantly differ, there was no evidence of a nonresponse bias.

Construct Measurement

Due to its successful use in the biotechnology industry, MO was measured using Appiah-Adu and Ranchhod's[12] adapted version of the Narver and Slater[20] instrument. For scale size consistency, a five-point Likert scale was used to assess companies' customer orientation, competitor orientation, and interfunctional coordination. Good reliability was achieved ($\alpha = 0.876$), as described by George and Mallery.[61] An un-weighted average of MO's 12 items was used as a composite index score to represent the construct in subsequent analyses.

AO was measured using Kandermir, Yaprak, and Cavusgil's[35] nine-item instrument. The five-point Likert scale was used to assess companies' alliance scanning, alliance coordination, and alliance learning. Excellent reliability was achieved ($\alpha = 0.919$), as described by George and Mallery.[61] An un-weighted average of AO's nine items was used as a composite index score to represent the construct in subsequent analyses.

PERF was measured using an adapted and broadened version of De Luca, Verona, and Vicari's[55] R&D Effectiveness instrument. The five-point Likert scale was used to assess companies' ability to generate new products, file or obtain patents, produce scientific output, recruit new talent, demonstrate technological leadership, attain new capital, and build partnerships. Good reliability was achieved ($\alpha = 0.844$), as described by George and Mallery.[61] An un-weighted average of PERF's eight items was used as a composite index score to represent the construct in subsequent analyses.

Discriminant Validity

Discriminant validity between MO, AO, and PERF was tested using composite index scores. Table 1 shows the correlations between MO, AO, and PERF group mean scores. The Pearson correlation coefficient between MO and AO was 0.470, the standard error was 0.098, and the 90 percent confidence interval was $0.296 \leq r \leq 0.622$. The Pearson correlation coefficient between MO and PERF was 0.303, the standard error was 0.118, and the 90 percent confidence interval was $0.133 \leq r \leq 0.525$. The Pearson correlation coefficient was 0.668, the standard error was 0.094, and the 90% confidence interval was $0.581 \leq r \leq 0.892$. These confidence intervals did not contain the number one, suggesting that acceptable discriminant validity between the group means was achieved.[62]

RESULTS

Hypothesis 1 predicted that the relationship between MO and PERF would be positive and statistically significant. The result from the first regression analyses is presented in Table 2. Findings showed that MO had a positive and statistically significant effect on PERF, thus supporting H1. According to Erdfelder and Buchner's[63] post hoc power analysis, with an effect size of $f^2 = 0.101$,

Table 1: Correlation Matrix

		MO	AO	PERF
MO	Pearson Correlation Sig. (2-tailed)	1		
AO	Pearson Correlation Sig. (2-tailed)	0.470 0.000	1	
PERF	Pearson Correlation Sig. (2-tailed)	0.303 0.007	0.668 0.000	1

Listwise N=79

Table 2: MO and PERF Regression Analysis

IV	DV	R^2	Beta	t-value	Sig.
MO	PERF	0.092	0.329	2.791	0.007

Table 3: AO and PERF Regression Analysis

IV	DV	R^2	Beta	t-value	Sig.
MO	PERF	0.446	0.737	7.877	0.000

an error probability of α = 0.05, one predictor variable (MO), and a total sample size of 79, achieved power (1-β) was 0.80, meeting the minimum power requirement (1-β = 0.80), as suggested by Cohen.[64]

Hypothesis 2 predicted that the relationship between AO and PERF would be positive and statistically significant. The result from the second regression analyses is presented in Table 3. Findings showed that AO had a positive and statistically significant effect on PERF, thus supporting H2. According to Erdfelder and Buchner's[63] post hoc power analysis, with an effect size of $f^2 = 0.805$, an error probability of α = 0.05, one predictor variable (AO), and a total sample size of 79, achieved power (1-β) was 1.00, exceeding the minimum power requirement (1-β = 0.80) as suggested by Cohen.[64]

Hypothesis 3 predicted that the MO and AO would have a positive and statistically significant additive effect on PERF. The result from the third regression analyses is presented in Table 4. Findings showed that AO had a positive and statistically significant effect on PERF and MO had a non-significant effect on PERF, thus only partially supporting for H3. According to Erdfelder and Buchner's[63] post hoc power analysis, with an effect size of $f^2 = 0.805$, an error probability of α = 0.05, two predictor variables (MO and AO), and a total sample size of 79 achieved power (1-β) was 1.00, exceeding the minimum power requirement (1-β = 0.80) as suggested by Cohen.[64]

Originally, MO had a significant influence of PERF as the sole predictor in the model, but its influence became non-significant as AO entered the model. This phenomenon resembles the mediation relationship described by Baron and Kenny.[65] Accordingly, a fourth regression analysis was performed using the insignificant predictor (MO) as the independent variable and the significant predictor (AO) as the dependent variable. The result of the fourth regression analysis is presented in Table 5. Findings showed that MO had a positive and statistically significant effect on AO, thus supporting the existence of a mediation relationship.

Table 4: MO, AO, and PERF Regression Analysis

IV	DV	R^2	Beta	t-value	Sig.
MO AO	PERF	0.446	–0.015 0.744	–0.141 6.976	0.888 0.000

Table 5: MO and AO Regression Analysis

IV	DV	R^2	Beta	t-value	Sig.
MO	AO	0.220	0.459	4.690	0.000

DISCUSSION

The finding from the first hypothesis confirmed that Canadian medical/healthcare biotechnology companies with high MO scores outperformed companies with lower scores. The finding from the second hypothesis confirmed that Canadian medical/healthcare biotechnology companies with high AO scores outperformed companies with lower scores. The third hypothesis envisaged that MO and AO would have a positive and significant additive effect on business performance. The results showed that AO had a positive and statistically significant effect, but MO had a non-significant effect, on PERF, thus only partially supporting H3. A post-hoc mediation analysis revealed that the effect of MO on PERF is fully mediated through AO. The mediation relationship suggests that MO influences AO which in turn influences PERF. In other words, market-oriented biotech companies are better at managing strategic alliances, of which leads to having better performances.

"Market orientation is the organization culture that most effectively and efficiently creates the necessary behaviors for the creation of superior value for buyers and, thus, continuous superior performance for the business" (p21).[20] MO is an organizational culture that encourages customer-oriented, competitor-oriented, and interfunctionally-coordinated behaviours. AO is a comprised of three organizational capabilities including alliance scanning, alliance coordination, and alliance learning.[35] "Alliance orientation will be strong when a firm possesses higher degrees of each of these capabilities and is able to skillfully configure and deploy them" (p326).[35] In the case of Canadian medical/healthcare biotechnology companies, perhaps MO is the foundation and AO is the vehicle for increasing PERF. Consequently, companies that encourage organizational behaviours including customer orientation, competitor orientation, and interfuctional coordination may be better equipped to engage in alliance scanning, alliance coordination, and alliance learning activities. Ultimately, it is

the successful execution of these alliance activities that appears to increase business performance.

The Canadian medical/healthcare biotechnology industry has embraced Narver and Slater's[20] market-oriented organizational culture, as companies in the industry understand its target markets and customers, recognize its competitors' strengths and weaknesses, and disseminate knowledge throughout its departments. Having this market-oriented organizational culture is necessary for, but not directly related to, performance. Canadian medical/healthcare companies have adopted Kandermir, Yaprak, and Cavusgil's[35] alliance-oriented organizational capabilities, as companies actively scan for new alliance partners, effectively manage existing alliances, and learn from its partners. The alliance management organizational capabilities act as catalyst that enables the realization of the full benefits of a market-oriented organizational culture.

In summary, a sequential relationship exists between MO, AO, and PERF, as a business' philosophy needs to be established prior to its undertaking of activities, and the execution of those practices, grounded in the organizational philosophy, perpetuates business performance.

LIMITATIONS

The first limitation of this study was the response rate. Although this study compared favourably to similar studies in terms of the number of responses received (N = 81), the response rate was comparatively lower (20.6%). The timing of the study may have negatively impacted the response rate. Specifically, data collection was conducted over the summer months, beginning in late May and ending in late August. It is possible that some executives were on holiday during the time of data collection. Another limitation of this study is the single-respondent approach, as one respondent per company answered questions related to marketing, alliance management, and performance. The final limitation of the study is the scope and nature of the investigation. This study investigated the importance of marketing and strategic alliances in determining business performance, a topic that was salient to the researcher. The hypothesized antecedents were generated from literature and guided by the researcher's knowledge and interests.

IMPLICATIONS AND CONCLUSION

Empirical data from this study lends support for the importance of market and alliance orientation in determining Canadian medical/healthcare biotechnology companies' performance. The findings from this study have several implications for biotechnology entrepreneurs and managers. First, the results provide evidence that behavioural orientations toward customers, competitors, and business units are the foundation needed to increase business performance. The findings also indicate that managers should pay particular attention to alliance scanning, coordinating, and learning, as these activities enable business performance. Third, managers should understand the sequential relationship between the market-oriented behavioural commitments, alliance-oriented activities, and business performance outcomes, as it can aid in business development. For instance, the sequential relationship between these behaviours, activities, and outcomes can act as a theoretical pathway to increase performance. Companies that were highly market-oriented were also highly alliance-oriented, and highly alliance-oriented companies were top performing companies. The apparent sequential relationship is not the only commercialization pathway, nor does it explain all of the behaviours and activities needed to be commercially successful, but it is important for managers and entrepreneurs to be mindful of its significance.

These findings produced several contributions to marketing and management academic research. First, Narver and Slater's[20] MO instrument proved to be successful with an unstudied population. The instrument's success in the Canadian medical/healthcare biotechnology industry contributed to a large body of research that confirms MO positively influences performance. Second, this was the first known study to comprehensively measure strategic alliance management activities in the biotechnology industry. This study employed the underutilized Kandermir, Yaprak, and Cavusgil[35] AO instrument, thereby expanding AO research and the use of the instrument. Moreover, the findings contribute to a large body of research that suggests strategic alliance management positively influences biotechnology performance. Third, this study goes beyond confirming MO and AO's importance in the relationship with PERF, as the existence of a mediation relationship was tested and confirmed. Fourth, and perhaps the most significant contribution was the development and successful use of the PERF instrument. The PERF instrument proved to be an effective instrument when measuring biotechnology business performance. Finally, the findings expand the scope of biotechnology marketing and strategic alliance management research. It may be fruitful to explore MO in other biotechnology subsectors, expand the use of the AO instrument in other industries and cultural contexts, utilize the newly developed and successful PERF instrument to measure biotechnology performance in other subsectors and cultural contexts, and investigate the influence of other possible antecedents to biotechnology business performance.

