Journal of COMMERCIAL BIOTECHNOLOGY

JULY 2013

VOLUME 19 I NUMBER 3

ISSN: 1462-8732 / eISSN 1478-565X

WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 19 NUMBER 3 JULY 2013

Contents

Commentary

Patenting human genes and mutations: A personal perspective

Received: June 20, 2013

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

Journal of Commercial Biotechnology (2013) 19(3), 3–5. doi: 10.5912/jcb.602
Keywords: Patent; human gene; mutation

I am the beneficiary of a June 16, 1980 US Supreme Court decision in *Diamond v. Chakrabarty (447 U.S. 303, 1980)* that granted patent protection of a genetically-modified life form — in this case an oil-digesting bacterium harboring multiple hydrocarbon-degradative plasmids. It is generally accepted that this 5-4 decision significantly encouraged the development of commercial biotechnology in the United States, as demonstrated by a thriving economy, by allowing patent protection to inventions related to live microorganisms, plants, animals, cells, genes, etc, including patenting of human embryonic stem cells and human genes isolated and purified from the chromosome with demonstrated utility. 33 years later, on June 13, 2013, a very different U.S. Supreme Court in a unanimous decision held that a) isolation and purification of a naturally occurring DNA segment is not eligible for patent protection because the 'invention' is fundamentally a product of nature and b) complementary DNA (cDNA) is eligible for patent protection because it is not naturally occurring. This decision reversed a 2-1 decision by the Court of Appeals for the Federal Circuit (CAFC) that two human genes BRCA1 and BRCA2, where certain mutations and gene rearrangements promote the onset of breast and ovarian cancers, are eligible for patent protection, but deciphering the mutations was a mental exercise and therefore ineligible for patenting. The Supreme Court did not address the issue of patenting of mutations in these genes.

In contemplating these rulings, it is important to understand what the patent laws in the US represent. The patent laws are in the US Constitution (35 USC section 101) framed in 1790 with basically two goals: (i) to promote the progress of 'any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement thereof ' and (ii) to ensure that 'ingenuity should receive a liberal encouragement', as articulated by Thomas Jefferson. Indeed, the first US patent was issued on July 31, 1790, to Samuel Hopkins of the City of Philadelphia and the patent was signed by President George Washington, Secretary of State Thomas Jefferson and the Attorney General of the United States Edm. Randolph to signify and demonstrate the deep commitment of the newly-independent country to encourage innovations in science and technology, and the protection of such innovations. Further, in 1980 when the U.S. Supreme Court found my engineered life forms to be patentable, it declared boldly that 'anything under the sun that is made by man' is patent eligible in the United States (447 US 303, 1980), provided such invention meets the statutory requirements of novelty (35 USC section 102), non-obviousness (section 103), detailed description for enablement (section 112) and utility (section 101 and 112), and according to the 2001 January affirmation of the US Patent & Trademark Office (US PTO), the utility should be specific, substantial and credible.

The fact that the early patents, including the first patent granted on July 31, 1790, were signed by the President of the United States, the Secretary of State and the Attorney General, demonstrates the deep commitment the framers of the US Constitution had in promoting and protecting through the patent system innovations in new and useful process, machine, manufacture or composition of matter. The two key words were that such innovations must be new and useful. While the Supreme Court dealt with the novelty issue in *Association for Molecular Pathology, et al., v. Myriad Genetics, Inc., et al* (No. 12-398), finding that simple isolation and purification of the BRCA genes from their neighboring sequences on the two chromosomes did not constitute patent-eligible

Correspondence: Ananda Mohan Chakrabarty, University of Illinois at Chicago, US. E-mail: pseudomo@uic.edu

invention, it did not address the issue of the utility of such genes. Since thousands of isolated and purified genes from various sources have been patented, it is hard to revoke all such patents by simply saying that such procedures do not involve any inventive steps. Much efforts over the years were spent just to localize the two genes that were believed to be tumor suppressor genes and where specific mutations led to a loss of this tumor suppressing activity of breast and ovarian cancer. A much better scientific rationale would have been to reject patent eligibility because of a lack of demonstrated utility of the isolated and purified BRCA1 and BRCA2 genes, as we have argued recently (1, 2). Myriad Genetics' patent claims on these two genes center on the use of such genes as wild type reference genes against which mutant genes from various sources can be compared to locate the mutations. While locating and identifying the mutations, which are central to the determination of cancer susceptibility, are the essence of seeking patent protection, it is hard to see how a reference gene can have such protection. A simple example will illustrate this. Imagine that an agricultural biotechnology company developed a new variety of roses by introducing a bacterial gene that improves both color and the fragrance of the rose, and that they seek patent not only for the genetically modified rose but also for patent protection of garden-variety roses against which the genetically modified rose was compared to determine its improved color and fragrance. It would obviously be unacceptable to allow patenting of the reference garden variety roses along with the genetically modified roses, indicating why a reference wild type BRCA gene should not be patent eligible. On the other hand, isolation and purification of a gene such as the human insulin gene, which was patented in the 1980s, is of great utility since such a gene can be expressed in *Escherichia coli* under appropriate promoters to bulk-produce human insulin for the treatment of diabetes. Bacterial expression of a purified human gene, which can be expressed to produce a product of great medical importance that was not previously available, makes an exceptionally strong case for patent eligibility of such a gene.

An important question not addressed by the Court was the question of the patent eligibility of BRCA1 and BRCA2 gene mutations. The importance of these mutations is that women with family history of breast or ovarian cancer can seek genetic testing to identify if they have mutations in these genes, and if they test positive for the mutations, they can take measures to prevent the onset of breast cancer. Thus a combination of isolation, purification and sequence comparison of BRCA1 and BRCA2 genes for the delineation of cancer-inducing mutations should be patent eligible, even though the CAFC ruled against the patent eligibility of such mutations as sheer mental exercises. It is important to note that there is Supreme Court precedent for allowing patentability of mental exercises when such exercises are tied to a useful invention, as follows from *Diamond v. Diehr, 450 US 175 (1981*), holding that application of the Arrhenius equation to a process of the determination of optimum curing of rubber as patent eligible under 35 USC 101.

The immediate impact of the Supreme Court decision on *AMP et al., v. Myriad Genetics*, *Inc. et al.,* coupled to the Court's March, 2012 unanimous decision on *Mayo Collaborative Services v. Prometheus Laboratories* denying patent protection of diagnostic dosing of drugs, will likely be in the arena of diagnostic test development and personalized medicine. A significant segment of biotechnology industry that relies on deciphering genetic changes and modifications in the DNA isolated from the chromosomes and not involving cDNA will be affected. An interesting outcome of this decision may also involve patent eligibility considerations of many natural products such as antibiotics or drugs developed from medicinal plants with great usefulness in combating disease. Since such patented products simply represent isolation and purification of the same naturally-occurring product, will their patent protection be in jeopardy because of this ruling?

Finally, the question of the patent eligibility of BRCA1 and BRCA2 mutations aside, an important question is what does a woman, particularly a young woman of child-bearing age but with a family history of breast or ovarian cancer, do when tested positive for mutations in these genes? One option is to remain vigilant, looking for early signs of cancer (2). An increasingly common, but a dreaded and traumatic option, is to surgically remove the breasts and the ovary. Unfortunately, current anticancer drugs have not only significant toxicity but they are also amenable to resistance development and have limited cancer preventive ability. What is sorely needed is a drug that not only exhibits very little toxicity but should have cancer therapeutic activity to interfere in multiple pathways through which cancer cells grow so as to minimize resistance development. Ideally, if such a drug exhibits cancer preventive activity, then the drug can be taken on a long term basis to evaluate its ability to prevent the onset of breast/ovarian cancer in vulnerable women. While no such drug currently exists because of the pharmaceutical industry's dependence on rationally-designed small molecule compounds, there appears to be on the horizon the emergence of protein/peptide drugs with low toxicity and both cancer therapeutic and preventive activities (1, 3). These protein/peptide drugs are of bacterial origin and certain pathogenic bacteria have been known for over hundred years to combat cancers. Some accelerated efforts to develop the new kinds of drugs with no toxicity but significant therapeutic and

cancer preventive activity are urgently needed now to help eradicate cancer in our lifetime.

REFERENCES

1. Fialho, A.M. and Chakrabarty, A.M. (2012) Patent controversies and court cases: cancer diagnosis, therapy and prevention. *Cancer Biol. Therap.* 13: 1229-1234.
2. Chakrabarty, A.M. (2013) Patenting of genes and mutations: recent US Supreme Court cases. Science in the Courtroom, 1: 000-000 (in press).
3. Chakrabarty, A.M. (2012) Bacterial proteins: a new class of cancer therapeutics. *J. Comm. Biotechnol.* 18: 4-10.

Commentary

The polyvalent scientist: The added value of management training

Received: February 6, 2013

Maria Theodosiou
is Junior Lecturer in the Department of Management of Technology & Strategy at the Grenoble Ecole de Management

Arsia Amir-Aslani
is Program Director in the Department of Management of Technology & Strategy at the Grenoble Ecole de Management.

ABSTRACT

The PhD is becoming more and more prevalent as a degree. However, PhD students are not adequately prepared for careers outside academia and most of them have trouble translating their skills to the job market. The biotech sector is a science-driven industry that is now mature and flourishing and requires business leaders that are technically trained. But technical skills are only a partial requirement, with in-depth industry education and knowledge being equally important. There is an inherent advantage to pursuing a PhD alongside education in management in the form of an advanced/professional master's degree. This will allow PhDs to explore alternative careers outside academia.

Journal of Commercial Biotechnology (2013) 19(3), 6–9. doi: 10.5912/jcb.602
Keywords: PhD; professional master's; dual skills

In most countries, the PhD is a prerequisite for an academic career. Although upon completion, all PhDs are considered equivalent regardless of subject area and where it was obtained, not all PhD holders have the same body of knowledge in terms of curriculum or experience in terms of communication skills in presenting their work.

The PhD became more prevalent as a result of the expansion of higher education demands following World War II. American universities were the first to respond to these needs and by 1970 half of the world's science and technology PhDs were educated in the US, a number that has doubled since then[1]. The number of PhDs awarded is increasing worldwide with 40% more PhDs accorded by OECD (Organization for Economic Co-operation and Development) countries between 1998 and 2006, whereas in Japan, there is an increase of 46% in awarded PhDs despite a shrinking youth population[1]. It can be argued that an increase in the number of PhD holders will lead to increased innovation, with the counterargument being that unchecked growth will lead to dilution of the quality of the PhD degree. While the debate is unresolved, it is undeniable that PhD students and postdocs are serving a function. Most of the research that takes place in universities is carried out by pre- and post-docs, thus boosting the research capabilities of universities and by extension, of countries.

More importantly, the increase in the number of PhD holders does not correspond to the needs of the job market. Although the PhD is a prerequisite for an academic career, recruitment of students does not match the academic job market. At the same time, business leaders are complaining that there is a shortage of high-level skills, suggesting that there is a void that could be indeed be filled with PhDs — if only they were taught the right skills.

It cannot be denied that PhDs are having trouble translating their skills to the job market, and the funding agencies behind the explosion in PhD conferment, are beginning to take notice. As a result, training in soft skills such as communication and teamwork is beginning to be offered as part of the curriculum in some universities[1]. In addition, government agencies such as the National Science Foundation are beginning to fund interdisciplinary programs such as the IGERT (Integrative Graduate Education and Research Traineeship) which are aimed at helping students gain career skills and tackle real world problems[2].

Correspondence: Arsia Amir-Aslani, Grenoble Ecole de Management, France. E-mail: arsia.amir-aslani@grenoble-em.com

Is the PhD in crisis? Or is the crisis still to come? One thing that is for certain is that the demands of the labor market are not being considered in this issue. Increased governmental spending is driving the increasing numbers of doctoral and postdoctoral students without any consideration as to how the labor market will accommodate the growing supply of PhDs. Case in point: 55% of US doctorates in the biological sciences secured a tenure track position within six years of PhD conferment in 1973, with only 2% in postdoctoral or other untenured positions[3]. In contrast, in 2006, only 15% were able to secure a tenure track position within six years with 18% in untenured positions[3]. This suggests that more and more PhDs are occupied in non-academic positions that may not require a PhD.

What lies at the source of the PhD glut? The academic job market collapsed in the 1970s, yet the rate of graduate school admissions has not changed to reflect this[4]. In the late 1980s, the notion that a wave of retirement of Korea vets was about to sweep through academia leading to bright prospects for young PhDs was spread[5]. Newly minted PhDs in the 2000s faced similar bright prospects with the expected retirement wave of baby boomers. In reality, these retirement waves were not observed and therefore had no impact on the academic job market. Adding to the problem is that PhDs enter the job market with no guidance as to how to find employment outside academia. Universities are producing more and more PhDs that cannot be absorbed in tenure positions. Fortunately, academia is not the only employer for PhDs who can be gainfully employed in industry, banks, government or non-profit organizations[5]. Most scientists find out the hard way that the years spent at the bench performing blotting, mini-preps or microscopy, is not the most appropriate way to become an investment banker, a market researcher, business developer or any other of the wealth of career options that exist for PhDs outside academia. Young scientists need to be aware of these career opportunities and to have the ability to acquire the necessary skills to be competitive for alternate careers.

While it can be argued that the mission of academic institutions is to provide knowledge and key skills and that it is up to the individual student to apply them as they see fit, what cannot be argued with is the current need for broader training. There are skills beyond the bench that scientists today need to develop in order to be successful. In science PhD programs, there is currently an overemphasis on the academic track, while at the same time alternate career paths are devalued[5]. Providing PhDs with tools for a wide range of careers would not necessitate a program overhaul while at the same time it can serve to alert students to alternate career options early on and prevent the disillusionment that a lot of graduate students feel at some point in their career to set in.

Why do governments continue to pour money into financing advanced science education when the job market is saturated? There are motives behind this spending. While all professionals can create jobs, science and engineering PhDs have the potential to create entire industries thus having a significant impact on the economy, and thereby justifying the investment of government funds into education. Biotechnology is such an industry where scientific advances and discoveries are poised to impact the business world. Some of the early biotechnology companies have benefitted from having science leaders with business vision. Before the emergence of biotechnology, scientists did not do business and businessmen did not do science. The ability to understand both is vital for the success of this sector. The capacity to innovate in an industry such as biotechnology, hinges not only on scientific discovery but also on the ability to translate new knowledge into products and services[6]. Success in the biotechnology sector is dependent on the effective information flow between scientists and non-scientists, in order to maximally capitalize the potential of the science[7].

Current PhD curricula are ill suited for industry careers, where the majority of employment opportunities are. The needs of industry and academia are not comparable-while both require scientific literacy, industry wants employees with business acumen[7]. In today's technology enhanced marketplace, venture capital firms, investment banks and consulting firms are desperately seeking candidates with dual expertise. They judge candidates on their scientific, as well as their business skills. Moreover, business skills are also an asset in the public sector, as decreased government funding requires scientists to secure external funding for their research. Management skills allow scientists to properly value R&D projects, identify licensing opportunities and negotiate partnerships with prospective industrial partners.

The specificity and complexity of the life sciences environment requires both scientific and management skills. To fill this need, advanced (professional) master degrees have been established. The foundation of this degree is being compared to the creation of the MBA degree in 1908[8]. Advanced master's degrees are specifically tailored to scientists, providing them with multidisciplinary training in areas such as management, finance, marketing, intellectual property, competitive intelligence, and business development to name but a few, in order to give scientists a working knowledge of the business aspects of science. In addition, skills such as communication which are essential for any career are also cultivated as part of such programs. Industry experts are quite supportive of

such professional programs that are driven by the needs of the market and prepare students for nonacademic work[8]. Advanced master's degrees are interdisciplinary and provide hands-on learning through case studies, team projects and internships, the goal being, to adequately prepare students to be competitive in today's labor market[6]. Thus, a niche market exists for professional master's graduates who thanks to their training can wear multiple hats within the same company filling various roles, something that is especially important in the context of start-ups and small companies where capital is lacking but need is overabundant.