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Original Article

Where is the eBay for intellectual property?

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ABSTRACT

This paper is an examination of the economics, organizational dynamics and structural factors inhibiting an electronic market for intellectual property. Several intermediaries exist to facilitate the transition of intellectual property (IP) from sellers to buyers. Over the past 20 years, a number of companies attempted to create an online "eBay for IP." These IP Exchanges (IPEs) failed to gain traction in competition with other mediums that provide channels to facilitate IP transactions. Compounding the problem is the concentration of intellectual property assets amongst a small group of institutions and within those institutions as well as organizational hurdles inherent in academic technology transfer offices. As a result, the business model for an online IPE market is fundamentally challenging, and no successful IPE exists to date.

Journal of Commercial Biotechnology (2014) 20(2), 41–47. doi: 10.5912/jcb646
Keywords: market orientation; intellectual property; technology transfer; intellectual property exchanges

INTRODUCTION

The business press remains awash in discussions about innovation. Yet, there is little discussion about the journey from innovation to commercialized asset. In some cases, innovation—typically manifested in intellectual property—is organically developed for a specific commercial purpose. In many cases, such as academic/non-profit research, intellectual property must be paired with the right commercialization entity to thrive. Technology creates opportunities for more efficient markets for a wide range of goods and services. Electronic markets enlarge the number of market participants and enable pricing transparency, reputation feedback mechanisms, and transactional support. With so many advantages on offer, why do we lack a significant electronic market for intellectual property?

The value proposition for buyers and sellers is clear: commercial organizations maintain significant investments in business development resources to "hunt" for new intellectual property. Academic and non-profit institutions are looking to offset a portion of decreasing budgets through royalties from commercialized IP. Despite these motivations, intellectual property transactions are still characterized by the same activities from twenty years ago: in-person meetings, industry conferences, telephone calls, and more recently, e-mail.

Methodology and Thesis

The seminal questions we addressed through our research are as follows:

- Why has no dominant IPE technology platform emerged?

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- Is the IP market evolving and elusive, or simply difficult to serve for many for-profit businesses?
- Were the strategies of IPEs flawed or poorly executed?
- Are there other factors to success that participants failed to address?

Our primary thesis was that there were several potential reasons why IPEs failed to fulfill the promise of being powerful platforms for connecting innovators and commercial users:

- Structural and organizational limitations—such as complex calculations for sellers involving more variables than total financial consideration, as well as the incentives of buyers and sellers to monetize all IP assets—are not aligned with IPEs
- The more innovative institutions did not require IPEs to commercial their most valuable, and by extension prominent, intellectual property assets
- IPEs struggle to create enough value to justify a margin that could self-sustain the business model, especially in low value, low margin transactions

We addressed these questions from the vantage point of agnostic commercialists:

- Mapped the IP landscape to understand the dominant business models and players and how the landscape has evolved over the past 15 years;
- Conducted economic and statistical research of the patent licensing market to understand which industries provide the greatest revenue potential for Technology Transfer Offices (TTOs), and to identify the dominant TTOs in terms of commercial licensing revenues;
- Conducted qualitative research of both the conventional and non-conventional literature (journal article review, media scanning and expert perspectives);
- Historical data of the non-profit TTO market was also performed to quantify the growth, industry focus and staffing model trends
- Generated and tested hypotheses to develop an analytically-driven point of view on the condition of the IPE marketplace.

In addition to the research above, study and analysis of past and existing players in the IPE market was conducted in order to address the viability and challenges of the various business models, including the following business types:

- 14 IP exchanges
- 6 IP consulting service providers
- 3 TTO service providers
- 2 IP software providers

FINDINGS AND RESULTS

The chasm between IP generators and IP end-users is wide and rough terrain. A number of intermediary and capitalist organizations serve the intellectual property market. Figure 1 illustrates the different types of participants:

Within this landscape, intermediaries help sellers value and promote their IP portfolios. Financiers construct instruments to monetize and collect revenue, while litigation specialists lead the legal prosecution in court or seek to avoid prosecution in the case of defensive patent pools.

The notion of a platform IP Exchange is at least a couple of decades old. Initially, the online IP exchange market was a "virtual Potemkin village": propped-up storefronts with limited inventories, few desirable features and substantial up-front investments. We studied more than two dozen players in the IPE market, and within this group, numerous variations of the business models evolved, yet no sustainable model for the online IP market emerged.

One current IPE founded in 2011 clearly states its goal to "accelerate the commercialization of global R&D through a marketplace that uniquely surfaces ideas, technologies and inventors; and quickly catalyze the connection between buyers and sellers of these assets." Many of the IPE's we studied stated similar goals, finding little success along the way. This article attempts to dissect both the simple assumption behind IPE's and the structural challenges that make achieving this goal so difficult.

In general, IPEs extracted limited value through subscription fees or transaction fees for completed deals. Academic institutions did not respond to either a flat subscription fee nor a percentage of a deal's value as compensation, and IP buyers were hesitant to pay for additional functionality or more formal finders fees. While subscription models have generated revenue for

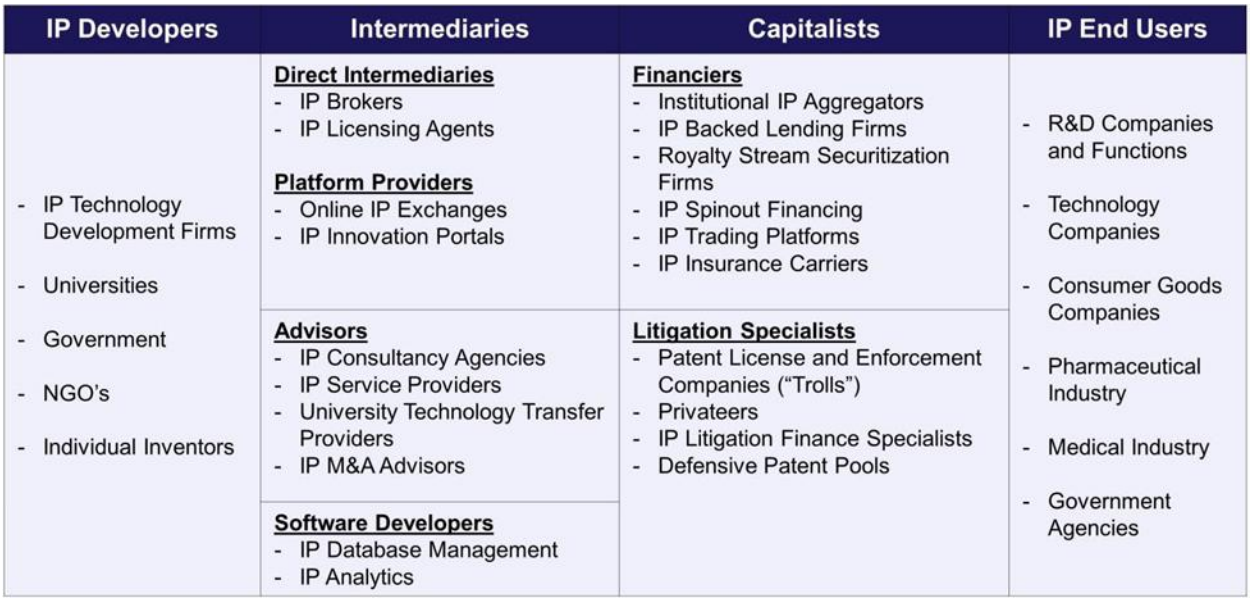

Figure 1: Intellectual property market map (Millien, 2013)

IPEs over the years, the lack of any IPE to maintain subscription fees over a long period (>5 years) suggests that members did not find enough value to merit renewal of the subscription.

Case Study — SparkIP: SparkIP formed in 2007 with seed money from former-Morgan Stanley CEO John Mack. At the time, CEO Ed Trimble said, "there's too much inefficiency from the time an idea is hatched to when it can be productized and sold. By creating a marketplace the links new technologies with potential investors, SparkIP aims to make the process more efficient."[1] After creating strong search algorithms and boasting 40,000 "Sparks Clusters," SparkIP struggled to form a sustainable business. Even after signing MIT, Stanford, JHMI and NIH, SparkIP could not consistently monetize the listing fees charged to institutions. In the end, SparkIP created exposure for the institutions represented, but it failed to convince buyers or sellers of the value SparkIP provided in transactions. SparkIP became "PriorIP" in 2011, with a focus on its 'cluster visualization' technology, before closing its doors shortly after.

None of the IPE's were able to successfully automate the development and maintenance of an IPE market. In almost every case, significant amounts of manual time—from both the IP seller and the IPE itself—are required to complete and service the otherwise automated delivery model. Other players attempted a different approach to the business model.

Case Study — The Dean's List: The Dean's List, established in 2003, became the first company to do live IP auctions in 2006. Despite a forecast of $170M in revenue and 200 members paying $100K each by 2012, The Dean's List (also known as Ocean Tomo) never came close to those goals, completing only 8 auctions in the first 3 years. Few buyers accounted for the majority of the volume, and the poor quality of the IP led to a sale of the business and rebranding in 2009. The company reformed under the name Intellectual Property Exchange International, Inc. (IPXI) in 2012.

IPXI bills itself as the world's first financial exchange that facilitates non-exclusive licensing and trading of intellectual property (IP) rights with market-based pricing and standardized terms. Despite a significant investment to launch—including investment from U.S. and European investors, including CBOE Holdings, Inc. and Koninklijke Philips N.V.a, IPXI is struggling to gain traction beyond a small network on founding institutions.[2] In 2013, the organization had a staff of 16 people with 45 members paying $5K each. Holding the membership fee constant, membership would need to more than quadruple just to support the headcount expenses associated with the business.