Helping the trend for such advanced master's degrees are industry demands for dual skills. While the original idea behind the advanced master's degree was to provide an alternative to the PhD by being specifically tailored towards careers in business and industry, the two degrees are not incompatible. Academic programs aimed to create individuals with skills in both business and science are of the utmost importance as this new generation of professionals can grow and manage science and technology based industries contributing to the global economy. Dual degree graduates are able to analyze and appreciate relationships between technology and productivity along the value chain of an organization within the context of a dynamic and uncertain environment while at the same time mastering the complex interactions of organizational purpose, scientific process and people leadership that generates competitive advantage for the company. The advanced master curriculum encompasses essential skills for the successful manager and an overview of the vast body of knowledge that is unique to the life sciences industry. This, combined with the scientific knowledge acquired during the PhD, allows for a deeper understanding of the complexities of technology management.

In light of the advantages presented by having skills in science and in management, and given the current marketability of PhD graduates that do not wish to stay in academia, there is an inherent advantage in pursuing the advanced master and PhD degrees concurrently. The primary appeal in pursuing the degrees concurrently would be in the interest of time, as well as being a cost saver. In the dual degree program, the required courses for the advanced master are taken concurrently with the required courses for the biological sciences PhD. In such case, the courses for the advanced master can be spread over the same time period as for the PhD (three years in Europe), while the professional thesis required for the advanced master degree can be completed either before or at the same time as the PhD thesis. The students can take advantage of online learning platforms, managing their own time and learning pace while simultaneously striving for their PhD. The curriculum is designed to provide students in the life sciences with a strong foundation in business concepts where students not only develop the necessary skills to become effective managers but also the vision to become leaders in their fields.

A concurrent dual degree program offers the fastest way to gain a professional and scientific qualification, bringing together academic knowledge and practical skills, which are highly valued in the business world. Students with this unique qualification will be able to "speak" the same language as senior managers, bankers, investors and consultants. As far as career opportunities are concerned, the dual degree affords the possibility to embrace novel career options through the ability to understand the relationships between science, technology, financial resources and customer value. As future leaders, dual degree graduates should be prepared to challenge the conventional assumptions and paradigms while actively seeking new technologies and strategies to strengthen the value creating and competitive processes within their organizations.

The industry focused curriculum and practical teaching approaches of basic management principles and business disciplines are some of the merits of a dual degree. In addition the students learn to think analytically, be proactive decision makers and efficient problem solvers, skills that are necessary in the business world where the stakes are high and the room for error is small.

Undeniably the mushrooming of professional master's degrees is an indication of the need of such skills in the marketplace. In the current economic environment skills must be continuously acquired and developed in order to remain competitive. Pursuing an advanced master/PhD degree is the ultimate way to equip students for multidisciplinary careers in either industry or academia and cultivate both their scientific curiosity and entrepreneurial spirit. There is no denying that a niche market exists for dual skilled scientists, who, thanks to their management training can wear multiple hats within the same company filling various roles, which is especially important for start-ups and small companies where capital is lacking but need is overabundant. Dual skills are also important in the context of project management and bringing a product to market. When businessmen lead science-based companies there is often a misunderstanding of expectations and timetables, resulting in the abandonment of promising projects. Scientists with business knowledge are able to bridge the communication gap and thereby promote common understanding and communication. Dual degree holders are able to see the big picture of a project; thanks to their science knowledge they can evaluate a project for scientific merit while thanks to their business skills they are able to assess the market potential of the technology/product.

REFERENCES

1. Anonymous (2010) Doctoral degrees: the disposable academic. *The Economist*.
2. McCook A (2011) Education: Rethinking PhDs. *Nature* 472(7343):280-282.
3. Cyranoski D, Gilbert N, Ledford H, Nayar A, & Yahia M (2011) Education: The PhD factory. *Nature* 472(7343):276-279.
4. Taylor M (2011) Reform the PhD system or close it down. *Nature* 472(7343):261.
5. Fiske P (2011) What is a PhD really worth? *Nature* 472:381.
6. Colwell RR (2009) Professional science Master's programs merit wider support. *Science* 323:1676-1677.
7. Hubbard KA (2005) Help wanted: science manager. *PLoS Biol* 3(1):e32.
8. Jensen MN (1999) Reinventing the Science Masters Degree. *Science*:1610-1611.

Original Article

A role for virtual biotechnology companies in drug discovery and development?

Received: March 21, 2013; Revised June 8, 2013

Dianne Nicol
is Professor of Law at the University of Tasmania, Australia.

Johnathon Liddicoat
is Research Fellow at the Faculty of Law, University of Tasmania, Australia..

Christine Critchley
is Associate Professor, Faculty of Life and Social Sciences, Swinburne University, Australia.

ABSTRACT

The orthodox business model of many drug discovery and development companies centres on adding value to early-stage discoveries prior to engaging with large pharmaceutical companies to bring products to market. Anecdotal observations suggest some companies are moving to a 'virtual' business model — instead of employing in-house scientists, a skeletal management team runs the company and out-sources all research and development. This article presents a novel method to determine whether companies are virtual, based on author bylines in peer-reviewed journal articles.

Applying this method to Australian companies in this sector, the size of the cohort identified as virtual was much larger than anticipated, around 52%. The accuracy of this method has been verified statistically using interview data. This article discusses the value and limitations of this method, positing that it can be used to analyse industry and policy implications that may result from widespread adoption of the virtual model

Journal of Commercial Biotechnology (2013) 19(3), 10–19. doi: 10.5912/jcb.611
Keywords: drug discovery; business models; virtual companies

INTRODUCTION

The drug discovery and development industry sector has the laudable goal of developing new market-viable therapeutics to alleviate human suffering caused by ill-health. Challenges encountered by participants in this sector on the road to market are many and varied, and include:

- the duration and expense of the clinical trials that are required to be undertaken to satisfy regulatory obligations, together with the need to secure long-term funding;
- the cumulative nature of innovation in the field and the need for deep and broad expertise; and
- the competing intellectual property claims at all stages of the innovation cycle.

For many years, the pharmaceutical sector successfully used the vertical integration model for drug discovery and development.[2] However, since the emergence of the biotechnology industry in the 1970s many large pharmaceutical firms have moved away from full integration, preferring instead to source many drug candidates only after small to medium sized biotechnology companies have taken them through pre-clinical and/or early-stage clinical trials.[2,3]

The virtual model for drug discovery and development is a further step away from vertical integration. The hallmark of the virtual model in life sciences

Correspondence: Dianne Nicol, University of Tanmania, Australia. Email: Dianne.Nicol@utas.edu.au

is that both research and development are outsourced using "fee-for-service" arrangements, at times using overseas contractors to increase capital efficiency. Use of these fee-for-service arrangements results in a situation where no "wet science" is conducted by company employees. The use of contract research organisations (CROs) for human clinical trials has been a standard mode since the 1980s.[14] Pre-clinical research and development has been reported to be a rapidly expanding business, and for some CROs it has become their primary focus.[8] What is less clear is the level of the adoption of the virtual business model by drug discovery and development companies.

The broad economic viability of the virtual business model has been subject to some analysis.[10] There is also some limited evidence to suggest that this model is gaining in popularity in biotechnology,[6,8] although no quantitative measures have yet been developed. Commentary to date predominantly focuses on the organisational structure and success of individual companies,[13] rather than sector or policy level analysis.

The rationale for the study reported in this article is to measure the extent to which the virtual business model is being adopted across the drug discovery and development sector. This article reports on a novel method to measure the relative proportions of virtual and non-virtual biotechnology companies in drug discovery and development in Australia. It argues that the methodology described below may have broader application in segregating virtual and non-virtual firms involved in drug discovery and development and in other life science sectors in Australia and elsewhere.

An understanding of the types of business models being adopted in the life sciences assists in further analysis of the factors that influence successful development of innovative new drugs and questions relating to the long-term viability of the industry. Together, analyses of this nature can provide indicators of success and impediments to success in the drug discovery and development sector for input into evidence-based business decisions and regulatory reform.

The study reported in this article is part of a broader analysis of the intellectual property and product development landscape in the Australian biotechnology industry. To give some context, although many large international pharmaceutical companies operate in Australia, none are Australian. Rather, Australian drug discovery and development companies are almost exclusively small to medium in size. The sector includes private, public unlisted and public listed companies. Many, but not all originated as spin outs from public sector organisations.[20]

Given that biotechnology industry participants in Australia and elsewhere are required to operate within an environment of diverse knowledge sources and complex intellectual property landscapes, this research project is aimed at testing whether they are generally able to work around impediments, take advantage of opportunities for collaboration and access the necessary intellectual property and other information and materials to innovate. The project as a whole includes analysis of: patent law; patent and company databases; inventor surveys; stock exchange disclosures and product-related data; and interviews with industry participants. Twenty-three interviews have been conducted during the course of the project with senior management personnel from companies that were operational between 2010-2011 and had originated clinical trials for new human drugs in the past 10 years. Three interviews were conducted face-to-face, the rest were via telephone. Interviews were carried out between 24 November 2010 and 16 June 2011. All were of around one hour duration.

Relevant companies were identified for interview using *Pharmaprojects*, Informa UK Ltd's proprietary database of drug discovery and development companies in Australia. An assessment of each of the companies was subsequently undertaken using publicly available information to ensure they still operated and confirm that they had originated clinical trials for new human drugs. In total, 44 companies were identified that fitted the criteria. All were contacted and 23 agreed to be interviewed, giving a success rate of 52%. There were no obvious differences in terms of firm type, size (by research and development expenditure over 5 years, where available), age or research focus between the interviewed and non-interviewed cohorts (Table 1). Drug discovery and development companies in Australia have diverse pipelines. Indications vary from the flu and immune disorders to pain management. However, cancer therapies are the most common, featuring in 13 of the 23 companies interviewed.

Business developers, CEOs, in-house counsel and/or intellectual property managers were interviewed. Before each interview, a detailed analysis was undertaken of publicly available information about the company, including annual reports, news releases and other documentation provided on company websites, stock exchanges, patent data and reports in trade journals. The interviews were primarily focused on relationships that are formed between firms and other organisations during drug discovery and development; referred to elsewhere as exploration and exploitation alliances.[16] The particular focus for inquiry centred on the influence of intellectual property in these relationships.

There were seven key points for discussion during the interviews:

Table 1: Interviewed and non-interviewed cohorts and company characteristics

	Age				R&D Spend ($million)				Public Listing		
	Median Age	Mann-Whitney U-Test	z-value	Asymp. Sig (2-tailed)	Median R&D Spend	Mann-Whitney U-Test	z-value	Asymp. Sig (2-tailed)	n (listed)	X^2-value	Exact Sig. (2-tailed)
Interviewed sample (n=23)	11	172	–1.641	.101	17.99	226.5	–.356	.722	16	.018	1
Non-interviewed sample (n=21)	10	-	-	-	20.56	-	-	-	15	-	-

Note. None of the t-values were significant at $p < .05$.

1. the company's approach to product development;
2. the role of patents in product development;
3. the role of collaboration in product development;
4. the relationship between patents and more complex forms of collaboration (beyond bare IP licensing);
5. the challenges involved in establishing and maintaining patents and collaborations;
6. the causes of product success and failure; and
7. attitudes towards more formalized collaborations (e.g. patent pools).

The virtual business model became interesting to investigate further because 11 of the 23 interviewees voluntarily identified it as the preferred management strategy for their firm, with another three describing their company as "moving in that direction". Recognising that there is already a small body of literature reporting uptake of the virtual model in biotechnology,[6,8,13] it was not expected that the model might be utilised by such a large percentage of the interview cohort (close to 50 percent). Consequently, it became interesting to further explore the uptake of the virtual model.

Interviews are a time consuming way to elucidate the business models utilised by companies, and are dependent on willingness to participate. There are a number of other methods that might be utilised to determine whether drug discovery companies are virtual. These include: analysis of disclosures in annual reports or other publicly accessible information that relates to business models, number of employees and/or external and internal research budgets. However, in Australia and many other countries such specific disclosures are often ambiguous and not necessarily mandatory, particularly for smaller companies. By contrast, the method relied upon in the present study is designed to be generally applicable, irrespective of type of company or the jurisdiction in which it primarily operates.

The central hypothesis around which this study is built is that, since virtual companies do not have their own laboratory scientists or facilities but rather rely upon external services, employees of virtual companies do not conduct the wet-lab work included in scientific papers. If this hypothesis is correct, and employees from virtual companies do not conduct wet-lab work, and employees of non-virtual companies do continue to publish, a search for company names in the bylines of authors listed in scientific publications should enable the identification of virtual companies.

METHODS

To test the hypothesis that employees of virtual companies do not publish, Thomson Reuters' Web of Science was searched for company names (including previous company names listed by the Australian Securities and Investments Commission) for each of the cohort of 23 companies that were interviewed in this study and each of the cohort of 21 companies that were not interviewed. Peer-reviewed publications were searched within the five-year period 2006-2010. This period was chosen because interviewees reported that some companies identified as virtual in interviews had moved to a virtual model within the last five years and this analysis is designed to capture companies that are currently virtual. Web of Science was chosen over other publication databases because it is comprehensive, allows author affiliations to be specifically searched, and is easy to use.

Taking into account long-accepted norms for order of authorship in scientific publications,[15] peer-reviewed publications with five or more authors were not ascribed to the company unless at least one of the first two authors was identified as being associated with the company. In the case of four authors or less, publications were credited to the company when the first author's byline included the company. The rationale for using only the first author when there were four or less authors, and the first two authors when there were five or more authors is based on anecdotes and empirical observations. Scientific papers generally feature multiple authors, with the authors listed first having completed the bulk of the laboratory experimentation. The authors that are listed last on biomedical publications are generally the laboratory/institution heads who oversee the project.[18] These last author bylines were not included in the analysis because the focus was on the conduct of the wet-lab itself, not research management. Indeed, during data collection, six companies that were identified as virtual through interviews had authors in peer-reviewed papers listed later than those counted for the purposes of this hypothesis. Moreover, it is not unusual for a lab head to have a position in a private organisation and to continue academic research.

Presentations were not included, nor were publications that were not peer-reviewed. The rationale for this decision to focus solely on peer-reviewed publications was that until research results have been subjected to the level of scrutiny that is accepted by the research community they remain non-validated. Although non-peer reviewed publications including government reports and books are recognised as useful research outputs in other areas of research, they do not carry the same weight in this context as peer-reviewed publications.

Table 2: Frequencies and expected frequencies (in brackets) for actual business model and publications in interviewed sample

Type of company	Publications		Total
	No	Yes	
Not Virtual	2 (6.3)	10 (5.7)	12
Virtual	10 (5.7)	1 (5.3)	11
Total	12	11	23

RESULTS

Using the publication-based assessment of virtual/non-virtual companies it was found that 20 of the 23 companies in the interview dataset (87%) were correctly identified from publications as virtual or non-virtual. Of the 11 companies identified as virtual in interviews, 10 had no publications and of the 12 companies identified as non-virtual, 2 had no publications (see Table 2).

To account for the small sample size, a number of non-parametric tests were calculated using SPSS Version 19 to compare publication status across company type (i.e., virtual, non-virtual). Specifically, exact and Monte Carlo (with a 99% confidence limit and 10,000 samples) significance tests were used to adjust for the small sample size, with all p value consistently less than .001 (see Table 3). This demonstrates a significant and strong association between a company's publications and their business model (i.e, virtual or non-virtual). The magnitude (i.e., –.742) of the Kappa statistic indicates strong agreement between adoption of a virtual business model and an absence of publications (and vice-versa). The data therefore suggests that there are good grounds for using publications as a proxy for identification of a company's business model.

Of the cohort of 21 companies that were not interviewed, it was found that 9 of these were included in relevant author bylines in peer-reviewed publications in the relevant timeframe, and 12 were not. For ease of explanation these two cohorts are reported as having virtual by proxy and non-virtual by proxy business models, respectively. Taken together, this means that by applying the methodology as a predictor of business model type, 23 out of the entire population of 44 companies (52%) have adopted the virtual business model.

It is plausible that other firm characteristics such as age or whether the company is publicly listed will also be associated with a firm's choice of business model. The first of these two propositions were examined by comparing

Table 3: Chi-square and symmetric test statistics for the relationship between business models and relevant publications in interviewed sample (n=23)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Std. Error	Approx T	Approx Sig.	Monte Carlo Sig.	Lower bound (99%)	Upper bound (99%)
Pearson Chi-Square	12.677	1	.000	.001	.001	-	-	-	-	-	-
Kappa	–.742	-	-	-	-	.138	–3.561	.000	.001	.000	.001
Phi	–.742	-	-	-	-	-	-	.000	.001	.000	.001
Cramer's V	.742	-	-	-	-	-	-	.000	.001	.000	.001
Contingency Coefficient	.596	-	-	-	-	-	-	.000	.001	.000	.001

Note. All standardised adjusted residuals were significant at p<.001.

median ages of the virtual and non-virtual cohorts in the interview sample (n = 23), the virtual by proxy and non-virtual by proxy cohorts in the non-interviewed sample (n = 21), and the whole sample (n = 44) using Mann-Whitney U Tests. The results of these analyses show that while the median age of non-virtual companies in each sample was slightly older than virtual companies, this was not significantly so (Table 4). Whether public listing was associated with a company's actual (from the interviewed sample) and predicted (based on publications as proxies in the non-interviewed sample) business model was also explored through chi-square tests and symmetry tests. Again, no statistically significant relationships were found (Table 5). The relationship between business model and R&D expenditure was not analysed because it is not possible to get a complete dataset as there is no requirement that non-listed companies disclose such information.

DISCUSSION

The methodology adopted in this study of using author bylines in peer-reviewed journal articles as proxies for companies that conduct research in-house suggests that that over half of Australian biotechnology companies involved in drug discovery and development use the virtual business model.

Measuring propensity to adopt the virtual model

The observation that some companies operating in the drug discovery and development sector have adopted a virtual model is not of itself novel. Genentech, Inc, which is one of the world's most successful biomedical drug discovery and development companies, was virtual from its inception in 1976 through to 1978. Professor Herbert Boyer, one of the company's founders, initially consulted from his university position, only later joining the company and establishing in-house wet labs.[1] Moreover, it has been known for some time that companies involved in drug discovery and development can exist anywhere along a spectrum from fully integrated at one end to virtual at the other.[2] As noted previously, what was unexpected here was the sheer number of companies located at the virtual end of the spectrum. There is only one other study that provides a similar estimate of virtual companies in this sector, Kamuriwo reported that 40% of UK drug discovery and development companies were virtual, but this was from a non-random sample.[13]

Table 4: Mann-Whitney U-Test for median company age in years and actual business models (from the interviewed sample) and proxy business models (from the non-interviewed sample)

	n		Median		Mann-Whitney U-Test		
	Virtual	Non-virtual	Virtual	Non-virtual	Mann-Whitney U Value	z-value	Exact Sig. (2-tailed)
Interviewed sample (n=23)	11	12	10	14	52	6.82	.384
Non-interviewed sample (using business model proxy; n=21)	12	9	9.5	12	44.5	–.679	.508
Whole population (using actual business model and proxy; n=44)	23	21	10	12.5	178	–1.499	.134

Note. None of the t-values were significant at $p < .05$.

It is recognised that the method of using bylines of authors as a proxy for business models will need to be further tested. While it seems logical that age and public listing could also be associated with choice of business model, no statistically significant relationship was observed. However, there is some suggestion in Table 4 that the non-virtual cohort as a whole is slightly older than the virtual cohort, and in Table 5 that more of the non-virtual cohort than the virtual cohort tend to be publicly listed. It is possible that a relationship may be observed between choice of business model and age and/or public listing in a larger population. However, the data suggest that the association is unlikely to be as strong as that between business model and publications.

A simple reason why one might expect to see more virtual companies in the younger, private cohort and more non-virtual companies in the older, public cohort is the prediction that the virtual model has only recently been adopted. Three interviewees from virtual companies stated that their company began with an active in-house R&D program but due to financial vicissitudes of the industry the virtual model turned out to be the most cash efficient structure for the company to adopt; this finding has been reported elsewhere in the literature.[8,21] Two interviewees, as well as other literature also suggest that high uptake of the virtual model by drug discovery and development companies is quite a recent phenomenon.[6,8] However, further empirical analysis is needed to evaluate whether this is true or not.

Another reason why the virtual and non-virtual cohorts might differ is to do with the expected longevity of virtual companies: several of the interviewees reported that the exit strategy of some virtual companies is to be taken over within a ten-year timeframe. Interviewees from a number of virtual companies reported that if they were able to exit projects by sale, take over or out-license, they would simply identify a new project and start again. Others said that their company structure was virtual from the beginning, and, for some, that they had no intention to establish an in-house research and development program at any stage of the company's development. While each of these firms continues to develop their own leads, they do so with a skeleton management structure and a very tight and regulated development plan with clearly defined exit points. In contrast, it is suggested that non-virtual firms with significant investment in infrastructure and employees are less likely to have a takeover in mind as their main exit strategy. Whether the combination of age and other firm characteristics is a better proxy for business model than publications alone remains to be explored.

Policy considerations

What is possibly the most significant policy consideration is whether, from a broader industry perspective, virtual companies facilitate more efficient and efficacious development of new drugs. Questions are already being asked about the sustainability of the business model of research-intensive biotechnology firms, which, more often than not, involves licensing-out core patented technology.[2,11] The primary role played by small biotechnology firms might be described broadly as: identifying new technologies and new leads in the public sector; value adding; on-licensing or on-selling; and moving on to develop new discoveries. From the interviews, this "value adding and moving on" role seems to be a realistic appraisal of the part played by small to medium sized biotechnology firms in the Australian drug discovery and development sector. In some instances, where the company is taken over, "moving on" will involve the entire management moving on to a new company. In other instances, where the company remains viable, it

Table 5: Chi-square and symmetric test statistics for business model and public listing in the whole population of companies (n=44)

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Asymp. Std. Error	Approx T	Approx Sig.	Monte Carlo Sig.	Lower bound (99%)	Upper bound (99%)
Pearson Chi-Square	2.127	1	.145	.194	.130	-	-	-	-	-	-
Kappa	.197	-	-	-	-	.131	1.458	.145	.192	.182	.202
Phi	.220	-	-	-	-	-	-	.145	.192	.182	.202
Cramer's V	.220	-	-	-	-	-	-	.145	.192	.182	.202
Contingency Coefficient	.215	-	-	-	-	-	-	.145	.192	.182	.202

Note. None of the t-values were significant at p<.05.

will involve moving on to develop new lead products. Anecdotal communications with other researchers in this area suggested that these approaches are not unique to Australia but universal for small to medium drug discovery and development companies around the world.

Other empirical research indicates that in the context of drug discovery and development, compounds taken through clinical trials by biotechnology companies are more likely to fail than those developed by large pharmaceutical companies.[7,19] These studies also suggest that compounds developed by small, research-intensive firms have a high likelihood of failure at some stage, whether before or after successful dissemination of their core technology to larger pharmaceutical firms.

Quite how the virtual biotechnology firm fits into the equation is presently unclear. In the study reported in this article, many of the interviewees from virtual companies expressed optimism about the potential for their firm to make a genuine contribution to the development of innovative new drugs. However, interviewees from non-virtual companies were less confident about the success of the virtual model on the basis that scientific expertise is needed in-house to make informed decisions about strategies for product development. The sanguine responses from virtual company executives seems to imply that, at least for the virtual companies interviewed, the virtual model is currently working, in that they have been able to attract interest from large pharmaceutical companies, engage in out-licensing and progress their lead candidates. It is anticipated that application of the methodology presented in this article may assist further quantitative analysis of various metrics for successful product development within a larger population.

While it seems that the virtual model has been adopted by over half of the small Australian biotechnology companies in Australia, it remains to be seen whether it is sustainable in the long term. One challenge that has been identified in the literature is the need to recruit proficient project leaders,[8] which may be a particular problem in Australia given the shortage of expertise reported by interviewees. Nevertheless, it has been asserted that the virtual model will remain a feature of the biotechnology sector because it "cannot afford to continue with capital-inefficient, vertically integrated structures".[8] It is tempting to suggest that business innovations of this nature have answered the call for new drug discovery and development business models,[12] but time will tell whether they are ultimately successful in increasing the flow of innovative new drugs and therapies into the healthcare market.

The scale of adoption of the virtual model tends to suggest that standardisation of some aspects of drug discovery and development may have occurred. It is

suggested that it would be difficult for many virtual companies to confidently out-source drug development without some expectation of the types of experiments that can technically be undertaken and the likely results. Some level of standardisation is expected to occur in any evolving industry as technologies diffuse and become routine.[5] However, it is not suggested here that standardisation is always a necessary prerequisite to outsourcing. Whilst some standardisation has clearly occurred in some fields of drug discovery and development, such as monoclonal antibody technology and various types of small molecular inhibitor technologies, it does not always appear to be required. It has been recorded by Chakma et al. that some companies may actually avoid a virtual model because it is difficult to outsource research related to cutting-edge discoveries.[8]

Various virtual firms included within the interview subset use unique, cutting-edge technology and describe themselves as being in intellectual property and technological "white spaces", meaning that they encounter no competing intellectual property or technology. Thus, it seems highly unlikely that they will be operating in a field where standards have already emerged. Rather, they are more likely to rely on out-sourcing of their discovery research to the highly skilled public sector scientists who originally developed the technology. However, it is expected that standardisation may still have some relevance, particularly at the delivery phase.

One of the virtual model's most attractive aspects is that it obviates the need to establish expensive laboratory facilities or skilled scientists, which may rapidly become obsolete or unnecessary. In this regard, the considerations for non-virtual companies in deciding whether or not to transition into a more virtual business model are expected to be more complex than for new companies, given that they will already have invested in establishing laboratories and hiring science teams on staff. It is likely that a significant focus for decision-making will be the question of whether moving to a virtual model will enable the company to capture more value through more rapid adoption of new candidate drugs or realising an end point such as out-licensing, merger or sale.[9,13]

The virtual model is by no means the only strategy being utilised by small biotechnology firms in the drug discovery and development sector. In the Australian sample companies with active research laboratories, with employee scientists embedded in public sector laboratories and with mixed arrangements were all observed. Indeed, the sample illustrates more generally the diversity of business models and strategies that are being adopted by small biotechnology companies in the drug discovery and development sector. A variety of collaborative agreements were observed, from bare licences to joint ventures, a mixture of revenue raising strategies, from lines of credit to sales of research tools and non-pharmaceutical products, and a mix of aims, from takeover to out-licensing to product delivery. Marked changes in the business models of some individual companies were also observed over time. Three interviewees commented that they are working in a very new and young area and that best practice business models are still evolving. As such, it would be wrong at this stage to talk about a single drug discovery and development business model.

Might it be the case that the virtual model is the most appropriate approach for certain technologies or indications, but not others? If so, which technologies are most suited, those with standards or those in white spaces? Or is it perhaps more appropriate at certain stages of the drug pipeline, for example discovery (exploration) rather than development (exploitation)?[16] By corollary, from the point of view of large pharmaceutical companies, is the virtual model more (or less) desirable in markets for know-how?[17] Use of author bylines to identify virtual and non-virtual companies provides a basis to answer these and related questions.

Another important policy consideration is whether the fee-for-service approach adopted by virtual companies could lead to a broader stifling of publication of scientific advancements in academic journals. It would be useful to test whether the purported link between adoption of the virtual model and lack of publication under a company's name is representative of a more systemic reduction in the quantum of publication of the results of research contracted out by virtual companies. As described in Robert Merton's seminal work,[4] a communal conception of science is imperative to ensure open communication of findings; accordingly publication is rewarded by esteem measures for public sector scientists. While the norm of open publication would appear to continue to be a feature of public research, businesses value secrecy and are more apt to support a closed model of limited disclosure. Whether disclosure in patents compensates for potential lack of disclosure in publication is another complex policy issue that needs to be explored in assessing relationships between patents and virtual companies.

Study limitations

One limitation of this study is that there may be some imprecision in relying on the position of authors in scientific publications to indicate whether a company is virtual or not. However, based on observations made during data collection, it appears that if the situation arises where a company does have wet-lab employees

whose contributions to certain papers are not recorded because they are not first or second authors, there are invariably other papers published by company employees that do count for the purpose of this assessment.

Other potential study limitations include the following: of the companies that do publish, not all publish every year, and therefore the selection of a 5 year period for publications may overlap with time periods in which companies change business structure; no companies that had gone out of business or were taken over were interviewed, potentially biasing interviewees responses; it is not always expected that scientists in private organisations will feel the same imperative to publish as public sector scientists even though they may be actively involved in wet-lab research; companies that had not been in existence for the full 5 year period were not analysed, and hence newly emerged companies or companies that cease to exist may alter the proportion of virtual companies.

Furthermore, it is recognised that the cohort for this study is small and based in one jurisdiction. It would be useful to follow up this study by testing the broader applicability of this method in other, larger jurisdictions in analysing the propensity of biotechnology companies involved in drug discovery and development to adopt the virtual model. Nevertheless, the results of this study indicate that it is timely to begin a discussion of integral policy implications resulting from widespread adoption of the virtual model.

CONCLUSION

This article has put forward a method by which to determine whether the business model adopted by drug discovery and development companies is virtual or not. Based on the data in this study, the use of author bylines in publications as a proxy for a company's business model appears to have some merit. Assuming the estimated quantum of virtual companies in Australia is accurate, various policy considerations do arise. Issues that are particularly pertinent and that warrant close scrutiny include: whether this model is a more or less efficient and efficacious method for producing drugs than other models on the fragmentation-integration spectrum; and whether the virtual company model might result in lower levels of disclosure of the outcomes of drug R&D. It would also be of value to compare these results with the situation in other countries, to see if there is anything unique about the Australian sector. For example, distance from major US and European markets might make the virtual model more attractive in Australia than elsewhere.

ACKNOWLEDGEMENTS

This research was supported by Australian Research Council Discovery Grant DP0985077. We thank interviewees as well as participants at the Workshop on the Innovation Pool in Australian Biotechnology: Assessing Strategies for Fostering Innovation through Patenting and Patent Pooling, in Hobart, Australia on 14-16 December 2011 for helpful discussions on the proposed methodology for measuring uptake of the virtual business model.

REFERENCES

Book

1. McKelvey, M. (1996) *Evolution Innovations: The Business of Biotechnology,* Oxford: Oxford University Press.
2. Pisano, G.P. (2006) *Science Business: The Promise, the Reality and the Future of Biotech,* Harvard Business Review Press.
3. Rasmussen, B. (2010) *Innovation and Commercialisation in the Biopharmaceutical Industry: Creating and Capturing Value*, Edward Elgar.

Edited volume

4. Merton, R.K. (1942) Science and technology in a democratic order *Journal of Legal and Political Sociology* 1, 115-126; later published as: Merton, R.K. (1973) Science and democratic social structure, in Storer, N.W. (ed.), *The Sociology of Science,* The University of Chicago Press, pp 267-278.
5. Steinmueller, W.E. (2003) The role of technical standards in co-ordinating the division of labour in complex system industries, in A. Principe, A. Davies and M. Hobday (eds), *The Business of Systems Integration,* Oxford: Oxford University Press, pp 133-152.

Article in journal

6. Aldridge, S. (2010) Biotechs go virtual. *Nature Biotechnology* 28, 189.
7. Arora, A., Gambardella, A., Magazzini, L. and Pammolli, F. (2009) A breath of fresh air? Firm types, scale, scope and selection effects in drug development. *Management Science* 55(10), 1638-1653.

8. Chakma, J., Calcagno, J.L., Behbahani, A. and Mojtahedian, S. (2009) Is it virtuous to be virtual? The VC viewpoint. *Nature Biotechnology* 27, 886-888.
9. Chesbrough, H. and Rosenbloom, R.S. (2002) The role of the business model in capturing value from innovation: evidence from Xerox Corporation's technology spin-off companies. *Industrial and Corporate Change* 11, 529-555.
10. Chesbrough, H.W. and Teece, D.J. (1996) Organizing for innovation: When is virtual virtuous? *Harvard Business Review* 74(1), 65-73.
11. Coriat, B., Orsi, F. and Weinstein, O. (2003) Does biotech reflect a new science-based innovation regime? *Industry & Innovation* 10, 231-253.
12. Friedman, Y. (2010) Time for a new business model? *Journal of Commercial Biotechnology* 16, 1-2.
13. Kamuriwo, D.S. (2009) Timing in business model and product market strategy tradeoffs: Performance implications. *Academy of Management Best Papers Proceedings.*
14. Mirowski P. and Van Horn, R. (2005) The contract research organisation and the commercialisation of scientific research *Social Studies of Science* 35, 503-548.
15. Riesenberg, D. and Lundberg, G.D. (1990) The order of authorship: Who's on first? *Journal of the American Medical Association* 264(14), 1857.
16. Rothaermel, F.T. and Deeds, D.L. (2004) Exploration and exploitation alliances in biotechnology: A system of new product development. *Strategic Management Journal* 25, 201-221.
17. Teece, D.J. (1981) The market for know-how and the efficient international transfer of technology. *The ANNALS of the American Academy of Political and Social Science* 458, 81-96.
18. Wren, J.D., Kozak, K.Z., Johnson, K.R., Deakyne, S.J., Schilling, L.M. and Dellavalle R.P. (2007) The write position. A survey of perceived contributions to papers based on byline position and number of authors. *EMBO Rep* 8(11) 988-991.