Other players, like Tyna, formed explicitly around the eBay theme, but never took off. Tyna still has an online marketplace, but is now essentially a patent broker, with no transactions completed online. Perhaps the longest continuous IPE in the mind of TTOs is

1 http://www.informationweek.com/applications/spark-ip-an-ebay-for-ideas/d/d-id/1060340?, Accessed March 3, 2014.

2 http://www.forbes.com/sites/tomgroenfeldt/2013/12/06/new-ip-exchange-promises-transparency-in-patent-pricing/ Accessed March 3, 2014.

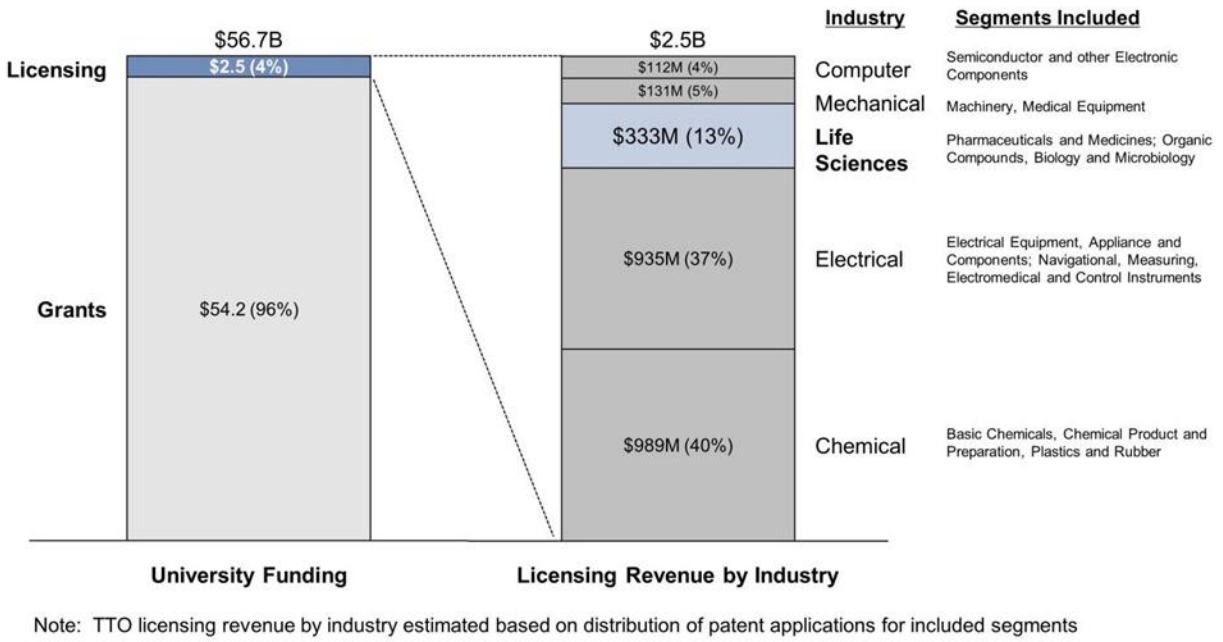

Figure 2: University Intellectual Property Size and Segments – 2011

the iBridge Network, which is a non-profit organization founded in 2005 by the Kauffman Foundation's Kauffman Innovation Network. With a goal of serving as a web-based network for the gathering of and dissemination of innovations such as research results, reports, innovations, intellectual property, and patents, the iBridge Network maintains a significant database of technologies. Yet, the technologies are not updated with any regular frequency, resulting in significantly out-dated "tired" listing that are not practical for many applications.

Taken together, none of the players examined cracked the code to a successful IPE business model. A few adept operators emerged with extensive databases, sophisticated search algorithms and clever IP ranking tools, but none have developed a significant IP exchange model. Of the more than two dozen companies analyzed, the vast majority have either changed their business models away from a pure IPE play, been acquired for less than the investment put in, or have gone out of business completely. Those that remain do not publicly comment on financial performance, but rather comment on the size of their networks. We found very few—if any—references to technologies successfully licensed through—and monetized by—an IPE. We were unable to find P&L statements for any current IPE to suggest that the business model has either broken even or is on course to be profitable in the immediate future.

A quantitative perspective of the problem revealed that the intellectual property market is more skewed than most rational markets. In 2011, the revenue for intellectual property from academic and non-profit institutions was greater than $2.5B[3] (Figure 2).

Critics of TTOs have long wondered whether TTOs can successfully maximize the value of innovation assets. There are many examples of private IP management firms successfully monetizing "tired" assets for significant sums through tactics that include identifying the ideal buyers and skillful pricing negotiations.

The Technology Transfer Office Dilemma

The vast majority of intellectual property licensing revenues tend to be concentrated across institutions and within individual institution portfolios[4]. Figure 3 illustrates the concentration of distribution of license revenue by TTO[5]:

Several conditions can foster success in an electronic market, including liquidity (inventory has a high probability of finding a buyer) and low transaction costs relative to the return on investment. In the market for intellectual property, significant amounts of intellectual property inventory either go unsold or are purchased/licensed for a very small amount. The transaction costs are typically high for each intellectual property asset:

3 (AUTM, Association of University Technology Managers, 2011)

4 (The IP Spinout Model, 2001)

5 (AUTM, Association of University Technology Managers, 2011)

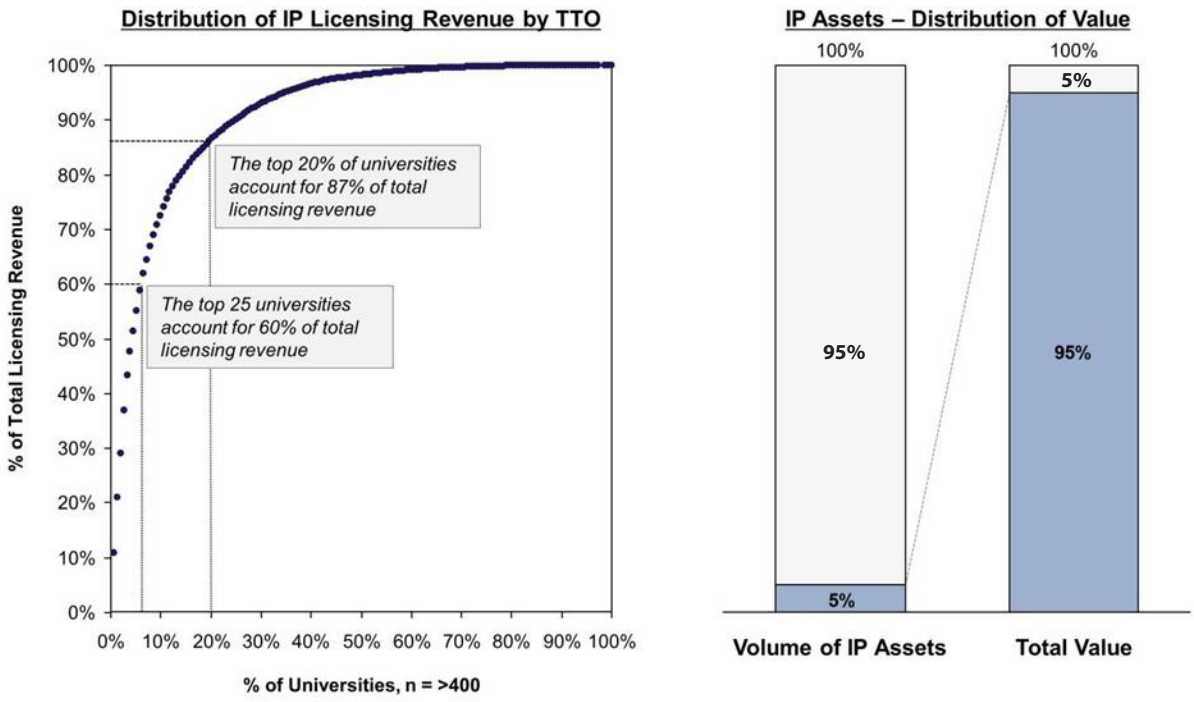

Figure 3: Distribution of IP Revenue and Asset Value

the seller usually needs to provide significant amounts of information and supporting data for an innovation.

Across portfolios of hundreds (or more) of assets, the initial investment is significant and there are maintenance costs that must be offset to keep information current. In addition, the lack of a point of aggregation increases the investment as sellers consider multiplying the investment across several IPE platforms. Once the assets are populated in an IPE, the sales cycle can be long, requiring additional discussions with inventors, experimental trials, and protracted negotiations in some cases.

Additionally, the quality of a patent—including whether it is enforceable and the reach of its claims—is hard to judge. These factors increase the time it takes for buyer and seller to reach agreement on a price. In addition to price, many TTOs take time to consider the value of the partnership with a particular commercialization entity. In some cases, the post-licensing investment in the technology becomes more important than the initial consideration provided for the technology. TTOs placing significant emphasis on post-licensing investment can result in sub-optimal matching in a strict, auction-based, *ex ante* financial sense. The risk-adjusted calculation for successfully commercializing a technology may differ than the *ex ante* consideration, making the notion of a marketplace even more challenging through the introduction of new variables. It also shifts the purpose of the marketplace from the highest bidder to the best commercialization partner, making a single IPE to serve the entire market more challenging.

Yet, in light of this time commitment, licensing only represents a portion of total activities for TTOs. Most TTOs maintain a lean staff (~4 FTEs)[6] and are not inclined to dedicate limited resources to address commercial functions relative to serving their academic communities. Figure 4 illustrates the various activities taking place in TTO offices[7]:

Given these dynamics, TTOs choose to spend their time licensing the top 5% of assets that generate the majority of the revenue. If the remaining assets find their way to an institutional web portal or IPE, the records are typically not updated and seldom promoted.