Research papers/reports/working papers

19. Guedj, I. and Scharfstein D. (2004) Organizational scope and investment: evidence from the drug development strategies and performance of biopharmaceutical firms. *NBER Working Paper 10933.*
20. Hopper, K. and Thorburn L. (2008) *2008 Bioindustry Review: Australia and New Zealand,* Innovation Dynamics.
21. Howard, N. (2003) *Exploring The "Virtual" Company Strategy Through Outsourcing In The Biotech Industry,* Mayer, Brown, Rowe & Maw LLP.

Original Article

The role of specialization in mutual fund investment strategies: An exploratory study of the life sciences industry

Received: March 4, 2013; Revised: May 31, 2013

Osne Frans Kirzner
is at the University of Amsterdam, Netherlands.

Lorraine Marie Uhlaner
is at EDHEC Business School, Lille (Roubaix) campus, France.

ABSTRACT

This paper explores possible differences in investment strategies between specialty and non-specialty funds in the life sciences industry. The results were based on proprietary information collected in telephone interviews from 28 mutual funds located in nine European countries. As predicted, specialty funds have shorter holding periods, are more event-driven, and are more likely to focus their investment strategies on established technologies. Counter to our predictions, specialty funds are no less likely to invest in novel technologies. Also counter to predictions, specialty funds place more importance on conventional finance methods in selecting firms, and they are no more likely to use non-conventional finance valuation or non-financial criteria when selecting companies for their portfolios. This exploratory study provides new insights into differences in investment strategies between specialty and non-specialty mutual funds, which may help to explain the underlying performance difference, found in previous research. Furthermore, this study may be helpful to alert life sciences entrepreneurs to the factors that these mutual fund managers are likely to consider when determining their investment strategies. Finally, it provides insights relevant to investors seeking to build better investment strategies for life sciences stocks.

Journal of Commercial Biotechnology (2013) 19(3), 20–33. doi: 10.5912/jcb.610
Keywords: specialty mutual funds; investment strategy; life sciences; biotechnology

INTRODUCTION

This paper aims to examine differences in the investment strategies of mutual funds investing in the life sciences industry based on whether those funds are primarily specialized in the life sciences industry, which we henceforth refer to as "specialty funds."[a] Although some researchers would argue that the level of fund specialization, including investment strategies, is trivial when seeking an explanation for differences in fund performance,[1, 2] this topic is still open for debate. Past research suggests that specialty funds in particular are better at selecting stocks and, as a result, outperform non-specialty mutual funds when controlling for style factors and risk measures.[3-8] Researchers have looked extensively at the performance factors, general fund characteristics, and risk measures of specialty and non-specialty funds. However, little research has been done on specific differences in the investment strategies of these funds.

Investment strategy differences between specialized and non-specialized funds may explain why specialty mutual funds are able to select better-performing stocks and, in turn, to generate higher performance

a The concept of "specialty funds", as used in this paper, is similar to what other researchers refer to as "concentrated" funds[4, 6, 8], or "sector" funds.[3, 5, 7]

Correspondence: Osne Frans Kirzner, University of Amsterdam, Netherlands. Email: o.f.kirzner@amc.uva.nl

returns than non-specialty funds. Such performance differences might suggest that specialty and non-specialty funds use different investment approaches. However, past research has not directly examined such differences. Thus, the focus of the present study is to examine the following research question: which investment strategies are positively associated with specialty (versus non-specialty) funds? This paper adds to our knowledge of such differences by analyzing proprietary data collected from approximately thirty funds investing in the life sciences. We examine several aspects of mutual fund investment strategies, including minimum holding periods for stocks and whether decisions are event driven. We also look at possible links between the specialization of the fund and the types of technologies in which a fund invests (novel or established). Finally, we examine whether specialty and non-specialty funds differ in the use of specific evaluation methods (financial and non-financial) in their investment processes.

One of the underlying assumptions in this study is that given their more narrow focus on life sciences companies, specialty funds have a better understanding of the fundamentals of the life sciences industry. As a result, they are better equipped to estimate risks and uncertainties in this industry and, in turn, can — and do — react to market and industry developments more quickly and efficiently with respect to stock purchases and sales. However, when it comes to general investment knowledge, we would expect specialty and non-specialty funds to be similar in the tools they use. We also explore whether the types of life sciences subtechnologies differ in the companies included in the portfolios of specialty and non-specialty funds.

This paper makes several theoretical and practical contributions to the portfolio management literature. First, although this is an exploratory study, it provides new insights into differences in investment strategies between specialty and non-specialty mutual funds, which may help to explain the underlying performance difference found in previous research. Second, our results alert life sciences entrepreneurs to the factors that mutual fund managers are likely to consider when determining their investment strategies. Third, it provides insights relevant to investors seeking to build better investment strategies for life sciences stocks.

The remainder of the paper is organized as follows. The following section presents the framework, hypotheses, and rationale to be tested. The remaining sections present the method, results, discussion, and our conclusions.

RATIONALE AND HYPOTHESES

This section presents the rationale and specific hypotheses to be tested in this research. It also elaborates on the overall research premise that certain investment strategies of specialty mutual funds in the life sciences industry differ from those of non-specialty mutual funds.

Active trading: Length of holding period and event-driven trading

Duan *et al.* (2009) note that the stock-picking ability of mutual fund managers is more evident among those funds in which portfolios hold high levels of idiosyncratic risk; that is, when firm-specific returns are more volatile than the aggregate market volatility.[9] The life sciences industry is a good example of such conditions.[10] For instance, the high level of innovation and intensity of R&D in the life sciences industry, which affect the uncertainty of expected future returns, mean that companies in this industry bear unusually high levels of idiosyncratic risk.[11] Furthermore, the average company in the life sciences industry, given its highly technical nature, faces a long time horizon in terms of product development. For this reason, mutual funds wishing to make good investment decisions must collect a great deal of company- and industry-specific information.

Based on a recent review of the drug discovery literature, Paul *et al.* (2010) estimate that drug development at a typical life sciences company takes an average of 10 to 15 years from initial concept to market introduction.[12] Furthermore, they estimate that only 7-11% of candidates in pre-clinical stages ever make it to market. Such factors greatly increase the costs, risks, and uncertainty associated with product development when compared with companies in other industries, and explain much of the volatility in life sciences stocks. Drugs showing early promise often disappear before they reach the market, and a complicated series of hurdles (validation of the drug target, pre-clinical trials on animals, and preliminary regulatory approval for the first phase of human testing on healthy volunteers) must be overcome before serious clinical trials on actual patients can begin. After these initial steps, the product must first be administered to a small group of patients to obtain a proof of concept before it can be administered to a large group of patients to ensure that the product has clinical significance and is safe to use. Only after full completion of such trials can a product be submitted to the regulatory authorities to be considered for licensing. At each step, the product may have to be scrapped due to poor results or a failure to obtain intermediate regulatory approvals.

Clearly, life sciences companies are subject to a great deal of uncertainty regarding the products under development. For mutual funds, this uncertainty is augmented by a continuous flow of new information coming out of companies regarding safety and efficacy trials, R&D alliances, quarterly financial statements, and industry reports, all of which must be interpreted and analyzed. The way a company moves through the different phases of the R&D process is an important factor for investors attempting to evaluate the attractiveness of a company and its products. As this flow of new information — commonly referred to as newsflow — is likely to have an effect on the companies' stock prices,[13-15] an investment strategy is needed that simultaneously incorporates the evaluation of company-specific information and industry-specific information about technological breakthroughs and failures. In other words, in order to make sound investment decisions, investors need to analyze life sciences companies dynamically and they must be prepared to quickly adjust their investment decisions as new information becomes available. We posit that specialty funds are more capable than non-specialty funds of making such adjustments. The former's enhanced ability to analyze company- and industry-specific information should translate into more rapid and accurate judgments of the potential impact of newsflow on stock prices. As a result, specialty funds should be more likely to trade on such information. Given their specialized knowledge, they can more confidently assess the right moment to trade (buy or sell) the stocks of life sciences companies.

For these reasons, we expect specialty funds to have, on average, shorter *holding periods* and be more *event-driven* than non-specialty funds. Therefore, we hypothesize as follows:

Hypothesis 1: Specialty mutual funds are more likely than non-specialty mutual funds to have a shorter holding period, on average, of stocks within their portfolio.

Hypothesis 2: Specialty mutual funds are more likely than non-specialty mutual funds to apply event-driven trading strategies.

Type of technology

Drug development in the life sciences industry as a whole is carried out by firms largely based on novel technologies (including stem cell, gene therapy, and RNA-based technologies) as well as others built on platforms of more established technologies (including small molecules, antibodies, and protein therapies), which have already been proven successful or profitable. Novel technologies can serve as interesting new platforms on which to develop potential products to address diseases with unmet treatment needs, but they are also largely unproven.

The authors of a recently published study report of alarming findings that, until recently, many publicly traded life sciences companies, especially those based on unproven or novel technologies, were funded by excessive capital from venture capital (VC) funds and became public in buoyant initial public offerings (IPO).[16] During that period, abundant capital flowed to the life sciences industry, and the intense scrutiny of proposed products that faces many of today's IPO candidates was lacking. As a result, many of these companies were unlikely to ever become profitable because they were unlikely to develop a marketable product based on the technology platform for which the company was founded and financed.[17,18] Indeed, most life sciences products developed on novel technology platforms find themselves stranded somewhere along the path to product introduction — during safety or efficacy trials, or in the final approval process. This has been previously elucidated by Pisano[19]. In his study of the biotechnology industry, he concludes that, given the typical combination of a long time frame for product development and low likelihood of ever achieving profits, the boom of US biotech companies based on novel technologies was probably nothing more than an investment bubble.[19] Furthermore, as a result of the flawed business model adopted by many these firms, an enormous backlog of potential products under development is based on new and unproven technological platforms.

In this regard, we explore, first, whether specialty mutual funds are more or less likely than non-specialty funds to invest in established technologies. We predict that specialty funds should be more likely to invest in established technologies than non-specialty funds based on the argument that specialty funds have a better understanding of the fundamentals of the life sciences industry. We posit that specialty funds can more easily identify the products under development that have a higher chance of success. Consequently, we expect specialty funds to more readily recognize the potential of established technologies and thus have more interest in such technologies, as these technologies have the best chance of success. As a result, we suggest that a specialty fund should be more likely to balance the risk in its portfolio towards stocks based on established technologies. Therefore, we hypothesize as follows:

Hypothesis 3: Specialty mutual funds are more likely than non-specialty funds to invest in established technologies.

Furthermore, we expect specialty funds, which are more knowledgeable of the risks and failure probabilities inherent in companies built on novel technologies, to be more reluctant to invest in such areas. For instance, over the last two decades, many company and industry reports have indicated that technological breakthroughs associated with such novel technologies as gene therapy, cell therapy and RNA-based technologies were on the horizon. Unfortunately, however, only a limited number of such breakthroughs have as of yet come to fruition.[20, 21] For example, it took more than twenty years after gene therapy drugs were introduced in clinical settings before a gene therapy drug was finally approved in the Western world.[22-23] We propose that specialty funds are more aware of the relationship between technological innovation (novel technologies) and the probability of success. As a result, we expect specialty funds to be less tempted to invest in these novel technologies. Therefore, we hypothesize as follows:

Hypothesis 4: Specialty mutual funds are less likely than non-specialty funds to invest in novel technologies.

Evaluation methods

Conventional financial valuation methods (including discounted cash flow (DCF), and financial multiples or ratios) are the methods most widely used to estimate the value of life sciences companies, regardless of a company's stage of development.[24] Given the widespread adoption of these methods, we would not expect differences in the use of the various valuation methods between specialty and non-specialty funds. Both types of funds probably employ equally sophisticated institutional investment managers and thus would probably use similar financial valuation methods. Therefore, we hypothesize as follows:

Hypothesis 5: Specialty mutual funds are *not* more likely than non-specialty mutual funds to use conventional valuation methods.

Although conventional valuation methods are widely used regardless of a company's stage of development, some authors argue that more sophisticated (non-conventional) valuation methods should be used to value life sciences companies, especially as those companies have a high level of uncertainty of expected future returns. These authors argue that non-conventional valuation methods (including real options valuation, the dividend discount model, and economic value added) are important tools for valuing life sciences companies.[24-26]

Furthermore, especially when these companies are in the relatively early development stages, investors have been found to focus heavily on newsflow. In such situations, non-financial criteria (including examinations of upcoming milestones and trigger events, quality of management, company track record, and commercial partnerships) may be more important than financial criteria for judging the likely success of life sciences companies.[15,16] However, to make use of both non-conventional valuation methods and non-financial criteria requires a solid understanding of the company and the industry in order to estimate the expected level of future returns and assess whether the stock of a life sciences company is trading at an attractive price. We expect specialty funds to be better equipped to evaluate the effect of newly published information on the probability that a product will make it through the development phases and eventually be approved for market registration. Therefore, we expect specialty funds, on average, to be more likely to use both non-conventional valuation methods and non-financial criteria in their investment process. We hypothesize as follows:

Hypothesis 6: Specialty mutual funds are more likely than non-specialty mutual funds to use non-conventional valuation methods.

Hypothesis 7: Specialty mutual funds are more likely than non-specialty mutual funds to use non-financial criteria.

METHOD

Sample and data collection

The survey was conducted on a convenience sample of actively managed mutual funds.[b] All of the included funds met two initial criteria: 1) they were customers of the life sciences securities division of a large investment bank based in the Netherlands; and 2) they traded stocks in life sciences companies on a regular basis. As we are particularly interested in how investment characteristics differ among the specialty and non-specialty funds, we chose only funds that did not mention any of the dependent variables that we evaluate in our analysis as predetermined investment characteristics in their prospectuses.

b For this study, we define a "mutual fund" as an investment company that buys a portfolio of securities, which are selected by a professional investment manager, and where the selection process is subject to a certain mandate to meet specific, predetermined goals [27].

In the spring of 2010, an introductory e-mail was sent to an initial list of fifty funds. A key informant approach was used, such that only one fund manager was surveyed in each participating company. A UK-based research firm was contracted to collect information through telephone interviews. This ensured the confidentiality of the data, as it was provided in anonymous form to the investment bank commissioning the study, thereby enhancing the expected accuracy of the data.[c] One month was planned for data collection, and thirty of the fifty funds agreed to participate, providing a response rate of 60%. Respondents included representatives from mutual funds located in one of the following nine countries in Europe: Belgium, Denmark, Finland, France, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom.

Eleven of the thirty mutual funds in the sample (36.7%) described themselves as generalists, with the remainder (63.3%) describing themselves as specialist investors in the life sciences. 75% of the specialty funds held more than 50% of their assets under management (AUM) in life sciences stocks.

Approximately 33% (10) managed a fund with up to €100 million in assets. The remaining 19 investors managed funds with between €100 million and more than €1 billion in assets. The mean fund size was between €100 million and €200 million, and the median fund size range was €200 million to €500 million. 30% (9) of the funds had no limitations regarding the market capitalization of their portfolio companies. Approximately 36% (11) invested in companies with a minimal market capitalization of €100 million. Another approximately 33% (10) invested in companies with a minimal market capitalization of €150 million to more than €1 billion.

The data analyzed for the current study are based on responses from 28 of the firms. Two firms were excluded from statistical analyses due to missing data for one or more items.

Variables

This section describes the measurement of each of the variables in more detail. A detailed description of each variable is also provided in Appendix A. To create scales for the dependent variables, items in similar categories (that is, technologies and evaluation methods) are examined in two separate exploratory factor analyses, using principal components analysis with orthogonal (Varimax) rotation (see Table 1). Cronbach alpha reliability coefficients were then computed for each scale. Given the small sample size, a confirmatory factor analysis was not carried out.

Specialization is a two-item scale (Cronbach-alpha (α) reliability coefficient =.86). In the introduction to the survey, respondents were told that the life sciences[d] sector encompasses companies in the fields of biotechnology, pharmaceuticals, medical devices and technologies, nutraceuticals, and cosmeceuticals, which devote the majority of their efforts to the various stages of research, development, technology transfer, and commercialization. Respondents were then asked whether they considered themselves generalist or specialist investors in the life sciences. For the item, % in life sciences, they were asked to estimate the percentage of their fund invested in life sciences companies. The original scale ranged from 1=less than 1% to 5=more than 50%, but was recoded as a dummy variable where 2 = more than 50%; 1 = 50% or less.

Holding Period is measured by asking respondents to describe their typical holding period for life sciences stocks or investments. Possible answers included: 1 = no typical holding period, 2 = up to six months, 3 = between six months and one year, 4 = between one year and three years, and 5 = more than three years.

Event Driven is measured as part of a broader question that asked fund managers about several possible investment strategies they might apply to their fund (including event driven). If the respondent mentioned that their strategy was event driven, this item was coded one, and zero otherwise.

Novel Technologies is a three-item scale (reliability coefficient (α=.83)) reflecting a fund's interest in certain therapeutic technologies, including cell therapy, gene therapy, and RNA-based technologies. These technologies are currently at the forefront of medical technological innovation. Responses to these items loaded on the

c Note that this precaution, which was put in place because highly confidential information was being requested, also prevented the researchers from matching firms to publicly accessible financial performance information.

d Athough the life sciences industry encompasses numerous subsectors, the largest part of the industry consists of companies engaged in bio/pharmaceutical research and development. This subsector can be further divided into two sectors. The first is biopharmaceuticals, which are pharmaceuticals that are biological in nature and are developed using biotechnology (involving the use of live organisms or their active components). These companies are more generally referred to as biotechnology companies. Drugs comprise the second major subset of pharmaceuticals and are chemical (non-biological) in nature. To date, the most established technologies in this sector are small molecules (pharmaceuticals), antibodies, and proteins drugs (biologicals). Novel (non-established) technologies include stem cells, gene therapy, and RNA-based technologies (biologicals).

Table 1: Results of exploratory factor analysis for the dependent variables[a]

	Established technologies	Novel technologies	Non-conventional valuation	Non-financial criteria	Conventional valuation
Small molecules	**.82**	.40			
Antibodies	**.84**	.23			
Protein drugs	**.82**	.11			
Cell therapy	.13	**.90**			
Gene therapy	.21	**.83**			
RNA-based technologies	.40	**.74**			
DCF valuation			.11	.08	**.81**
Financial multiples			.06	–.07	**.87**
Real options valuation			**.78**	.28	–.12
Dividend discount model			**.76**	.00	.35
Economic value added			**.76**	-.03	.06
Upcoming milestones			.07	**.75**	.00
Quality of management			.19	**.72**	–.41
Track record			–.40	**.69**	.23
Commercial partnerships			.39	**.58**	.08
Eigenvalue	3.46	1.07	2.44	1.96	1.50
Percentage variance explained	57.73	17.83	27.08	21.82	16.68
Cronbach alpha reliability coefficient	.83	.83	.73	.65	.68

a: *Due to the small sample size, factor analysis to develop scales were carried out separately for technology and evaluation items. The first two columns report factor loadings for the technology items, for a Varimax rotated principal components factor analysis. The third, fourth and fifth columns report factor loadings for the evaluation items. Items in bold are included for the variable in each column, with the Cronbach alpha reliability coefficient reported in the last row.*

first of two technology factors in the exploratory factor analysis (see Table 1). Companies in these subsectors are extremely R&D intensive and are typically unsuccessful in developing new products. Moreover, these technologies, although initially viewed as promising, have not shown positive performance results.[20-24] The novel technologies scale was computed by taking an average of the responses to these three items (with 2 = mentioned and 1 = not mentioned).

Established Technologies is a three-item scale (α=.83) reflecting a fund's interest in more established therapeutic technologies – technologies already proven successful or profitable. Such technologies include small molecules, antibodies, and protein therapies. Responses to these items loaded on the second of two technology factors in the exploratory factor analysis (see Table 1). The established technologies scale was computed by taking an average of the responses to these three items (with 2 = mentioned and 1 = not mentioned).

Conventional Valuation is a two-item scale (α=.68) based on a survey question regarding the importance of two valuation approaches – discounted cash flow analysis (DCF), and financial multiples or ratios. The conventional valuation scale was computed by taking an average of the responses to these two items (with 1 = not at all important; 2 = not very important; 3 = somewhat important, 4 = very important, and 5 = extremely important). (See Table 1 for factor loadings).

Non-conventional Valuation is a three item scale (α=.73) which measures the use of less common valuation methodologies in investment decisions. On the basis of the same scale as in the previous valuation variable,

this variable is measured by averaging responses regarding the importance of three valuation methods for investment decisions: real options analysis, economic value added, and the dividend discount model.

Non-financial criteria is a four-item scale (α=.65), which measures the importance of certain other (non-financial) criteria in the fund's decisions to invest in life sciences. On the basis of the same scale as in the two valuation variables, this variable is measured by averaging responses regarding the importance given to each of four factors: evaluation of upcoming milestones/triggers/news events, quality of management, track record of company/ability to deliver, and the company's commercial partnerships.

Fund Size is widely viewed as an important factor in terms of fund performance. As fund size has been found to negatively correlate with fund performance,[28-30] we control for this variable. Respondents were asked to indicate fund size according to five possible categories: 1) up to €100 million, 2) €100 million to €200 million, 3) €200 million to €500 million, 4) €500 million to €1 billion, and 5) more than €1 billion.

Minimal Market Capitalization refers to the smallest market capitalization a company must have to be included in a fund's portfolio. Past research suggests that specialty (versus non-specialty) funds are more likely to invest in small cap stocks.[4] To measure this variable, respondents were asked to indicate their requirements regarding the minimum market capitalization of portfolio companies using seven possible categories:[e] 1) no (minimum) limitation, 2) €100 million, 3) €150 million, 4) €250 million, 5) €500 million, 6) €1 billion, and 7) more than €1 billion.

Data analysis

Each hypothesis is tested using hierarchical regression analysis. Effects of fund specialization are calculated with respect to each dependent variable, when specialization is added alone in a second block after the controls, using two-tailed significance levels for the significance of Delta (Δ) R^2.

e Small cap stocks are typically defined as companies with a market capitalization of less than €1 billion. Only one of the interviewed funds reported a minimum market capitalization of more than €1 billion. For the reported analyses, the seven-point scale was used. However, other analyses (available from the authors) show no differences when dummy variables were substituted (no minimum versus a minimum of €100 million; a minimum of €100 million or less versus a minimum of more than €100 million).

RESULTS

Descriptive statistics and bivariate relationships

Table 2 reports the bivariate correlation coefficients between all variables used in the study as well as the mean and standard deviation for each variable. Although they are not used to test the hypotheses, bivariate correlations are significant for holding period, event-driven, and established technology, consistent with the predictions of Hypotheses 1, 2, and 3. However, the non-effect for novel technologies and the positive effect for conventional valuation are counter to the predictions made in Hypotheses 4 and 5, respectively. Furthermore, the bivariate statistics do not support the predictions made in Hypotheses 6 and 7.

Tests of hypotheses

The results of the multiple regression analysis (controlling for fund size and minimal market capitalization) lead to conclusions similar to those found in the bivariate analyses. The results of the multiple regression analyses are reported in Table 3.

As shown in Table 3, fund specialization has a significant, negative effect on the dependent variable, *holding period* ($\beta = -.62$, $p < .001$). Furthermore, the results suggest that fund specialization, when entered after the controls, explains 39% of the variation in holding periods among mutual funds in the life sciences industry (ΔR^2 specialization = .39; $p < .001$). Thus, we accept Hypothesis 1.

Fund specialization also has a significant, positive effect on the second dependent variable, *event driven* ($\beta = .51$, $p < .01$) Furthermore, when entered after the controls, the results suggest that specialization explains 26% of the variation in event driven strategies among mutual funds in the life sciences industry ($p < .01$). We therefore accept Hypothesis 2.

Third, fund specialization has a significant, positive effect on the dependent variable, *established technologies* ($\beta = .54$, $p < .01$) Furthermore, the results suggest that specialization, when entered after the controls, explains 30% of the variation in established technologies among mutual funds in the life sciences industry ($p < .01$). Consequently, we accept Hypothesis 3.

Counter to predictions, fund specialization, when entered after controls, has no significant effect on the dependent variable, *novel technologies* ($\beta = .31$, ns). Furthermore, when entered after the controls, the results suggest that fund specialization explains only 10% of

Table 2: Correlations between variables used in the analysis

	1	2	3	4	5	6	7	8	9	10
1. Fund specialization										
2. Holding period	–0.62**									
3. Event-driven	0.51**	–0.21								
4. Established technology	0.55**	–0.43*	0.36							
5. Novel technology	0.31	–0.16	0.44*	0.55**						
6. Conventional valuation	0.41*	–0.09	0.10	0.28	–0.03					
7. Non-conventional valuation	–0.19	0.14	0.00	0.15	0.00	0.30				
8. Non–financial criteria	–0.17	–0.11	0.16	–0.02	0.10	–0.14	0.34			
9. Fund size	–0.03	–0.03	0.04	–0.21	–0.05	–0.15	0.10	0.05		
10. Minimal market cap	–0.02	–0.02	0.02	0.26	–0.04	0.19	0.27	0.15	–0.02	
MEAN	1.57	2.66	1.38	1.86	1.55	3.34	2.09	3.73	2.48	2.41
SD	0.46	1.11	0.49	0.30	0.43	0.88	0.81	0.55	1.32	1.38

**p < 0.05; **p < 0.01; N: = 28 due to missing data*

Table 3: Prediction of fund specialization in relation to each of the dependent variables

Dependent variable:	Holding Period	Event Driven	Established Technology	Novel Technology	Conv. Val.	Non-Conv. Val.	Non-Financial Methods
	β-value (*t*-value)[a]	β-value (*t*-value)[a]	β-value (*t*-value)[a]	β-value (*t*-value)[a]	β-value (*t*-value)[a]	β-value (*t*-value)[a]	β-value (*t*-value)[a]
Fund Size	–0.05 (–0.29)	0.05 (0.31)	–0.20 (–1.26)	–0.04 (–0.20)	–0.13 (–0.76)	0.10 (0.53)	0.05 (0.24)
Minimal market Capitalization	–0.03 (–0.21)	0.03 (0.20)	0.26 (1.71)	–0.03 (–0.17)	0.19 (1.10)	0.27 (1.45)	0.15 (0.76)
Specialization	–0.62** (–3.96)	0.51** (3.00)	0.54** (3.53)	0.31 (1.65)	0.41* (2.30)	–0.19 (–0.99)	–0.17 (–0.86)
R^2	0.39	0.27	0.41	0.10	0.22	0.12	0.05
Adjusted R^2 [(b)]	0.31	0.18	0.33	–0.01	0.13	0.02	–0.06
F-statistic	5.25**	3.03*	5.69**	0.94	2.36	1.15	0.47
DF (df1, df2)	3,25	3,25	3,25	3,25	3,25	3,25	3,25
ΔR^2 specialization[c]	0.39***	0.26**	0.30**	0.10	0.16*	0.04	0.03

** p < 0.05; ** p < 0.01, *** p < 0.001. N: = 28*
a: β values represent standardized regression coefficients in the multiple regression analysis.
b: Adjusted R^2 adjusts for the number of variables in the model.
c: Δ R^2 represents the change in R^2 when specialization is added to the model in the second step of the hierarchical regression analysis

the variation in novel technologies as an investment strategy, but this amount of variation is not significant. We therefore reject Hypothesis 4.

Also, counter to our prediction of a non-effect of fund specialization on the use of conventional valuation as an investment strategy, we actually find a positive effect of fund specialization on *conventional valuation* ($\beta = .41$, $p < .05$). In this case, 16% of the variation in the use of conventional valuation is explained by fund specialization ($p < .05$). Thus, we reject Hypothesis 5.

Finally, counter to our predictions in Hypotheses 6 and 7, neither non-conventional valuation nor non-financial criteria are predicted by fund specialization ($\beta = -.19$, ns, and $\beta = -.17$, ns, respectively). As a result, we reject both Hypotheses 6 and 7.

DISCUSSION

The results of this study of European mutual funds confirm a number of interesting similarities and differences with respect to the investment strategies of specialty and non-specialty funds in the life sciences industry. The investment strategies of specialty funds have shorter holding periods, are more event-driven, and are more likely to focus on established technologies (e.g. small molecules, antibodies, and protein therapies). These results are consistent with the predictions made in Hypotheses 1, 2, and 3. However, rather than finding a negative relationship between specialization and investments in novel technology (Hypothesis 4), we find a positive (but non-significant) effect. In terms of evaluation methods, the results are surprising. Counter to our predictions, we find that specialized funds are more likely than non-specialized funds to use conventional valuation methods (Hypothesis 5), but are no more likely to use non-conventional and non-financial criteria (Hypotheses 6 and 7).

Directions for further research and limitations of the present study

This study provides some initial insights into mutual funds in the life sciences industry and highlights several useful directions for future research. One obvious limitation is the small sample size. Future research would benefit from a larger, (and if possible, random) sample and one that would allow for stronger geographic representativeness. Furthermore, given the self-report nature of the data collection it may be possible that interviewed fund managers may not have provided accurate information in all cases.

Research that examines specialization, active trading, and performance in a single study could be particularly enlightening. Past research on active trading and fund performance has led to contradictory conclusions. Some researchers argue that active trading has a positive effect as a consequence of savvy stock picking. In this regard, specialty funds may be able to uncover market inefficiencies and mispricing in individual stocks earlier, which may enable them to take advantage of this information.[31] However, others argue for a negative relationship due to increased transaction costs[28] resulting from active trading. Although the conclusions permitted by our current research are limited with respect to performance, the overall pattern of findings in the present and past research strongly suggests that future research on active trading should control for fund specialization and that it should consider potential interaction effects between specialization and active trading, (i.e. moderator effects of specialization) when predicting performance. Given our limited data, we cannot check for such effects, but such a relationship could be explained by the underlying rationale presented in this paper that given their greater expertise (e.g. in life sciences in the present study), specialty funds are better positioned than non-specialty funds to intelligently react to new information in the market (such as promising research or disappointing results). In addition, future research could attempt to identify other characteristics of investment strategies that may explain differences between specialty and non-specialty funds, such as a focus on certain diseases or geographical regions. Moreover, researchers might examine how specialty funds build teams that are capable of analyzing company- and industry-specific information.

Future research could also test for possible mediation effects of various investment strategies (e.g. investing in established technologies) in the relationship between specialization and performance. Tests for possible mediating effects of investment strategies on performance, such as those studied in the present research, may also provide new insights into why past research has demonstrated specialty funds to outperform non-specialty funds. Finally, in-depth qualitative research regarding how such investment strategies are implemented by specialty funds could provide valuable insights into how investments in highly technical and volatile industries could be improved.

Implications for theory and practice

This study suggests that specialty funds adopt investment strategies that differentiate them from non-specialty funds. Key characteristics of such strategies include a

shorter holding period for stocks and more event-driven investment choices than in non-specialty funds. One explanation for such differences is that specialty funds are able to respond more quickly and confidently to breaking news (i.e., newsflow) given their more specialized knowledge of the life sciences industry. They can more readily assess the potential of such news events on stock prices and can trade on such information. Counter to our expectations, we find that while specialty funds are no less likely to focus their investment strategies on novel technologies, they are more likely to focus their investment strategies on "established technologies" that have already been proven successful or profitable. In terms of the lack of differences in interest in novel technologies, it might be that both specialty and non-specialty funds demand some exposure in their portfolios to technological breakthroughs. However, we have not measured whether the weighting of stocks in novel technologies varies. This could be explored in future research.

Our results further show that specialty funds are more likely than non-specialty funds to use conventional valuation tools in their investment processes. Both types of funds appear to use non-conventional valuation methods and non-financial criteria in their investment processes. Theories of rational behavior would lead us to expect specialized funds to use these evaluation methods, while we would not expect them to be used by non-specialized funds. Thus, non-specialized funds may use financial and non-financial evaluation methods that are beyond their qualifications, and they may rely on evaluation tools that they do not fully understand or master. Although this study does not enable us to determine whether specialty funds are able to evaluate such criteria (e.g. achieved milestones or quality of management) more accurately, such differences may help to explain why specialty funds are able to select better-performing stocks and, as a result, outperform non-specialty funds, as shown in earlier research.