While full transparency is counter to the prevailing logic in hyper-competitive markets, un-willingness to embrace a more open or crowd-sourcing environment for innovation is resulting in inefficiencies across the IP landscape. It is also reducing the potential for breakthrough development, resulting in a significant opportunity cost for society. Related to this mindset are structural and operational factors such as resourcing/staffing models, metrics and rewards, and maladaptive interfaces between the innovation community and business leaders.

6 (AUTM, Association of University Technology Managers, 2011)

7 (AUTM - Association of Technology Managers, 2009)

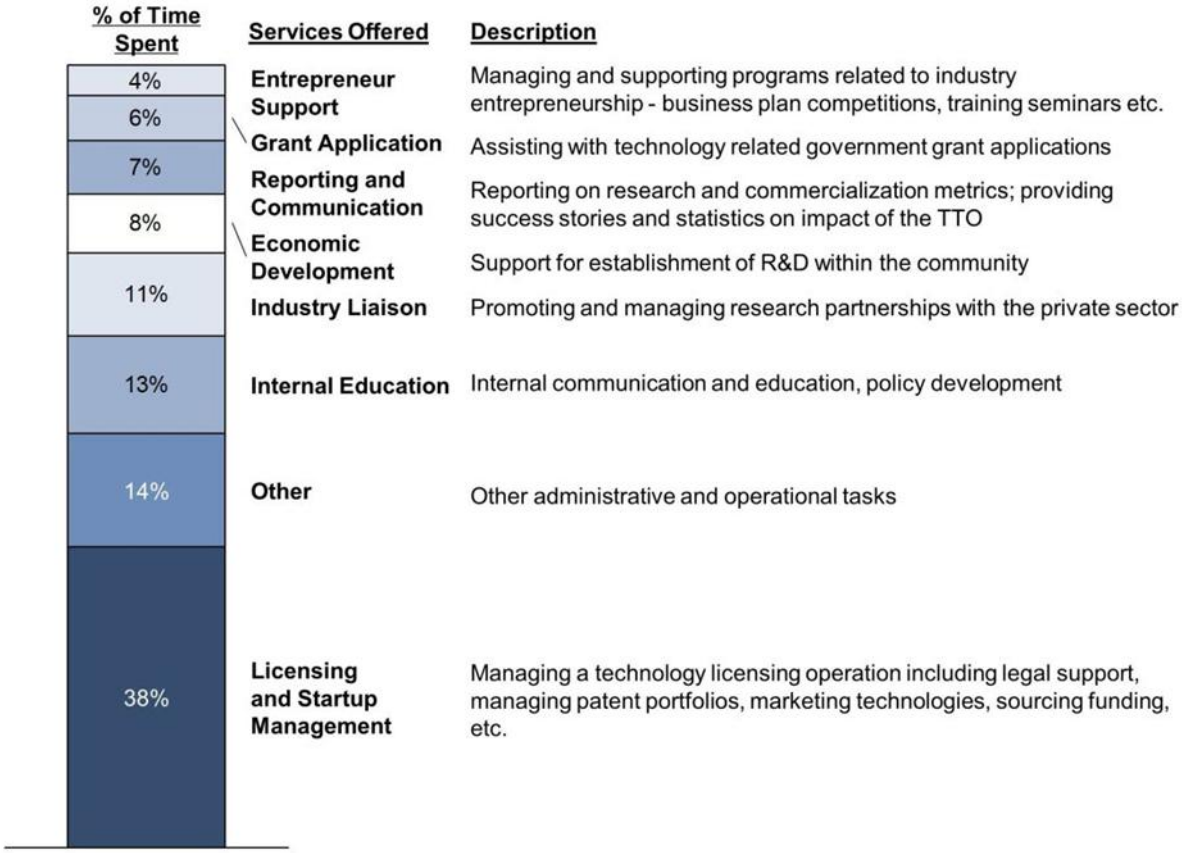

Figure 4: TTO Activities (% of total time spent)

CONCLUSIONS

So would the "Killer App" for IPEs be sufficient to connect innovators with the R&D functions of large corporations, whose success depends on effective identification and commercialization of emerging technologies? Our research on the different players across the IP landscape (e.g., business and revenues models, relative strengths and weaknesses, criticality to IP licensing and commercialization) suggests there is something more profound at play[8].

It's been nearly 20 years since the emergence of intellectual property exchanges. Despite increasingly sophisticated technology platforms, well-funded and experienced management teams, and a relatively well-accepted market need, no IPE emerged as a point of aggregation. The greatest inhibitors to successful IPEs may not be limits on capital, imagination or competence, but rather structural factors that may be difficult to overcome.

Specifically, a bifurcation between technologies that could be auctioned to the highest bidder relative to more nuanced opportunities could help define the true addressable market for an "eBay" marketplace. It would be interesting to see whether TTOs or other IP holders would make technologies of significant commercial value available in this format. If TTOs would only make "tired" technologies available in a pure auction format, then the process would have to be extremely efficient for the IPE to profit from the thin margin likely to be generated for those transactions. However, even with an efficient process, it is not clear that the volume in a low margin format would be significant enough to support a self-sustaining, for-profit business model.

Already there are signs that some of the more recent IPEs are experiencing IP holders carving out certain high value IP from the market place. IPXI will make a suite of patents around display screen applications from Philips available, while Philips will retain IP around lighting for the technology. Questions around quality and value are likely to remain until several high-profile examples prove the model.

8 (Are there "Institutional Failures" in Intellectual Marketplaces?, 2013)

For more nuanced technologies, which will be defined by significant dialog between the TTO and the buyer, it is difficult to see how an IPE will create enough value for all parties to justify a margin significant enough to support the IPE business model. In these cases, one of the only value drivers the IPE creates is connecting the parties. Once buyer and seller are matched and communicating, using an IPE as an intermediary would in theory only complicate the negotiation, which is likely to be defined by phone calls, in-person meetings, and e-mails.

Other channels may already substitute for IPEs by matching sellers with potential buyers. Industry journals and poster sessions at conferences could be the oldest, and perhaps the most viable "channels" for promoting intellectual property. For assets that have significant potential, TTOs are happy to assign resources to promote the asset and field discussions from potential purchasers or licensees. These interactions tend to drive the highest value for TTOs as opposed to an IPE model.

While the concept of an IPE can be compelling, numerous attempts highlight the reasons why an eBay for intellectual property does not exist. The IPE business model is confounded by the difficulty of valuing the contribution of IPEs to the transaction. Long sales cycles combined with robust amounts of data create high transaction costs, especially initially to add an intellectual property asset to an IPE database. The concentration of high value assets—both across institutions and within individual institutions—lends itself toward targeted promotional campaigns for high value assets as opposed to an open market approach, where high value assets could be lost in the noise. A successful IPE could eventually emerge, but a number of structural challenges need to be addressed to enable success. IPEs in their current form have exhausted themselves and the best hope for future models will help predict or even create new innovation opportunities as a way of connecting the innovators with the consumers of technology.

Acknowledgements

The authors wish to thank Paul Schneck for helpful comments and guidance, as well as the Association of Technology Managers (AUTM).

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From the Boardroom

Biotech IPOs steam ahead in 2014

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Journal of Commercial Biotechnology (2014) 20(2), 48–50. doi: 10.5912/jcb654

If you walk into most private biotech company boardrooms today, it is likely that you will hear a discussion about whether to go public. Companies at every stage of development are either getting ready to file for an initial public offering or thinking about it. Although the slowdown in new issues at the end of 2013 gave observers pause that the robust biotech IPO market of 2013 might slow down in 2014, the reality has been just the opposite. By the middle of March, 28 life sciences companies had completed initial public offerings on U.S. exchanges, raising $1.8 billion in new capital, and collectively on average trading 47.4 percent above their initial offering price.

With another 25 companies having publicly filed their intention to go public, and unknown others having filed confidentially and testing the waters, the wave of life sciences IPOs shows little sign of abating any time soon. It is a particularly attractive time for life sciences companies as biotech stocks continue to trade up and investors remain interested in the sector.

Castlight Health, the latest health-related company to complete an initial public offering in the United States, raised $178 million in an offering priced above its target range. The digital health company provides web-based tools for employers and consumers to gain clarity around their healthcare costs, usage, coverage, and choices—in other words, price transparency in a healthcare market that is growing price conscious. It soared 149 percent in its trading debut, a sign of the importance of digital tools for the transformation of healthcare.

Life sciences stocks in general and biotechnology stocks in particular had a stellar year in 2013 as investors flocked to the sector to capture gains driven by macroeconomic and healthcare specific factors. Wall Street had one of its best years in the past decade as the U.S. economy improved and investors poured new money into the capital markets to take advantage of the upward movement of stocks. At the same time, good M&A premiums, Big Pharma's investment in external innovation, and the growing importance of healthcare in an aging world all drove biotech stocks to new heights. While the Nasdaq Composite Index ended 2013 up 38.3 percent, the Burrill Biotech Select Index closed the year up 61.5 percent, its best performance since the index was started in 1994.

The 39 new drug approvals in 2012 was an indication to investors that the U.S. Food and Drug Administration and industry could work well together. As new, innovative drugs reached market and promising ones in the pipeline advanced with encouraging clinical data, investors who had previously shunned the biotech sector, now embraced its potential to deliver groundbreaking products to help patients. New regulatory rules and programs to speed the development of innovative medicines also stimulated investors' appetite.

Big biotech companies, once the stepchild of Big Pharma, began supplanting pharma's place at the top of the drug development ladder. Gilead Sciences, Celgene, and Amgen now rival their Big Pharma counterparts in terms of market capitalization. Growing revenues and earnings, and the rising value of their shares have propelled them to the forefront in revenue growth and dealmaking.

All of these factors have fueled the market for both new and follow-on issues, especially for drug developers. Since the beginning of 2014, these companies have collectively raised $1.4 billion in 22 IPOs and $4 billion through follow-on offerings on U.S. exchanges. In 2013, U.S. drug developers raised $2.8 billion in 38 IPOs (not counting Zoetis' $2.6 billion IPO) and $6.6 billion through follow-on offerings.