Furthermore, the investment strategies used by specialty funds could also be adopted by other investors (non-specialty funds as well as retail investors) to build a better investment strategy for their life sciences holdings. In spite of the buzz one hears about high technology bubbles, our results would suggest that the specialty life science funds search for proven technological platforms and use conventional valuation methods. The focus of specialty life sciences funds on established vs. novel technologies is a strategy easily copied by other investors. Moreover, it should be encouraging for non-specialty funds and retail investors to learn that even specialty funds do not find the more sophisticated valuation methodologies of high importance for their investment decision. Instead, it would appear that they make careful financial evaluations, using straightforward conventional valuation methods (i.e., discounted cash flow or financial ratios). The biggest challenge, however, in emulating specialty fund investment strategy may be their dynamic approach to tracking newsflow. This requires not only added effort but likely also the ability to analyze company- and life sciences industry-specific information. In summary, those wanting to emulate the investment strategy of specialty funds should combine a focus on proven technologies and the financial fundamentals, with a dynamic investment approach that tracks newsflow.

With respect to life science entrepreneurs, practical implications are two-fold. First, although it may seem counterintuitive, one implication of our research for life science entrepreneurs is that those firms with more "established" technologies should target specialty life science funds. We find, namely that while specialty funds and non-specialty funds are equally likely to focus their investment strategies on novel technologies, the former are more likely to focus their investment strategies on "established technologies" that have already been proven successful or profitable. Second, in preparing their business presentations, especially for specialty funds, life science entrepreneurs should take heed to pay close attention to the financial fundamentals: The numbers have to work.

Summary and conclusions

This paper aims to explore the relationship between typical investment strategies of mutual funds in the life sciences industry and the degree of specialization of those funds. In particular, as predicted, even when controlling for fund size and minimum market capitalization, specialty funds have a shorter holding period, are more event-driven, and are more likely to focus their investment strategies on established technologies. Though counter to predictions, they also are no less likely to invest in novel technologies. Furthermore, also counter to predictions, they place more importance on conventional valuation methods in selecting firms and are no more likely to use non-conventional valuation methods or non-financial criteria when selecting companies for their portfolios.

Our results are based on largely proprietary information on 28 mutual funds from nine European countries collected in confidential interviews. Although the manner of data collection prevented the gathering of financial data, the results point to possible explanations for why specialty funds are able to select better-performing stocks. In particular, we highlight significant

differences in the investment strategies of these two fund types. The findings presented here have important theoretical and practical implications. Some of these differences may have useful implications for life science entrepreneurs aiming for funding as well as to investors seeking to build better investment strategies for life sciences stocks.

REFERENCES

1. Cuthbertson, K., Nitzsche, D. and O'Sullivan, N. (2010) Mutual Fund Performance: Measurement and Evidence, Financial Markets, Institutions & Instruments 19: 95–187.
2. Kaushik, A., Pennathur, A. and Barnhart, S. (2010) Market timing and the determinants of performance of sector funds over the business cycle. Managerial Finance 36(7): 583–602.
3. Dellva, W.L., DeMaskey, A.L. and Smith, C.A. (2001) Selectivity and market timing performance of Fidelity sector mutual funds. The Financial Review 36: 39–54.
4. Kacperczyk, M., Sialm, C. and Zheng, L. (2005) On the industry concentration of actively managed equity mutual funds. Journal of Finance 60(4): 1983–2011.
5. Kjetsaa, R. (2005). The performance of sector mutual funds relative to benchmarks. Journal of Academy of Business and Economics. 5(2): 85–99.
6. Brands, S., Brown, S.J. and Gallagher, D.R. (2005) Portfolio concentration and investment manager performance. International Review of Finance 5(3-4):149–174.
7. Burlacu, R., Fontaine, R. and Jimenez-Garces, S. (2006) Industry specialization and performance: a study of mutual funds. Finance 27: 33–70.
8. Huij, J. and Derwall, J. (2011) Global equity fund performance, portfolio concentration, and the fundamental law of active management. Journal of Banking & Finance 35: 155–165.
9. Duan, Y., Hu, G. and McLean, R.D. (2009) When is stock-picking likely to be successful? Evidence from mutual funds. Financial Analysts Journal 65(2): 1–29.
10. Mazzucato, M. and Tancioni, M. (2008) Innovation and idiosyncratic risk: An industry- and firm-level analysis. Industrial and Corporate Change 17(4): 779–811.
11. Golec, H. and Vernon, J.A. (2009) Financial risk of the biotech industry versus the pharmaceutical industry. Applied Health Economics and Health Policy 7(3): 155–165.
12. Paul, S.M., Mytelka, D.S., Dunwiddie, C.T., Persinger, C.C., Munos, B.H., Lindborg, S.R. and Schacht, A.L. (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature Review Drug Discovery 9(3): 203–214.
13. Dohlman, E., Hall, T. and Somwaru, A. (2002) Regulatory events and biotech firm share prices. Applied Economic Perspectives and Policy 24: 108–122.
14. Bastin, V. and Hubner, G. (2006) Concentrated announcements on clustered data: an event study on biotechnology stocks. Financial Management 35: 129–157.
15. McNamara, P. and Baden-Fuller, C. (2007) Shareholder returns and the exploration–exploitation dilemma: R&D announcements by biotechnology firms. Research Policy 36(4): 548–565.
16. Lazonicka, W. and Tulumb, O. (2011) US biopharmaceutical finance and the sustainability of the biotech business model. Research Policy 40(9): 1170–1187.
17. Silverman, E. (2006) Who took the tech out of biotech? Nature Biotechnology 24(3): 255–256.
18. Pisano, G.P. (2006) Can science be a business? Lessons from biotech. Harvard Business Review 84(10): 114–125.
19. Pisano, G.P. (2006) Science Business: The Promise, The Reality, and The Future of Biotech. Boston: Harvard Business School Publishing.
20. Hopkins, A.L. and Groom, C. R. (2002) The druggable genome. Nature Review Drug Discovery 1: 727–730.
21. Kramer, J.A., Sagart, J.E. and Morris, D.L. (2007) The application of discovery toxicology and pathology towards the design of safer pharmaceutical lead candidates. Nature Review Drug Discovery 6(8): 636–649.
22. Büning, H. (2013) Gene therapy enters the pharma market: The short story of a long journey. EMBO Molecular Medicine 5(1): 1–3.
23. Lam, P. et al. (2013) The innovative evolution of cancer gene and cellular therapies. Cancer Gene Therapy, advance online publication 1 February, doi: 10.1038/cgt.2012.93
24. Hartmann, M. and Hassan, A. (2006) Application of real options analysis for pharmaceutical R&D project valuation—empirical results from a survey. Research Policy 35(3): 343–354.
25. Copeland, T.E. and Keenan, P.T. (1998) Making real options real. The McKinsey Quarterly 3: 128–141.
26. Villiger, R. and Bogdan, B. (2005) Getting real about valuations in biotech. Nature Biotechnology 23(4): 423–428.

27. Investment Company Institute. (2012) A review of trends and activity in the U.S. investment company industry. Investment Company Factbook, http://www.icifactbook.org/2012_factbook.pdf, accessed 13 September 2012.

28. Switzer, L.N. and Huang, Y. (2007) How does human capital affect the performance of small and midcap mutual funds? Journal of Intellectual Capital 8(4): 666–681.

29. Fletcher, J. and Ntozi-Obwale, P. (2008) Arbitrage bounds and UK unit trust performance. Journal of Business Finance and Accounting 35(3-4): 580–600.

30. Yan, X. (2008) Liquidity, Investment Style and the Relation between Fund Size and Fund Performance. Journal of Financial and Quantitative Analysis 43(3): 741–768.

31. Cremers, M.J.K. and Petajisto, A. (2009) How Active Is Your Fund Manager? A New Measure That Predicts Performance. The Review of Financial Studies 22(9): 3329–3365.

Appendix A: Further description of survey items used in the study

Items	Question	% yes[a]	Mean (SD)	Range of values
Independent variable:				
Specialization	*Specialization* is measured by averaging responses to two items, fund description and % in life sciences			
Fund description	Do you consider yourself a generalist or a specialist life sciences investor? 1 = Generalist; 2 = Specialist	63.3	1.6 (0.5)	1-2
% in life sciences	What percentage of the fund is invested in life sciences companies? 1 = 50% or less; 2 = More than 50%		1.5 (0.5)	1-2
Dependent variables				
Holding period	*Holding period* is a single item variable based on the response to the following question: Which of the following best describes your typical holding period for life sciences stocks or investments? 1 = No typical holding period; 2 = Up to 6 months; 3 = Between 6 months and 1 year; 4 = Between 1 and 3 years; 5 = More than 3 years.		2.6 (1.1)	1-5
Event driven	*Event driven* is also a single item variable based on a question which asked fund managers about the investment strategies they applied to their funds. 1 = Not event-driven; 2 =Yes, event driven	36.7	1.4 (0.5)	1-2
Technology:	For the *technology* variables, respondents were asked: Which of the following therapeutic technologies have your interest currently? 1 = No; 2 = Yes			
Established technologies	*Established technologies* is a three-item scale based on mention of the following three technologies:			
Small molecules	Small molecules	82.8	1.8 (0.4)	1-2
Antibodies	Antibodies	87.9	1.9 (0.3)	1-2
Protein drugs	Protein drugs	86.2	1.9 (0.4)	1-2
Novel technologies	*Novel technologies* is a three-item scale based on mention of the following three technologies:			
Cell therapy	Cell therapy	51.7	1.5 (0.5)	1-2
Gene therapy	Gene therapy	48.3	1.5 (0.5)	1-2
RNA based technologies	RNA based technologies	65.5	1.7 (0.5)	1-2

Items	Question	% yes[a]	Mean (SD)	Range of values
Evaluation:	The three evaluation variables (conventional valuation, non-conventional valuation, and non-financial criteria) are derived from a set of survey questions asking respondents how important various valuation approaches are to the fund when making an investment decision in the life sciences sector? The scale used for all items in this section is: 1 = Not at all important; 2 = Not very important; 3 = Somewhat important; 4 = Very important; 5 = Extremely important			
Conventional valuation	Conventional valuation is based on a mean of the following two items:			
DCF valuation	Discounted cash flow valuation (risk adjusted net present value)		3.6 (1.0)	1-5
Financial multiples	Financial multiples/financial ratios		3.1 (1.0)	1-5
Non-conventional valuation	*Non-conventional valuation* is based on the mean of the following three items:			
Real options valuation	Real options valuation		1.8 (0.97)	1-5
Dividend discount model	Dividend discount model		1.9 (0.90)	1-5
Economic value added	Economic value added		2.4 (1.1)	1-5
Non-financial criteria	*Non-financial criteria* is based on the mean of the following four items:			
Upcoming milestones	Upcoming milestones/triggers/news events		3.6 (0.9)	1-5
Quality of management	Quality of management		4.2 (1.0)	1-5
Track record	Track record of company/ability to deliver		4.0 (0.6)	1-5
Commercial partnerships	Commercial partnerships of the company (ability to deliver)		3.1(0.8)	1-5
Controls				
Fund size	What is your fund size in thousands of euros? 1 = Up to €100 million; 2 = €100 million to €200 million; 3 = €200 million to €500 million; 4 = €500 million to €1 billion; 5 = More than €1 billion		2.6 (1.4)	1-5
Minimum market capitalization	Which of the following comes closest to the minimum market capitalization for life sciences companies you invest in? 1 = No limitations; 2 = €100 million; 3 = €150 million; 4 = €250 million; 5 = €500 million; 6 = €1 billion; 7 = More than €1 billion		2.4 (1.4)	1-7

Original Article

Culture and the principles of biomedical ethics

Received: January 24, 2013; Revised: June 3, 2013

Kola Abimbola
is Lecturer in Law and Forensic Science at the University of Leicester, UK.

ABSTRACT

This paper examines the roles of culture in the principles of biomedical ethics. Drawing on examples from African, Navajo and Western cultures, the paper maintains that various elements of culture are indispensable to the application of the principles of biomedical ethics.

Journal of Commercial Biotechnology (2013) 19(3), 34–42. doi: 10.5912/jcb.598
Keywords: principlism; cultural goods of medicine; personhood; practical-beliefs; scientific methodology

INTRODUCTION: CULTURE IN PRINCIPLISM

This paper maintains that the principles of biomedical ethics are *always* culture specific in the sense that their validity, applicability and moral force of persuasiveness is dependent upon the assumption of a plethora of cultural categories. These categories often operate tacitly as background assumptions in the architecture of reasoning, thereby giving the illusion that biomedical decision making on the basis of principles is culture-free.

Deontological ethics is one of the three main approaches to biomedical ethics. It is an approach that emphasizes principles, rules and duties as the basis of moral justification. Deontological ethics can be contrasted to virtue ethics (which emphasizes moral character as the basis for ethical decision-making) and consequentialism (which emphasizes the consequences of actions and rules).

Principlism is a deontological theory that relies on the application of a set of four basic principles in the resolution of biomedical ethical dilemmas. These principles are: respect for autonomy (physicians should respect the voluntary healthcare choices of rationally competent patients); nonmaleficence (physicians should not needlessly intentionally inflict harm or injury); beneficence (health care should be of benefit to the patient); and, justice (fairness is important in the allocation of resources— "*give to each that which is her due*"). Principlism is considered by many to be the Gold Standard for the resolution of biomedical ethical dilemmas. This is because these four principles are claimed to be culture free, universal, context independent, and globally applicable.

Suppose, for example, that T, an unconscious 25 year-old woman, was admitted to hospital after a car accident. T is known to everyone in the local community (including the attending doctor) as a devout Jehovah's Witness who has on many occasions preached against blood transfusion. Her purse has a card that confirms her objection to blood transfusions on religious grounds. Without blood transfusion the doctors cannot perform the required surgery to save her life. However, her mother insists on blood transfusion. A utilitarian assessment of this dilemma would look into the consequences of actions (or rules) to determine what the doctors ought to do to maximize wellbeing in this situation. A virtue ethicist would appeal to character traits such as generosity, benevolence, or trust. A deontologist would base her decision on a moral rule like "Do unto others as you would be done by", or the principle of autonomy which requires respecting T's right to self-determination.

Suppose further that T was admitted at a hospital somewhere in the Western world where the primary focus of biomedical ethics is on the application of these four principles of principlism to the doctor-patient relationship. Since some of the physician's main duties include respect for autonomy and the need to gain fully informed consent, the morally correct decision for the

Correspondence: Kola Abimbola, University of Leicester, UK. Email: kola.abimbola@le.ac.uk

Western physician is to respect the implications of T's religious beliefs.

Suppose, however, that T had been admitted to a hospital in a rural village in the Southwestern parts of Nigeria. Suppose further that the physician is an indigenous medical practitioner and that the hospital is African-Western because it incorporates the best of both worlds. The supposition is not so far-fetched. An example of one such fusion is the "Aro Village System" introduced by Professor Thomas Adeoye Lambo at the Aro Psychiatric Hospital, Abeokuta, Nigeria:

> *The world recognition of the hospital came about during the pioneering effort of Late Professor Thomas Adeoye Lambo (CON) when he started way back in 1960, the "ARO VILLAGE SYSTEM" of treating the mentally ill. The thrust of this system was a community participatory system of treatment of the mentally ill that involved the psychiatric professionals, the relatives of the patients and the co-tenants, neighbours and the community where the patients were admitted. This treatment paradigm was achieved by creating "Aro Village System" a few kilometers from Aro Hospital where patients were admitted into "normal" houses where there were other tenants alongside their relatives. The principle of the village system was subsequently adapted all over the world and virtually opened the hitherto locked gates of psychiatric hospitals. (http://neuroaro.com/history Last viewed 28 September 2012)*

So, suppose that T had been rushed to the emergency unit of Aro Psychiatric Hospital, where fully trained Western and indigenous Yoruba physicians are on call. As Gbadegesin (2007) has observed, in this alternative Yoruba Western-indigenous world, parents often serve as surrogates for their children (including adult children); just as children could serve as surrogates for their parents. As such, T in the West is more likely than T in South-Western Nigeria to have her wishes of no blood transfusion respected. Does this mean that the principles of biomedical ethics are not respected in the Yoruba indigenous-Western world? Gbadegesin makes some important observations:

> *First, it is clear that … in traditional African health care systems … family members assume the role of health care givers, acting as de facto nurses, physician's assistants, medication dispensers, and so on. This is usually in addition to their roles as family members … Second, it is important to note that family members, especially parents even of adults, are perceived as metaphysical extensions of their wards. Mother's destiny is tied to daughter's destiny. … Third, there is an expansive notion of the self, which makes the patient* see her mother *as part of her extended identity … There is an enlarged notion of patient autonomy, which includes daughter and mother as one entity. It is a notion that daughter, like mother, internalizes and accepts. For if circumstances were to change and the mother becomes ill, the daughter will play the same role that the mother is now playing. It is a notion that is perhaps different from contemporary Western notion of self, but which is not thereby morally deficient. (Gbadegesin, 2007, p.40-41.)*

Since some of the indigenous physician's main duties include respect for autonomy (*Mother's destiny is tied to daughter's destiny* in the sense that daughter is the metaphysical extension of mother; hence *the individual* here is a "mother-daughter" dualism) and the need to gain fully informed consent before treatment (in this *mother-daughter dualism*, the voice of the entity is currently that of mother), the morally correct decision for the physician is to respect the decisions of the mother.