Barring a big market correction, 2014 IPOs are on pace to best biotech's performance in 2013 in terms of the number of new issues. On average the companies completing offerings this year are performing in the aftermarket as well as the companies that completed IPOs in 2013. They are also pricing the offering more rationally as far as investors are concerned, with the final offering price just 9.6 percent below the midpoint of the original target price. That compares to an offering price 13.9

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Table 1: Biomedical IPOs in the United States: 2014 vs 2013 averages by category

Therapeutics	2014	2013	Change
Average capital raised* (USD M)	61.7	69.8	-11.6%
Return from IPO	56%	54.1%	3.5%
Raised vs target	6.9%	6.4%	7.8%
Price vs target	-8.9%	-15.5%	42.6%
Shares offered vs target	21%	31.6%	-33.5%
Median: Stage of lead product	Phase 2	Phase 2	
Insider buy-in: percent of total deals	73%	65%	12.3%
Median buy-in: percent of total deal value	23.5%	26%	-9.6%
Medical Devices	**2014**	**2013**	**Change**
Average capital raised (USD M)	40.4	97.5	-58.6%
Return from IPO	11.6%	64.6%	-82.0%
Raised vs target	-26.8%	10.4%	-357.7%
Price vs target	-31.2%	3.6%	-966.7%
Shares offered vs target	7.2%	6.4%	12.5%

*Average excluding Zoetis' IPO

percent below the midpoint of the original target price for 2013 IPOs.

In terms of total capital raised, the size of this year's crop of offerings have averaged $61.3 million per IPO. That compares to $69.8 million on average per IPO in 2013 when Pfizer's animal health unit Zoetis' $2.6 billion IPO is excluded. One reason for the smaller deals is that fewer companies increased the total number of shares offered compared to their original targets. Companies going public in 2014 increased the number of shares offered by an average of 17.7 percent compared to a 22.8 percent average increase in the number of shares offered by companies going public in 2013.

A closer comparison of therapeutics IPOs in 2014 compared to those in 2013 finds some differences that suggest that initial public offerings are being priced more reasonably and that aftermarket price appreciation has become more rational, a sign that there may be fewer generalist investors chasing quick pops from IPOs in hot demand to sector investors interested in the fundamentals of a company and its long-term potential to build value.

For example, the percentage of companies pricing within their original target range increased to 53.6 percent in 2014 compared to 44.2 percent of IPO pricings in 2013. In 2014, about one-third of companies priced their offerings below their expected target range compared to 2013 when 42.3 percent of companies completed offerings priced below their expected target range.

Companies at all stages of development are going public in 2014 but are generally not more seasoned than their counterparts in 2013. In 2014, 82 percent of drug developers that completed IPOs have lead products in mid-stage development or beyond, compared to 92 percent of companies that went public in 2013. In both years, the majority of companies going public have lead products in mid-stage development, 45.5 percent of companies in 2014 compared to 60.5 percent of companies in 2013.

Though existing investors participated in a greater percentage of drug developers' initial public offerings so far in 2014, 73 percent versus 65 percent of such offerings in 2013, the median buy-in amount was less, 23.5 percent of the offering in 2014 compared to 26 percent of the offering in 2013.

Five companies that completed IPOs in 2014 are focused on treating pain, but high-risk areas such as gene therapies, RNA-based therapies, and rare diseases have garnered the strongest interest by investors. Top performers include companies such as RNA-based drug developer Dicerna Pharmaceuticals, up 135 percent in mid-March. The biotech priced an upsized IPO at the end of January at $15 a share, above its target range, to raise $90 million. Shares opened their first day of trading at $30 and kept on climbing, ending the day at $45.50, up 203.3 percent, the largest opening day gain of any biotech IPO in at least nine years. Dicerna plans to begin clinical testing of its experimental treatment for hepatocellular cancer and other solid tumors by mid-2014.

One day later, UltraGenyx Pharmaceuticals, priced its upsized IPO above the target range to raise $121 million. Its shares also soared in the first day of trading, rising 101 percent. The biotech, which develops therapies for rare genetic metabolic diseases, was up 185.7 percent in mid-March. UltraGenyx' pipeline includes five experimental compounds with its most advanced product, an extended-release formulation of sialic acid, in mid-stage testing for hereditary inclusion body myopathy, a genetic muscle-wasting disorder.

Auspex Pharmaceuticals (up 153 percent) and Revance Therapeutics (up 136 percent) are two other top performers among the companies that have completed IPOs in 2014. Auspex is focused on treatments for rare neurological diseases. It lead therapeutic is in a late-stage study to treat the rapid uncontrolled movements associated with Huntington's disease. The biotech plans to submit an NDA for the drug's approval before the end of the year. Revance Therapeutics is developing a Botox gel that

is in late-stage development and is designed to smooth wrinkles, the first topical formulation of the neurotoxin.

Given the favorable market conditions on Wall Street, companies in Europe and Israel are choosing to go public in the United States instead of in their home countries. Dutch biotech UniQure, a developer of gene therapies, raised $92 million in an upsized IPO above the target range in the beginning February, and was followed by U.K. biotech Egalet, and Israeli firms Lumenis and Galmed Pharmaceuticals. Several European and Israeli companies are in the IPO queue.

The stream of European companies looking to go public in the United States may slow to a trickle, however, as the successful IPO of cat-allergy drug developer Circassia on the London Stock Exchange in mid-March raised hopes that interest in biotech IPOs will cross the Atlantic. Circassia raised $333 million, the largest life sciences IPO so far this year. Another British biotech, Horizon Discovery, has lined up to go public in London, while three French biotechs have announced their intention to IPO on the NYSE Euronext exchange.

While boom years for biotech have been followed by years of drought in the past, the industry has matured. There are more than 900 drugs in late-stage development today. The biotechnology industry has moved from one with little revenues to a profitable industry in the aggregate. No longer is it an industry driven on promises, but instead it is driven by its strengthening fundamentals and the value it provides for patients. And investors are making money betting on its ability to produce value.

From the Boardroom

Valuation of early-stage companies in the biotechnology industry

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ABSTRACT

The prospect of government regulation, product liability lawsuits, and customer reliance on third-party payers contribute to the complexity of valuing biotech start-ups. In addition, the inherent complexity of biologic drug manufacturing and storage creates secondary risks that must be considered in a valuation.

Journal of Commercial Biotechnology (2014) 20(2), 51–58. doi: 10.5912/jcb648
Keywords: valuation; start-up; risk; biologics

INTRODUCTION

The biotechnology ("biotech") industry consists of companies using living organisms or molecular and cellular techniques to provide chemicals, food and services that meet human needs. As part of the biotechnology industry, biopharmaceutical companies ("biopharmas") engage in manufacturing and developing large molecules medicines that are similar or identical to bodily proteins. The biopharma industry comprises thousands of small firms, whose identities change as new start-ups are formed and established firms grow, merge, or are acquired by other established companies. Mergers or acquisitions are used as an exit strategy for smaller biotech firms who often have financial difficulties, such as few or no marketable products and low cash-to-sales ratios. Partnerships and acquisitions of pharmaceutical start-ups, including biopharma start-ups, account for between one-quarter and one-third of most large firms' pipelines. The number of large

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pharmaceutical companies seeking to bolster a lagging product line by finding late-stage drug development projects that could be launched quickly is decreasing and valuing start-ups with early- stage projects is becoming increasingly common.

There are three well accepted valuation methods that should be considered when valuing early-stage biotech companies:

- ***Asset Approach*** – used to calculate a business's value as the fair market value of a company's assets less the fair market value of its liabilities;
- ***Income Approach*** – used to calculate a business's value based on the present value of expected future cash flows; and
- ***Market Approach*** – used to calculate a business's value based on metrics from guideline publically traded pharmaceutical companies and privately held businesses.

Of the three valuation methods identified above, the most commonly used method for valuing early-stage biotech companies is the income (or Net Present Value "NPV") approach. The NPV approach involves the quantification of expected revenues, costs, and potential risk parameters.

Revenues are forecasted by considering market size, market share, and market growth opportunities for the biotech company's potential drug or drugs. The number of patients receiving treatment, the price of treatment per patient, and existing sales data of products in the same therapeutic class as the drug candidate of interest are considered in determining the market size. Market share is determined by analyzing competition from other available treatments and whether other companies have similar products in their development pipeline. Pricing, the relative advantages of the subject drug compared with current treatments, clinical evidence of efficacy, and patient and physician product loyalty to pre-existing treatment options will influence market penetration. Market growth is generally affected by changes in the patient population, spread of illness, frequency of occurrence, frequency of diagnosis, and treatment practice. Rates of product ramp-up, historical peak sales, and rates of market erosion are often analyzed. If patent technology relating to the subject drug is present then it is important to understand if and when patent protection will expire and also whether critical generic competition may occur.

Development costs are broadly grouped into four categories as follows: (1) *Discovery and pre-clinical development costs* related to the discovery of the chemical compound or the biological agent; (2) *Clinical development costs* including trial design, patient recruitment, clinician, monitoring, and close-out and reporting costs; (3) *Regulatory review costs* required to gain regulatory approval; and (4) *Launch, manufacturing and marketing costs.*

Although historical data for products in the same therapeutic class as the drug candidate of interest can be valuable resources for forecasting, significant uncertainty exists around forecasting revenue potential, development cost, and risk. Values derived from quantitative modeling are sensitive to changes in revenue and risk parameters, which explain why it is important to understand the challenges and risks involved in valuing early-stage biotech companies. This article is intended to address both common challenges in forecasting revenues, costs, and risk, and to highlight specific risk factors related to early-stage biopharma companies.

CHALLENGES AND RISKS TO CONSIDER

Incorrect assumptions involving drug development costs, anticipated revenues, or risk can have a significant impact on any valuation. Early-stage companies in the biopharma industry face market and scientific challenges that valuation professionals must understand. These risks depend not only on the stage of development and the experience of the company, but also the types of drugs being developed.

The biopharma industry encompasses various risk factors and hurdles that must be overcome prior to attaining a commercially successful drug. Start-up biopharmas face a highly regulated global industry, increasing research and development ("R&D") costs, escalating costs of litigation, reimbursement risk, growing threats to patent life, and the rise of generic competition. In a 2013 study DiMasi, et. al. reported that only 32 percent of biologics that entered Phase I trials were approved. The same study found that the approval rate was even lower for oncology biologics at just 12 percent. Notably, as of 2012, only 15.4% of all orphan designated drugs in the U.S. were approved.

Increasingly, new drug ideas originate in small companies, which often then license-out their drug compounds to more experienced firms for later-stage drug development, regulatory review, and commercialization. While these start-ups may focus on traditional chemical compounds, many develop biological drugs, otherwise known as "biologics," which are complex substances derived from living sources. Start-ups also often focus on orphan drugs, which are either classified as traditional chemical compounds or as biologics, and are defined in

the U.S. as treatments for diseases affecting 200,000 or fewer people.

Many start-ups will never reach the stage of pursuing an initial public offering ("IPO") or being acquired and many drugs being developed by small cap companies will never see the light of day. Understanding not only the risks that face all pharmaceutical companies, but additional challenges faced by biotech start-ups in particular, is important to conducting a valuation. An overview of the complexity of the drug development process as well as sources of costs and risk inherent to the pharmaceutical industry follows.

Underestimating Cost and Risk in the Drug Development Processes

In the U.S., a newly discovered chemical or biological entity must overcome numerous regulatory hurdles: pre-clinical development is followed by application for permission to proceed, three phases of drug approvals in the U.S., final Federal Drug Administration ("FDA") approval, and at times, additional Phase IV studies. The entire development process takes on average 12 years for traditional drugs and between 10 and 15 years for biologics, which includes initial basic research and frequent delays in the approval process. The percentage of drugs that fail during the various clinical stages is approximately 90 percent (and can be as high as 95 percent for biologics).

Orphan drugs and biologics frequently experience difficulty in recruiting patients, due to the rarity and severity of diseases the drugs are intended to treat. Center Watch, a source of information regarding clinical trials, estimated that difficulties in recruiting patients can delay 81 percent of drug trials related specifically to biopharmaceuticals for up to six months. Furthermore, additional costs may be incurred if regulators demand post-marketing studies and the establishment of patient registries, which is frequent for orphan drugs. The development of orphan drugs is further complicated by a lack of data on the natural course of the disease, poor or late diagnosis, limited expertise in the medical community, and major logistical difficulties in the organization of clinical trials. Moreover, once clinical proof of principle is established for an orphan drug for which there is no alternative, the manufacturer may be under enormous pressure from patients, physicians, and/or politicians to provide the therapy in development to patients, especially to children, under a compassionate use program. Thus, apart from any financial aspects, this pressure may undermine the ability of a company to perform controlled clinical trials.

Biopharma start-ups often focus on novel drugs, banking on a greater return on investment upon drug approval. Thus, regulators may require larger numbers of patients and longer durations of exposure for truly novel agents to assure that a rare serious adverse event will not be missed. The sponsor of the first product in a drug category to reach regulators will have to negotiate all the criteria for approval and the size of safety database with the regulators. Regardless of the novelty of the drug candidate in question, there is evidence that success depends not only on the potency of the subject biologic, but also on knowledge of the regulatory approval process. Pharmaceutical companies, including biopharma firms, which received prior regulatory approval have a 51 percent chance of receiving approval on the first submission, as opposed to a 30 percent approval rate for companies which had received prior New Drug Application approval. As a result, companies that do not have a strong relationship with the FDA are likely to experience costly delays in obtaining regulatory approval.

As of 2010, the average pharmaceutical industry return on R&D was less than nine percent. Smaller pharmaceutical companies, despite their smaller size and inherent efficiencies, generally are no more productive at R&D than are large pharmaceutical companies. Many drugs will fail in the last two clinical stages of drug development, clinical trial Phases II & III, which are the largest, most expensive, and most lengthy clinical trials in the drug development process. Only 84 percent of biologics transition from Phase I to Phase II, only 53 percent transition from Phase II to Phase III, and only 74 percent transition from Phase III to regulatory approval. Despite the high rates of failure in later stages, Phase III clinical trials cost approximately 18 times more than does basic research, and approximately 11 times more than the cost of the initial discovery and the costs of preclinical trials. For orphan drugs, Phase III clinical trials represent over 90 percent of development costs. Underestimating the cost of drug development or the risk of late-stage failure can have a significant impact on the valuation of a startup or early-stage biopharma company.

Risk of Overestimating Patient Population

Another risk facing biotech companies, namely those targeting rare diseases, is the potential to overestimate the patient population. The actual number of patients that need to be treated, as compared to an extrapolated estimated prevalence, is often uncertain. Overestimation of the prevalence rate of many rare diseases is most probably related to the fact that prevalence studies are usually done in regions of higher prevalence and usually based on hospital data. Even if a drug

candidate receives regulatory approval, overestimation of the patient population can have a significant effect on forecasted revenues, and as a consequence, the value of the startup.

Reimbursement risk

An important consideration when valuing early-stage biopharma companies is the insurance status of target patients – notably whether they are covered at all as well as the scope of coverage and the limits placed on coverage. It is essential that a specific drug be included on preferred drug lists, especially on the list of Medicare and Medicaid reimbursable drugs. Preferred status translates into lower patient cost, which decreases the impact of the price variable. Features of the Medicare Part D plan could significantly affect beneficiary access and costs, including "tiered" cost sharing, requirements for prior authorization or coverage and step therapy, and quantity limits.

In the case of specialty drugs, such as many biologics and orphan drugs, rather than paying a fixed copayment per prescription as is typical for less expensive drugs, beneficiaries must typically pay a percentage of the cost of medication in the specialty tier as coinsurance. For the 2010 plan year, the median coinsurance rate for medications in the specialty tier across plan was 30 percent. As of 2010, 46 percent of orphan drugs were included in specialty tiers by 50 percent or more of stand-alone Part D plans. One-third of orphan drugs were subject to prior authorization requirements before coverage was granted by 50 percent or more of stand-alone plans.

In the case of biologics, the expense of these drugs, as well as increased budget constraints, has already led to risk sharing, which includes performance-based contracts, efficiency stipulation schemes or effectiveness guarantee schemes. In other words, risk sharing allows payers such as private or public insurers to pay only if the treatment is effective. Just as in the case of overall lower prices in Europe, their single payer system enhances their ability to obtain such risk-sharing concessions. Moreover, regulatory authorities in countries such as the U.K. are beginning to impose "fourth hurdle" requirements that drugs must demonstrate cost effectiveness, not just safety and efficacy.

In an environment of intense pricing pressure, new drugs that treat unmet medical needs stand the best chance of commanding higher prices. However, there is a risk that patients will most likely not be able to afford to pay for these higher priced drugs (e.g., orphan drugs) directly and payment to the pharmaceutical company will be through a third-party payer. Therefore, pharmaceutical companies, including biopharma companies, anticipating the high prices commanded by drugs for rare diseases have to deal with the risk that their revenues will be severely harmed if drugs fail to receive reimbursement approval through Medicare, Medicaid, or private insurance.

Risk of litigation

Litigation risk is another area for consideration when valuing early-stage biotech companies. In spite of extensive risk management efforts and input to board committees of pharmaceutical companies, there has been a rise in the number of settlements for violations of a variety of laws in the last two decades. Between 1991 and 2011, more than 165 cases of civil and criminal actions by federal and state governments were settled in the U.S. by pharmaceutical companies, with total criminal penalties of approximately $19.8 billion. Awards of damages or settlements involving 73 percent of these cases occurred between 2006 and 2010.

In April 2010, the U.S. government amended the Fraud Enforcement and Recovery Act of 2009 to narrow down its public disclosure provision, making it easier for whistleblowers to bring lawsuits; which has resulted in massive recoveries in subsequent years. Additionally, in July 2010, the U.S. government passed the Dodd-Frank Act, which increased the authority of the U.S. Securities and Exchange Commission ("SEC") to reward whistleblowers with a newly established, $451 million fund and provided them with enhanced protection against retaliation.

Settlements and financial penalties stem from various types of violations, but drug safety issues accounted for over 50 percent of major lawsuits. Therefore, it is important to note that the complexity of biologics and many orphan drugs, precisely the drugs produced by biotech companies, may increase product safety risk. Large-molecule drugs are sensitive to even minor changes in the manufacturing process, and subtle changes can significantly affect the safety and efficacy of these products. For instance, during clinical testing, 31 percent of orphan drugs had more pronounced side effects than did non-orphan drugs and 13 percent of FDA approved orphan products provoked more side effects than were anticipated.

In addition, because biologic products are defined by a manufacturing process, biotech companies may be at greater risk of design defect claims. Since design defect claims apply to every product sold, they therefore pose a greater threat of litigation damages as opposed to standard manufacturing claims which only apply to individual products or lots.

Increased liability due to adverse drug effects could pose significant risks to the financial stability of a biopharma company and its ability to fund R&D for future revenue growth. Public litigation could also have detrimental consequences for the reputation of a new drug. Despite this growing risk, the threat of adverse drug effects on the pharmaceutical industry can never be eliminated, only managed; and therefore, should be considered in any valuation.

Human resources risk

A study of U.S. biotechnology companies also shows that the lack of human capital is a barrier to growth prospects of a biotech company. Human capital problems facing firms are often a result of an inability to find experienced managers and regulatory personnel. There is an intensifying global "war" for talent in the pharmaceutical industry. There is a risk of shortages of highly skilled personnel in developed industrial economies due to two principle factors: (1) an increased demand and higher wages for personnel in their foreign counties of origin; and (2) international agreements that limit "brain drain", the large-scale emigration of large groups of technically-skilled individuals, which could increase the cost of hiring highly skilled migrants.

Thus, locating and retaining highly competent and experienced staff, who also know how to navigate the FDA approval process, is a growing concern to biopharma companies. Not only could a lack of appropriate talent potentially hinder the FDA approval process and cause additional delays, it could also drive wages upwards. Human resources risk could significantly impact estimated future profits, and therefore, the accuracy of any valuation.