In what follows, I highlight the ways in which culture shapes, influence and directs biomedical decision making on the basis of the four principles of biomedical ethics.

THE COMMON/UNIVERSAL MORALITY AND ITS IMPLICATIONS FOR PRINCIPLISM

One recent development in biomedical ethics is the idea of "common morality." Tom Beauchamp and James Childress, two of the most influential defenders of principlism, use this notion as the starting point of their position. I will make use of Beauchamp and Childress' version of common morality and principlism in my critique of the claim that the principles of biomedical ethics are culture-free.

The central claim of the idea of a common morality is that all humans — at least all morally conscious humans — have a "pretheoretical" awareness of certain moral norms. According to this view, every normal (i.e., cognitively competent) human has an intuitive ability that endows them with pretheoretical moral knowledge such as: it is wrong to lie, kill or break promises. These intuitive insights are *empirical* in the sense that they are, *as a matter of fact*, relied on in moral judgments. Moreover, they are *universal* in the sense that *all* thoughtful and rational persons have an intuitive

awareness of their moral force of appeal. Hence, failure to act in accordance with these pretheoretical insights generates feelings of remorse, moral criticism, and moral rebuke. Particular moralities, according to Beauchamp and Childress, are not universal. They are content-rich, and are made-up of the concrete norms, ideals aspirations and attitudes of specific/individual cultures.

Beauchamp and Childress' version of common morality and principlism commit them to the following claims:

i. … [T]he common morality is a product of human experience and history and is a universally shared product. The origin of the common morality is no different from the origin of the norms of particular morality in that both are learned and transmitted in communities. The primary difference is that the common morality is found in all cultures, whereas particular moralities are found only in one or more cultures forming a subset of all cultures.
ii. … [W]e accept moral pluralism (some would say moral relativism) in *particular* moralities …, but reject a historical pluralism (or relativism) in *common* morality. The common morality is not relative to cultures or individuals, because it transcends both.
iii. … [T]he common morality comprises moral beliefs (what all morally committed persons believe), not standards prior to moral belief.
iv. … [E]xplications of common morality … are historical products, and every *theory* of common morality has a history of development by the authors of the theory." (2009, p.3-4).

Implicit in these four claims are two general types of assumptions:

a. **Historical assumptions** about the origins of both universal and particular moralities. Both are "pre-theoretic" in the sense that they originate in, and can be found within specific cultures. They can be learnt and transmitted from generation to generation and across cultures. They are empirical in origin "and they make no appeal to pure reason, rationality, natural law, a special moral sense, or the like" (2009, 387).
b. **Philosophical/theoretical claims** about the normativity of common/universal morality, and of the four principles, which are supposedly derived from them. "Our common-morality theory does not hold that *customary* moralities qualify as part of common morality. An important function of the general norms in the common morality is to provide a basis for the evaluation and criticism of groups or communities whose customary moral viewpoints are in some respect deficient. Criticisms of those customs and attitudes are warranted to maintain fidelity to common morality." (2009, p. 387.)

Since the pretheoretical assumptions of the common morality are "abstract, universal, and content thin" (2009, p.5), the four principles of biomedical ethics "which [are] derived from considered judgment in the common morality" (2009, p.25) are also abstract, universal and content thin.

THE CULTURAL GOODS OF MEDICINE

The word, culture, has at least two everyday usages: on the one hand, it means "high culture." That is, the "best" exemplars of a society's achievements and products in the arts, literature, music, science and technology. A second sense of the word culture is that in which it refers to the *artificial* cultivation and growth of microscopic organisms, species, plants, ideals, beliefs and social mores. This second sense of the word derives its meaning from the verb "to cultivate", "to husband" (in the sense of a "tending activity"). These two senses of culture are linked. For, not only are achievements in the arts, literature, science, etc., "artificial" in that they are *artefacts* of human creations, the elements of "high" (and, of course, "low") culture also have to be cultivated, learnt, nurtured and transmitted—otherwise, they will wither away and die. (Locke, 1989). Implicit in these two senses of culture is the dialectic of opposition between the artificial and the natural (Eagleton, 2000).

Social anthropological discussion of culture therefore recognize that it is about the full range of learnt human behavioural patterns, including "knowledge, belief, art, morals, law, custom, and any other capabilities and habits acquired by man as a member of society" (Taylor, 1871, p.1). Culture is a complex combinational arrangement with various parts playing numerous roles and functions in their import on individuals and societies. Culture, is "the distinctive way of life of a group of people, their complete 'design for life'" (Kroeber & Kluckhohn, 1952 p.86). In effect, the everyday and the

technical items of culture are themselves constituent elements of a larger complex that is also culture, and which has other elements. No item of culture exists on its own. Its meaning, signification and use are always embedded within layers of other cultural elements.

The development of the vaccine for smallpox by Edward Jenner in the 1790s illustrate the confluence of various cultural elements within medicine, medical practice and, ultimately, in biomedical ethics. Jenner was a naturalist who was committed to the Enlightenment's secular, empirical and rational approach to scientific methodology. He was an English country doctor in Berkeley, Gloucestershire, England. Sometimes during the 1770s, he heard a dairymaid boasting as follows: "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face." (Stern and Markel, 2005, p.613). Investigating this boast further, Jenner discovered that it was common knowledge among the local farming community that dairymaids who had been infected with cowpox became immune to smallpox, a disease which periodically ravaged Gloucestershire.

Jenner set out to test this boast and the local knowledge. He took some pus from a cowpox lesion on a dairymaid's hand, and then inoculated eight-year old James Phipps with cowpox. Six week later, Jenner variolated Phipps with smallpox. James Phipps was unaffected by the variolation, nor was he affected by subsequent outbreaks of smallpox. Jenner conducted twelve further experiments and sixteen case studies.

Two different aspects of culture informed Jenner's observations, theory, experiments, and his subsequent discovery of the smallpox vaccination. First, there is the *customary factual knowledge* (and belief) amongst the local farming community that dairymaids already infected with cowpox became immune to smallpox. Second, as an Enlightened naturalist, he was knowledgeable of the contrasts between Asian and African techniques of inoculation by variolation (deliberately blowing infectious scabs into nostrils so as to infect an individual with a mild form of the disease, but thereby making the person immune to the full disease), and the alternative European and American method of inoculation by vaccination (subcutaneous punctures on the skin).

The foregoing indicate that medicine is cultural since it is an encapsulation of a society's factual, theoretical and methodological knowledge in its quest to understand itself as the biological knower (best exemplars of a society's achievement), just as much as it is about the cultivation and transference of methodological knowledge about how to enhance our wellbeing as the medical subject (to husband — a tending activity).

To these two cultural goods of medicine, three further dimensions of culture in medicine can be identified: the communal/sociological, the individualistic/psychological, and the practical/heuristic action-guiding dimensions.

Third, medicine is communal. It is the shared set of beliefs, practices and methods that make up a society's communal bank of knowledge on the prevention, alleviation and curing of diseases and injuries. Medicine in this communal sense is reflected in the social activities of a people *as a group*. In this sociologistic/communal sense, medicine is learned; structured, dynamic and variable.

Fourth, medicine is cultural in the *psychological* sense that it is a manifestation of individual and societal beliefs about ontology, metaphysics and methods for the realization and achievement of health, wholeness and wellness. In understanding ourselves as the knowing subject, we uphold various medico-cultural beliefs. These beliefs operate as biomedical assumptions that are embedded within medical practice and medical culture.

Fifth, at a "practical-belief" level, all the four different types of cultural assumptions above form the content of heuristic action-guiding principles that moderate and affect human biomedical action and decision-making. This practical-belief layer of commitment to medical culture should be distinguished from all the other layers because individuals and societies do not always follow the concepts, ideas, words, methods and other symbolic structures they claim to rely on. In this fifth sense, medicine as a cultural good is about the application of fact, beliefs and values in biomedical action and choices. Cultural assumption can therefore be found in those unstated convictions that implicitly guide and govern practical conduct in issues of health, wholeness and wellness. We may refer to this cultural dimension of biomedical culture as *practical beliefs*.

The five cultural goods of medicine (i.e., ways in which culture is indispensable to the practice of medicine) can be summarized as follows:

i. Medicine is a repository of a society's factual, theoretical and methodological achievements in the human sciences. These achievements rely on
ii. cultivated techniques that have to be learnt, nurtured and transmitted; and in the process of accepting and transmitting (i) and (ii), these two goods of medicine
iii. become part of a community's or society's general belief structures, *and* at the same time,
iv. they become part of the specific beliefs accepted by specific individuals.
v. Acceptance and reliance on (i) to (iv) makes medical beliefs *practical-beliefs*.

> That is, they become heuristic action-guiding principles on the basis of which we moderate, regulate and control action and inaction in issues of health, wholeness and wellness.

The foregoing account of the cultural goods of medicine (i.e., the claim that culture is indispensable to medical practice in the five senses above) should be relatively uncontroversial when applied to medical facts and beliefs. However, these cultural goods of medicine also have implications for value, methodology and reasoning in biomedical decision making; and this gives culture some moral weight in the principles of biomedical ethics.

CULTURE IN BIOMEDICAL VALUES

Western discourse on biomedical ethics emphasizes the need for physicians to gain fully informed consent from their patients before treatment. In the United States case of *Schloendroff v Society of New York Hospital* (1914), Cardozo J famously claimed that "every human being of adult years and sound mind has a right to determine what shall be done to his own body; and a surgeon who performs an operation without his patient's consent commits an assault."

Medical treatment is *prima facie* a legally forbidden act. It is informed consent that transforms this illegality into a legally permissible act. Neill LJ makes this claim explicitly in the United Kingdom case of *F v W Berkshire HA (1990)*: "treatment of surgery which would otherwise be unlawful as a trespass is made lawful by the consent of the patient."

Beauchamp and Childress (and many other deontologists) base the moral justification of informed consent on the principle of autonomy: "… Respect for autonomy … provide[s] the primary justification of rules, policies, and practices of informed consent." (2009, p.118). And since "respect for the autonomous choices of persons runs deep in common morality as [a] principle," (2009, p.99) informed consent is proclaimed to be one of the universal and culture-free principles of biomedical ethics.

Autonomy literally means self-rule. It is the capacity to think, decide, and act on the basis of one's own thought without let or hindrance. In very general terms, three conditions have to be satisfied before consent can be regarded as "full" and "informed":

1. The patient must be competent to make the particular decision in question;
2. The patient must understand the true nature and purpose of the procedure or intervention she is consenting to; and,
3. The patient's decision must be *voluntary* in the sense that it is free from the coercion and undue influence of *other persons*.

Implicit in these three conditions is a Western conception of the person in which *selfhood* is *a state* or *quality* of *being.* In this state of being, an *autonomous person* is conceived of as separate, distinct and distinguishable from *other persons. A person is an individual who possesses his or her own needs and goals, and therefore, has the freedom and liberty of thought, will and action in the making of healthcare choices.*

But surely, this account of autonomy (just as any account of autonomy) is culture-dependent! The idea of an *autonomous being* requires metaphysical, theoretical, and or spiritual/religious assumptions about what constitutes a person. The predominant Western medical conception of the self is based on some version or the other of René Descartes' dualism. In Cartesian dualism, a person is made up of two different *substances* or *things*: the mind and the body. The body is extended in space, it has dimensions and a location, and it is publicly observable. The mind, however, is the exact opposite of this: it is indivisible, it has no special dimension or location, and it cannot be publicly observed.

There are other Western ideas of the self: idealism (persons are nothing but bundles of ideas in God's mind); materialism (the mind is nothing but a by-product of brain function; it is a process generated by the activities of the brain and not a separate substance); and other versions of dualism. For example, the German philosopher Leibniz developed the dualist view called "parallelism" in which the mind and body do not interact with each other. The body has no causal effects on the mind, and activities of the mind do not bring about changes in the body. In Leibnitz's dualism, the mind and body only appear to interact because God has pre-established a harmony between the activities of these radically different substances. These alternate Western ideas of the self are not implicit or assumed in Western medicine.

The Cartesian style substance dualism on the basis of which modern Western medicine is predicated has one Achilles' heels: if the mind and the body are so radically different substances, they must be incommensurable. How, then, could they ever possibly interact? Yet, interact they must have if pharmacology, psychiatric medicine, neurology, toxicology and some other branches of medicine are to be valid.

Empirical studies by Blackhall et al. (1995) have also shown that Korean-Americas and Mexican-Americans

operate like the Yoruba of West Africa in the sense that they adopt a family-centred model of biomedical decision making in which the autonomous unit is not the individual, but the family. As such, if the metaphysical, ontological, epistemological and other assumptions on the basis of which a culture operates were to be different from those of the type currently assumed in Western medicine, the conclusions about the morally right or wrong choices would be different.

It could be objected that the Yoruba, Korean or Mexican "extended" notions still rely on a unit as "autonomous"; namely, "the family". Hence, the argument could be made that Beauchamp and Childress are still correct in their claim that "respect for the autonomous choices of persons runs as deep in common morality as any principle, but little agreement exists about its nature scope and strength." (2009, 99) The differences between *individual autonomy* and *family autonomy*, the Beauchamp-Childress defence might continue, are merely about the precise *nature* and *scope* of autonomy.

This defence of the Beauchamp-Childress position would, however, entirely miss the point. These cultural differences are not just about scope. Rather they point to the more fundamental point that these principles cannot be applied unless one assumes a conception of culture in which a complex mix of fact, knowledge, belief, values and methods is already present. The principles of biomedical ethics are by nature ampliative reasoning tools for arriving at conclusions and as such, they have their content-increasing capacities embeddedness within culture. This is precisely what examples such as Edward Jenner's development of a vaccine for smallpox, or the case of T in the West or T in Africa, indicate. Questions about who the *person* is affect the validity of bioethical decisions at a practical level. If we vary the ontological and metaphysical cultural assumptions, the outcome of the decisions would be different.

Another objection could be raised against my position. It could be argued, for instance, that many physicians, in particular psychiatrists, no longer uphold the Cartesian view of personhood that I have outlined above, and that as such, my arguments are defective in some ways. This objection would also miss the essence of my arguments. My position does not rest on the empirical claim of whether all, most, many or a few physicians uphold the Cartesian view of personhood. Rather my claim is that whatever conception of autonomy one upholds, that conception of autonomy has contained within it a conception of personhood (Cartesian or otherwise).

My position here is somewhat akin to the claim that mathematics is culture dependent because the amounts of digits we choose to represent our numbers with are themselves cultural variables. Whether 2 + 2 = 4 depends on the place-values system adopted within each mathematical and logical culture. The current global dominant way of expressing numbers uses the Base 10 place-value system. However, there are other Bases: 2, 3, 4, 20, etc. And these other Bases are not just options reserved for advanced computerised systems that no real persons use. In actually fact, there are many living cultures were logic and mathematics still relies on non-Base 10 place-values. Hence, because the Base 10 system is now the global standard, people within these cultures constantly switch between the standard global mathematical and logical systems, and their own local systems. Helen Verran has written extensively on one such mathematical system.

The implications of the foregoing on principlism are staggering. Unlike mathematics and logic where there are standardised place-values that are now globally embedded within all human cultures (such that even in African cultures where people still use indigenous counting systems, people have to constantly switch between local and global mathematical value systems), there are no standardised global value systems in medical ethics. Hence, not everyone accepts the Cartesian conception of personhood; but accept *one* conception of personhood they must. Irrespective of whether one tacitly assumes or is explicitly conscious of one's conception of personhood, we cannot apply the principle of autonomy without some prior notions of precisely what *that entity* that is supposedly autonomous is.