Risk of outsourcing

Due to slow revenue growth in the pharmaceutical industry, pharmaceutical companies including biopharma firms, are tempted by the short-term cost savings that outsourcing can provide. Contract research organizations ("CROs") are increasingly able to offer specialized services and capacity at lower costs. However, many CROs have been hurt by increasing competition, resulting in the pressure to hire less qualified staff. Failure to complete work on time or on budget is a risk, as is the potential for low-quality work. Because the pharmaceutical industry is so highly regulated, there exists more opportunity for CROs to violate rules concerning clinical trials, manufacturing, and/or distribution. Furthermore, a biotech company's reputation can be placed in jeopardy if the third party contractor engages in unethical or inappropriate activities, even during drug development before a start-up company partners or is acquired. As a result, outsourcing risks should be considered when valuing early-stage biotech companies.

Risk of counterfeit drugs

Similar to increased litigation and outsourcing, the augmented quantity of counterfeit drugs worldwide poses significant reputational risk to biotech companies. Ernst & Young observed that as of 2008, counterfeit drugs accounted for approximately 10 percent of the world's pharmaceutical product supply. However, according to the Counterfeit Incident System managed by the Pharmaceutical Security Institute found that only 1.23 percent of counterfeits are biologics. Nevertheless, counterfeit biologics pose an exceptional risk greater than its statistical representation. The probability of a counterfeiter successfully creating a biologic with any therapeutic value is miniscule. Biologics require continuous testing and validation to prevent even slight variations. Despite the difficulty in manufacture, counterfeit biologics are extremely challenging to detect, and they are extremely vulnerable to environmental degradation, more so than other drugs. Moreover, biologics, especially vaccinations, are frequently administered to a large number of persons at one time, increasing the potential for a catastrophic event.

At present, of the 191 WHO member states, only about 20 percent are known to have well developed drug regulation. Of the remaining member states, about 50 percent implement drug regulation at varying levels of development and operational capacity. The remaining 30 percent of member states either have no drug regulation or have very limited capacity to do so. Inadequate, ineffective, or weak drug regulatory control could promote unregulated importation, manufacture, and distribution of biologics. Counterfeit biologics thus pose a significant risk to a pharmaceutical company's reputation if the drugs are ineffective or unsafe.

Risk of parallel trade

Parallel imports, or gray-market imports, are drugs that are legally produced under patent protection, placed into circulation in one market, and then imported by an intermediary into a second market without the authorization of the local owner of the intellectual property. Parallel trade thrives when there are significant price disparities between countries, and it is legalized in many countries, including those in the European Union. As a result, the

ability of pharmaceutical companies to price discriminate is diminishing as more countries adopt national price regulatory policies that reference prices in other countries and/or legalize parallel trade. Pharmaceutical companies are thus encouraged to delay or not launch new drugs in low price markets. This launch delay or the decision not to launch new drugs, in turn, would shrink the potential market size and projected revenues for biotech companies. Moreover, parallel trade could reduce safety and potentially harm a company's reputation due to the circumvention of domestic inspections.

Supply chain and distribution risks

Potential risks related to a biotech company's supply chain and distribution network occur prior to commercial manufacturing and also during clinical trials. In many cases, clinical trials are conducted globally, and protecting intellectual property rights throughout the supply chain can be a serious concern. Furthermore, the consequences of producing suboptimal quality or quantity on a commercial scale can be detrimental because of the amount of material consumed and also the scope of those receiving the drugs is potentially wide and much more difficult to contain. One lost shipment of a critical compound, due to improper storage, transport, or administration, can lead to an entire phase of a clinical trial being delayed or aborted. For a small cash-constrained start-up, this could have major business implications if replenishment supply involves cost and time lines that it can ill afford.

Risk of biosimilars

The risk of generic "biosimilars" entrants is an important risk factor that should be considered. The introduction of generic alternatives that are less expensive, effectively truncates the life of a patent. In 2010, the Biological Price Competition and Innovation Act was passed that provided 12 years of market exclusivity for biologics, but opened the door for biosimilars. This means that after 12 years, generic companies can start marketing cheaper biosimilars. Prior to this legislation, there was no regulatory pathway to approve biosimilar products and therefore, most biologics were afforded the benefit of never having to compete with generic products.

In addition, the 12 year exclusivity afforded to biologics under this act may not provide the expected protection. Exclusivity does not necessarily prevent a "non-similar" product (e.g., a small molecule versus a biologic) from receiving orphan drug designation for the same therapeutic indication as an existing product or prevent that product from reaching the market. Furthermore, as stipulated in the orphan drug regulations of the U.S. and the European Union, a clinically superior product, even if similar, can break the market exclusivity of a marketed orphan drug.

In international markets, the introduction of generics can precipitate even greater impacts on branded drugs. For instance, several world markets including Germany, the Netherlands, and New Zealand, have established reference pricing. In reference pricing, products are often clustered by therapeutic group. Consequently, if the reference price is based on the least expensive drug in the cluster, once generic entry occurs, all products in a reference group drop to that price, effectively truncating patent life for the newest drugs in a reference category. Reduction in patent life due to reference pricing, as well as the limits to market exclusivity of biologics, ultimately translates into lost revenues for a biotech company.

CONCLUSION

Various risks are present throughout the drug development process, from the discovery of biologics to final FDA approval, to market introduction, and day-to-day sales. While the development of traditional drugs involves risks, orphan drugs and biologics commonly produced by biotechs present additional complexity with accompanying increased risks. The risk is further compounded when the developing company is small with insufficient resources and little experience with the regulatory approval process in the U.S. or abroad.

Early-stage biotech companies often lack the resources to tackle risks such as parallel trade, counterfeiting, global supply chain disruptions, and potential theft of intellectual property. Likewise, these small biotech companies may have no choice but to outsource, opening the door to drug safety concerns. They may face the risk of exclusion from preferred drug lists and other cost containment hurdles that reduce revenues. These early-stage biotech companies operate in an industry with substantial rates of litigation that could bankrupt an otherwise promising company while producing biological products with an elevated risk of safety concerns.

Whether these small firms, often with a single drug, remain independent, are acquired, or enter in partnership arrangements ultimately depends on their perceived value. Understanding the challenges and risks that face start-up and early-stage companies in the biotech industry is important to forecasting revenues and costs; and therefore, must be considered in any valuation. In this article we discussed various factors that should be evaluated and analyzed with respect to early-stage biotech companies, specifically biopharma firms. Each valuation

must be based on the facts and circumstances specifically relating to the subject company as of the valuation date. Accordingly, the factors discussed above may or may not be pertinent in every given valuation.

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From the Boardroom

Unlocking the funding challenge

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ABSTRACT

Canada plays a significant role in the global advancement of scientific discoveries and their translation into commercial opportunities, but is viewed as not fully realizing its commercial potential. A significant problem has been a lack of sufficient venture capital to take early-stage companies to the next level. Several recent developments may signal the arrival of a more positive venture-funding environment for life sciences and health technology enterprises, including the development of the Canadian government's C$400 million Venture Capital Action Plan; pharmaceutical companies electing to establish or investing in venture funds and providing strategic support to early-stage ventures, including through the creation of research centres; and recent successful liquidity events for venture investors.

Journal of Commercial Biotechnology (2014) 20(2), 59–61. doi: 10.5912/jcb649
Keywords: Canadian; venture capital

THE CHALLENGE

Canada has a wide variety of participants from the life sciences and health technology sector, including drug and medical device manufacturers and distributors and internationally top-ranked researchers, universities and teaching hospitals. In several regions the industry operates on a scale comparable to other large-scale bioclusters. However, the majority of early-stage ventures are privately owned small and medium-sized enterprises, with 50 per cent having fewer than 20 employees. These ventures face the challenge of seeking to advance complex innovations that on average take 10 to 15 years and hundreds of millions of dollars to develop. While Canada plays a significant role in the global advancement of scientific discoveries and their translation into commercial opportunities, it is not fully realizing its commercial potential. Among the problems is a lack of sufficient venture capital to take early-stage companies to the next level.

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Concerned that Canada was lagging behind other countries in business R&D spending, commercialization of new products and services, productivity and growth, in 2010 the federal government commissioned the "Jenkins Report," an independent study of innovation in Canada. The report concluded, among other things, that a history of poor returns has contributed to a lack of venture capital to fund emerging life sciences and health technology firms. It also found that although Canada tends to have adequate funding from government, not-for-profit and angel investors at the very early stages of ventures, beyond the initial few million dollars invested, companies were struggling to find additional capital.

History has played a role in the funding challenge. The enthusiasm for venture investing between the mid-1990s and the early 2000s brought a five-fold increase of capital into the venture space. As often happens when supply exceeds demand, poor investment decisions resulted in poor overall financial performance for funds and made investors far more conservative regarding future investments. These factors coupled with the recent economic downturn have made it difficult to attract venture capital to the life sciences and health technology sector during the past decade.

WHAT THE FUTURE HOLDS

Capital availability through the federal government's venture capital action plan

Several recent developments may signal the arrival of a more positive venture-funding environment for life sciences and health technology enterprises.

Following the Jenkins Report, the federal government committed to supporting Canada's venture capital industry. In January of 2013, after extensive consultations with key stakeholders to determine how best to support a sustainable, private sector-led venture capital industry, the federal government announced its Venture Capital Action Plan. The plan calls for the investment of C$400 million of government funds over seven to 10 years. The funds will be used to:

- Establish new, large, private-sector-led funds of funds in partnership with institutional and corporate investors
- Recapitalize existing large private-sector-led funds of funds
- Invest directly into existing high-performing venture capital funds

It is anticipated that these investments will attract nearly C$1 billion in new private-sector investments. The life sciences and health technology sector is already feeling the effects of this commitment.

In September 2013, the following government-funded venture funding commitments were announced:

- BDC Venture Capital, the venture capital arm of the Business Development Bank of Canada, announced that it allocated an additional C$135 million to the BDC Venture Capital Health Care Fund to be used for direct venture investments into innovative health-care technology products and services, doubling its financial commitment to the fund.
- BDC Venture Capital and Fonds de solidairité FTQ announced a C$35 million commitment to Sanderling Ventures, an investment firm with a 35-year track record of building new biomedical companies. Consequently, Sanderling is well on its way to achieving its US$250 million target for its Sanderling Ventures Fund VII and has agreed to create a permanent facility in Montréal to facilitate the development of early-stage life sciences investments.
- BDC Venture Capital announced its commitment to invest C$35 million in two Canadian life sciences venture funds, C$15 million going into the CTI Life Sciences Fund II and C$10 million going into the Lumira Fund II.

Capital provided by the pharma industry

Another growing source of venture funding and other forms of support for early-stage life sciences and health technology companies is the pharmaceutical industry. Many pharmaceutical companies have significantly reduced their internal R&D programs and farmed out the risk of drug development to start-up companies. However, faced with expiring patents on a number of significant drugs and fewer blockbuster drugs coming to market, the pharmaceutical industry's need for new products remains critical. Consequently, pharmaceutical companies have a significant interest in the success of early-stage drug companies and are taking various steps to identify and partner with or invest in strategic early-stage companies.

One tactic adopted by a number of pharmaceutical companies is establishing or investing in life sciences venture funds. For example, in 2011, GlaxoSmithKline established the C$50 million GSK Canada Life Sciences Innovation Fund. In 2012, Merck Canada committed C$35 million to the Merck Lumira Biosciences Fund and C$5 million to Lumira Capital II LP, and Eli Lilly joined Teralys Capital and others in investing in the C$150 million TVM Life Science Ventures VII fund. Each of these funds has a mandate to invest in early-stage life sciences companies.

Another approach has been to provide early-stage ventures with strategic support, including through the creation of research centres. In 2012, AstraZeneca and Pfizer Canada Inc. partnered with the Province of Quebec to create the NEOMED Institute, a life sciences research institute that acts as a bridge between academic research and the private sector. The NEOMED Institute was established with a commitment by its founders to invest C$100 million over five years. In early 2013, MaRS Innovation announced a strategic partnership with Pfizer Inc. to advance early-stage technologies. Through this collaboration, MaRS and Pfizer will identify investment opportunities to which Pfizer will provide funding over a three-year period. In late 2013, MaRS and Pfizer announced the first project to receive financial support under the collaboration. Also in late 2013, Johnson & Johnson Innovation and its Janssen unit announced collaborations with both the NEOMED Institute and MaRS Innovation.

Improving liquidity opportunities

Liquidity events for venture investors typically come in the form of a sale of shares in an initial public offering or through the sale of the business to a strategic investor. For a number of years, there seemed to be little opportunity for life sciences companies to undertake an initial public offering (IPO) or alternative "going public" event (such as acquisition by a publicly traded capital pool company or a reverse take-over). In 2013, the eleven "going public" events for life sciences companies reported by the Toronto Stock Exchange and TSX Venture Exchange was more than double the number in the prior year. In addition, this number does not take into account Canadian companies, such as Acquinox Pharmaceuticals, that elect to pursue a U.S.-only IPO. However, it is important to recognize that, while this increase represents a significant improvement over past years, it does not match the approximately five-fold increase in the number of life sciences IPOs seen in the US in 2013.

The past year also saw significant M&A activity, including the acquisition of several significant public Canadian life sciences companies, including LifeLabs Medical Laboratory Services' acquisition of CML HealthCare Inc., Patheon Inc.'s going-private transaction, Endo Health's acquisition of Paladin Labs, Emergent BioSolutions' acquisition of Cangene Corporation and many other significant acquisitions, such as Cardiome Pharma Corp's acquisition of Correvio LLC.

The example set by these successful liquidity events will play an important role in attracting further investment capital to Canadian life sciences and health-care technology industry participants.

CONCLUSION

While the question of how Canada can effectively and efficiently address the lack of adequate venture capital for life sciences and health technology companies is not fully answered, these developments appear to signal an improvement in funding and liquidity opportunities and the prospect of further improvements. With creativity, flexibility and a bit of luck, early-stage companies can access the investment capital required to take their projects to the next stage, and investors can find successful liquidity events.

From the Classroom

Bioentrepreneurship education and training (BEET) trends

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ABSTRACT

Biomedical and health entrepreneurship continues to expand around the world. Driven by global pressures to optimize the allocation of scarce resources, life science bioentrepreneurs are creating innovative products, platforms, service and systems that deliver more value. As a result, the demand for biomedical and health professional entrepreneurial talent has increased and biomedical and health innovation and entrepreneurship education and training (BEET) programs are growing to fill the gap.

This paper highlights 10 trends in bioentrepreneurship education and training.

Journal of Commercial Biotechnology (2014) 20(2), 62–63. doi: 10.5912/jcb647
Keywords: bioentrepreneurship; education

Biomedical and health entrepreneurship continues to expand around the world. Driven by global pressures to optimize the allocation of scarce resources, life science bioentrepreneurs are creating innovative products, platforms, service and systems that deliver more value. As a result, the demand for biomedical and health professional entrepreneurial talent has increased and biomedical and health innovation and entrepreneurship education and training (BEET) programs are growing to fill the gap.

However, there are still significant barriers to the growth and development of sustainable BEETs.[1]

1. They engage participants in endeavors that get short shrift on campuses: teaching and innovation. Generating clinical and grant revenue takes priority. Few campuses reward faculty or students for developing or commercializing an idea or paying them extra to teach the courses.
2. Money is tight and little is available to support these programs. They run on a shoestring and are expected to be self funded,and require uncompensated time from faculty being paid by other disciplines.
3. Biomedical entrepreneurship rests on a four legged stool that includes education, networks, experience and money. The last are difficult to create , scale and sustain.
4. Bioentrepreneurship educators have nohome. It is not yet a recognized academicdomain, there are limited places to publishpeer reviewed research and manuscripts (the *Journal of Commercial Biotechnology* is an exception), and promotion andtenure committees attribute little or no value to the enterprise.
5. By its very nature, bioentrepreneurship education is an interdisciplinary, multicampus effort with all of the bureaucratic and systems issues that engenders. There is frequently a lack of alignment of academic entities driving growth and short term money issues trump long term investments in entrepreneurship education innovation.

Despite these obstacles, enterprising educational entrepreneurs are devising ways to overcome them. Here are 10 trends that exemplify that theme:

1. Bottom up initiatives are displacing top down initiatives. Community based programs and educational offerings are displacing the requirement for university centricity. Free massive online open courses (moocs), the flipped classroom and the lean startup movement have commoditized and

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democratized entrepreneurship education. Recent examples include a free online courses on Coursera (www.coursera.com), The Harvard Business School and Udacity (www.udacity.com)

2. Community based accelerators, generators, co-working spaces and incubators are exploding, particularly in the area of digital health. While their business models are different, there are still lingering questions about their value propositions, their success rates and metrics and whether they produce products and services that are clinically validated.[2]
3. Faculty and administrators are experimenting with different structures, processes and pedagogical techniques to deliver the most value for their students. They are experimenting with flipped classroom techniques, MOOCS and much more. Some are designed for undergraduates and some for graduate students. Others offer certificates or formal degrees. Courses are either face to face, hybrid or entirely online.[3]
4. All BEET is local, depending on the culture, leadership, vision, strategy, resources and student demand. Programs reflect assets on the ground the ability of program directors, faculty and adminstrators to overcome local hurdles.
5. No two programs are exactly alike. When you've seen one program, you've basically seen one program.
6. The value or these programs are still questionable. We need long term, valid ways to measure the appropriate outcomes. Those outcomes go beyond short term economic development and technology transfer metrics. Since value creation and the life science innovation roadmap is a long and tortuous one, patents, licensing revenues and job creation don't always capture the long term value proposition.
7. Educators and administrators are trying to establish BEET as a legitimate international academic domain. Like international entrepreneurship, peer recognition will require peer reviewed research, publications, grants and other criteria imposed by the academy.
8. Most universities don't have the structure, policies or culture to launch and sustain BEET programs. They are being developed by entrepreneurial educators who believe in the mission and are getting it done despite their universities.
9. BEET educators are educational social entrepreneurs themselves who need support and recognition if they are to be successful.
10. The demand for BEET will increase, particularly as pressure to get "impact" out of research increases.

We have witnessed the birth of a new discipline, International Bioentreprneurship, in the last 5 years. In the future, we will see the continued growth and development and, hopefully, the validation of the value proposition: creating graduates with a global biomedical and health entrepreneurial mindset.[4]

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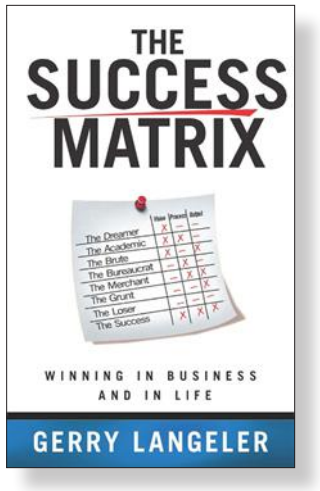

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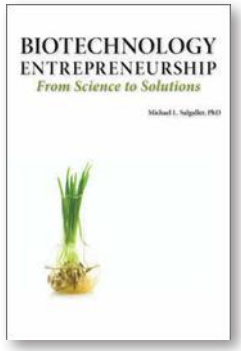

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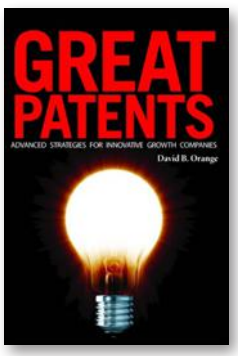

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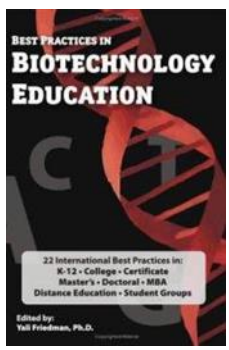

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