The point is that the principles of biomedical ethics are not abstract and content-less. Autonomy is not just autonomy *simpliciter*. Autonomy is not *pretheoretical*. It is a complex notion that already includes the acceptance of certain cultural (i.e., culture in the five senses identified above) items of knowledge. Hence, making use of the principle of autonomy (or any other principles) already includes an implicit (or explicit) reliance on culture in practical decision making process.

In 1990, the Patient Self-Determination Act (PSDA) was passed to enshrine the Principle of Respect for Autonomy into United States law. The response of the Navajo to this Act shows clearly that there is no such thing as content-thin autonomy. Unlike the Yoruba of West Africa, or Korean-Americans and Mexican-Americas, the problems of informed consent that arose for the Navajo had nothing to do with an *extended-family conception of "the self"*. It had to do with other ontological beliefs about illness, words and the nature of causation.

The Navajo believe that *thought* and *language* in themselves have the ability to control the future. If you have negative or bad thoughts, or if you use negative words in speech, *the thinking* and *the utterance* of these

negative words *will themselves* bring about these negative consequences. As a result of this, *Hozhooji* ("positive ritual language") has always been an important element of health, wellness and wellbeing for the Navajo. Indigenous Navajo medical practitioners never described the prognosis of health issues in negative terms. And contemporary Navajos across the United States would tell their healthcare providers: *Doo'ajiniidah* – "Don't talk negatively." When healthcare issues have negative prognosis, the Navajo do not want to hear about it. Rather, they prefer some version or other of *paternalism* in which the physician makes a decision about the best healthcare options available, and then communicates these choices to the patients positively. A Navajo man, for example, refused to go ahead with a heart bypass after the physicians informed him that he might not wake up from the surgery. He told them that they had just handed him a "death sentence" because describing the prognosis in those negative terms now has control over the future. The only way he could change that *uttered future* was to avoid the surgery altogether.

CULTURE AND THE HISTORIOGRAPHY OF BIOMEDICAL ETHICS

Thomas Kuhn's *The Structure of Scientific Revolutions* opens with the following revolutionary claim:

> *History, if viewed as a repository for more than anecdote or chronology, could provide a decisive transformation in the image of science by which we are now possessed ... This essay attempts to show that we have been misled by [the old image] in fundamental ways. Its aim is a sketch of a quite different concept of science that can emerge from the historical record of the research activity itself. (Kuhn, 1962, p.1)*

What exactly is "the image of science by which we [were then] possessed"? Kuhn is surprisingly unclear. Nevertheless, we can identify various counts on which Kuhn's view of science differ from the "traditional" views of philosophers like Sir Karl Popper and Henri Poincaré. The old image held that there is a sharp distinction between observation and theory, Kuhn denies this. Proponents of the old image held that observation and experiment provide the foundations for the rational acceptance of theories over their competitors; but Kuhn seems to claim that theory-choice is not a rational (or at least not a fully rational) affair. Proponents of the old image held that science can sharply be demarcated from non-science; Kuhn seems to deny this as well.

The most fundamental contrast between the *old image* and the *new revolutionary image* is in their different approaches to the relationship between scientific method, scientific beliefs, scientific practice, and history. According to the older image, scientific beliefs, practices and theories may come and go, but the principles for the objective ranking of such beliefs, practices and theories are timeless. The old image is that of an *ahistorical* methodology in which the correct rules and standards of evaluation have remained stable and invariant throughout history. Methodology was regarded as invariant because the principles, rules and standards of theory appraisal were taken to be *presuppositionless*, or at any rate not dependent upon any specific substantive, empirical, or cultural claims for their validity. Since methodology was regarded as independent of substantive science, traditional philosophers also claimed that the rules and principles of appraisal served as the neutral set of criteria for judging change and progress in science. In short, methodology was the basic tool of rationality, and traditionalists believed that once they had hit upon the *correct* characterization of the criteria of scientific merit, these criteria were valid for all times – past, present, and future.

Principlism defends an ahistorical, presuppositionless, non-substantive, methodology. Principlism thinks it has discovered the only correct culture-free principles for the evaluation of all biomedical decisions – past, present and future. Contrariwise, I have maintained that substantive contents of culture play important roles in the applications of the four principles. A brief history of bioethics further illustrates this point.

The standard historiography of bioethics traces its origins to early Greek thought. Often times, this history starts with the oath of Hippocrates; the discussion of mutilation, flagellation, incarceration, homicide and suicide by Saint Thomas Aquinas in *The Summa Theologica*; the celebrated *Medical Ethics* of T. Percival in 1803; post Second World War reflections on the roles of the medical profession in genocide; and this pre-history of bioethics culminates with van Rensselaer Potter's 1970 "Bioethics: The Science of Survival." Indeed, Potter is acknowledged as the author of the term "bioethics." This usual lineal history, however, overlooks the import of: (i) the writings of Thomas Kuhn and the revolutionaries on the nature of scientific reasoning; and (ii) the implications of this revolution on biomedical standards of decision making.

As scholars such as Atwood D. Gaines and Eric T. Juengst have emphasized, the fundamental assumptions, implications and legitimacy of bioethical decision is crucially dependent upon the historiography we construct about the origins of the field itself. Gaines and Juengst maintain that the "origin

myths" we accept have foundational implications for the principles, standards and rules we choose to apply in bioethics. They identify three general origin myths as follows:

1. **Bioethics as Reactive:** Some scholars begin their historiography of bioethics by conceiving of it as a reaction to moral concerns about the increasing reliance of medicine on technology. The underlying assumption of this historiography is that new moral dilemmas always accompany the usage of new technology. Hence, it is always prudent to regulate the applications of new science and new technology in "bio" issues. The implication of this "origin myth" is that the correct methods of biomedical decision making are subject to change in light of new technologies.
2. **Bioethics as Proactive:** Proactivism is a social movement that begins with the assumption that power is an intricate aspect of bioethical decision making. The power relations in societies inevitably imply that some minority voices will be left out if justice is not the focal concern of applied medicine. Hence, advance directives, genetic screening, hospital ethics committees and the like are important methods for including various perspectives. Just like the reactive historiography, diversity in valid standards is embedded within this origin myth.
3. **Bioethics as Continuity:** This historiography is the dominate origin myth "by which we are now possessed" in biomedical ethics. According to this dominant historiography, biomedical ethics began with Hippocrates, the Greeks, and the objectively rational second order critical reasoning of philosophy. As such, differentiation across human cultures, groups, societies and other types of social variables have no role to play in the principles of biomedical ethics.

Principlism, the so-called gold standard of biomedical decision making, assumes the origin myth in which bioethics is a continuation of the love of the philosophic wisdom discovered by the early Greeks. Principlism assumes that the methods of bioethical decision making can be independent of its subjects and the cultures within which these subjects are embedded. This presupposition-less origin myth is enunciated in principlisms claim that there is a "pretheoretical" common/universal human morality.

CONCLUSION

This paper has been a critical evaluation of the position that the four principles of biomedical ethics are universally valid norms that are devoid of cultural content and context. I have maintained that the adequacy, acceptance and applicability of these principles change in light of the different cultural network of commitments that give them meaning.

The argument here should not be construed as a defence of "cultural relativism" in biomedical ethics. Contrariwise, it is a critique of the version of deontological ethics espoused by principlism. The decision of T's doctor in the West and T's doctor in Africa *cannot both* be *morally* valid, just as informed consent cannot be valid everywhere in America, except on the Navajo Reservation. What has been established is that cultural elements of fact, knowledge, method, ideational beliefs, and practical beliefs are required for the application of the principles of biomedical ethics. To fully and adequately assess the ethical value of biomedical decisions, we need to augment a discussion of principles with an axiology of the categories that make these principles usable and applicable.

REFERENCES

1. Beauchamp, T. and Childress, J. (2009) Principles of Biomedical Ethics. New York: Oxford University Press.
2. Beauchamp, T. (2003) Methods and principles in biomedical ethics. Journal of Medical Ethics 29: 269-274.
3. Gbadegesin, S. (2007) The moral weight of culture in ethics. In L. Prograis Jr and E.D. Pellegrino (eds.) *African American Bioethics: Culture, Race, and Identity*. Washington: Georgetown University Press, pp. 25-46.
4. Gbadegesin, S. (1993) Bioethics and culture: an African perspective. Bioethics 7(2/3): 257-262.
5. Locke, A. (1989) The ethics of culture. In L. Harris (ed.) *The Philosophy of Alain Leroy Locke: Harlem Renaissance and Beyond*. Philadelphia: Temple University Press, pp. 175-186.
6. Eagleton, T. (2000) The Idea of Culture. Malden: Blackwell Publishing.
7. Taylor, E. (1871) Primitive Culture. New York: Harper.
8. Blackhall, L., Murphy, S., Frank, G., Michel, V., and Azen S. (1995) Ethnicity and attitudes toward patients autonomy. Journal of the American Medical Association 274(10): 820-825.

9. Kroeber, A. and Kluckhohn, C. (1952) Culture: A Critical Review of Concepts and Definitions. New York: Vintage Books.
10. Jenner, E. (1801) An Inquiry Into The Causes and Effects of the Variolae Vaccine, A Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Know by the Name of Cow Pox. London: D.N. Shury.
11. Stern, M., and Markel, H. (2005) The history of vaccines and immunization: familiar patterns, new challenges. Health Affairs 24(3): 611-621.
12. Evans, H. (2005) Is medicine a "cultural good? Medical Journal of Australia 182(1): 3-4.
13. Taylor, J. (2004) Autonomy and informed consent on the Navajo reservation. Journal of Social Philosophy 34(4): 506-516.
14. Verran, H. (2001). Science and An African Logic. Chicago: University of Chicago Press.
15. Kuhn, T. S. (1962). The Structure of Scientific Revolutions. Chicago: University of Chicago Press.
16. Popper, K. (1965). The Logic of Scientific Discovery. New York: Harper & Row.
17. Poincaré, H. (1958). The Value of Science. London: Dover Paperbacks.
18. Aquinas, T. (2009). Summa Theologica: Translated by Fathers of the English Dominican Province. Mobile Reference.
19. Percival, T. (1803). Medical Ethics: Or, a Code of Institutes and Precepts, Adapted to the Professional Conduct of Physicians and Surgeons: to which is Added an Appendix; Containing a Discourse on Hospital Duties; Also Notes and Illustrations. S. Russell.
20. Potter, V. R. (1970). Bioethics, the science of survival. Perspectives in Biology and Medicine 14(1): 127-153.
21. Gaines, A. D., and Juengst, E. T. (2008). Origin myths in bioethics: Constructing Sources, Motives and Reason in Bioethic(s). Culture, Medicine, and Psychiatry 32(3): 303-327.

Original Article

Patent licensing considerations for biologics under the BPCIA

Received: May 21, 3013

Sheila Swaroop
is a partner at Knobbe Martens Olson & Bear LLP, where she focuses her practice on litigation of intellectual property disputes. Her experience includes pre-litigation counseling, strategic enforcement, and litigation of disputes through trial and appeal. Ms. Swaroop has an undergraduate degree in molecular biology from Harvard University and a law degree from U.C. Berkeley. She has litigated patent disputes under the Hatch-Waxman Act on behalf of various pharmaceutical companies, and has also litigated a wide variety of other intellectual property disputes involving multi-jurisdictional litigation, litigation at the International Trade Commission, and concurrent Patent Office proceedings.

Carol Pitzel Cruz
is a partner at the Seattle office of Knobbe Martens Olson & Bear LLP. Ms. Pitzel Cruz represents various clients in all aspects of intellectual property disputes, with a focus on patent litigation. Ms. Pitzel Cruz has an undergraduate degree in Chemistry from the University of Washington and a law degree from the George Washington University. She is experienced in the area of pharmaceutical litigation, especially litigation involving Abbreviated New Drug Applications under the Hatch-Waxman Act. Prior to law school, Ms. Pitzel Cruz worked in the biotechnology industry in Seattle, Washington.

ABSTRACT

The Biologics Price Competition and Innovation Act (BPCIA) provides a new pathway in the United States for regulatory approval of products that are biosimilar to an already approved biologic product. The structure of the BPCIA creates unique issues for patent licenses in the biologics area. This paper addresses common licensing provisions relating to notice, confidentiality, enforcement, and standing that should be evaluated by both Reference Product Sponsors and Biosimilar Applicants in view of the timing and pre-litigation patent exchange requirements of the BPCIA.

Journal of Commercial Biotechnology (2013) 19(3), 43–48. doi: 10.5912/jcb.617

INTRODUCTION

The Biologics Price Competition and Innovation Act (BPCIA), which was enacted in March 2010 and codified at 42 U.S.C. § 262, creates a new pathway in the United States for regulatory approval of products that are biosimilar to, or interchangeable with, a previously approved biologic product. Prior to the BPCIA, holders of approved biologic products were entitled to an unlimited period of regulatory exclusivity. The BPCIA now limits this regulatory exclusivity to twelve years.

In addition to regulatory exclusivity, approved biologic products may also have exclusivity in the form of patent protection. Most approved biologic products are protected by a complex patent portfolio, which can include patents covering the product, methods of manufacturing the product, methods of treatment using the product, and analytical tools used to characterize the product. Such portfolios may include not only patents owned by the sponsor of the biologic product, but also patents exclusively licensed from third parties.

The BPCIA recognizes that there will be patent disputes over proposed biosimilar products. As part of its abbreviated regulatory pathway, the BPCIA creates a framework to determine the patents that will be the subject of litigation involving the proposed biosimilar. In particular, litigation under the BPCIA will involve patents owned or exclusively licensed by the holder of an approved biologic product.

A biosimilar applicant may also develop or license its own patent portfolio that could have strategic value in litigation under the BPCIA. Given the complex nature of biologics, a biosimilar applicant will likely develop its own patented technology and/or in-license patented technology in order to develop and manufacture a biosimilar. In addition, in order to demonstrate biosimilarity

Correspondence: Sheila Swaroop, Knobbe Martens Olson & Bear LLP, US. Email: sheila.swaroop@knobbe.com

or interchangeability with an approved biologic product, an applicant will likely need to use an extensive characterization process to analyze both the biosimilar and the approved biologic product. This characterization process could utilize methods that are in-licensed from third parties and/or new patentable methods developed by the biosimilar applicant. It is also likely that these characterization methods could be required by the FDA as part of the post-approval quality control measures for the biosimilar product. Finally, given the number of joint ventures for biosimilars that have been publicly announced, there may also be a host of patents that are licensed between the various parties to the joint ventures. Any of these patents owned or licensed by a biosimilar applicant could potentially be used for cross-licensing and/or settlement leverage during negotiations with the biologic product sponsor.

Accordingly, it is important for both biologic product sponsors and biosimilar applicants to consider the unique provisions of the BPCIA in drafting and negotiating patent licenses, as well as reviewing and revising current licenses. This article reviews the relevant provisions of the BPCIA and identifies several common licensing provisions that may be impacted by this statute. These include provisions relating to disclosure, notice, confidentiality, control of litigation, and participation in patent enforcement actions.

OVERVIEW OF THE BPCIA

The pre-litigation patent exchange

The patent exchange provisions of the BPCIA contemplate two primary participants. The first participant is the Reference Product Sponsor (RPS), who is the entity that has rights to an approved biologic product. The second participant is the biosimilar applicant seeking to utilize the abbreviated regulatory pathway of the BPCIA to seek approval for its proposed biosimilar or interchangeable product. In those instances in which the RPS has exclusively licensed patents from a third party patent owner, the patent owner may also have some involvement.

The patent exchange process begins when the biosimilar applicant seeks FDA approval for its product and is notified by FDA that its application has been accepted for filing. 42 U.S.C. § 262(l)(2). Within twenty days of this notice, the biosimilar applicant must provide the RPS a copy of its application as well as a description of the process(es) used to manufacture the proposed biosimilar product. 42 U.S.C. § 262(l)(2)(A). While there is no requirement in the BPCIA to notify third party patent owners that a biosimilar application has been disclosed, the RPS may share the application with a third party patent owner if certain conditions, discussed below, are met. 42 U.S.C. § 262(l)(1)(B)(iii). The biosimilar applicant and RPS then proceed through a series of exchanges to determine which patents will be included in the patent infringement lawsuit (referred to as the first wave of litigation). The patents involved in the exchange, and eventual litigation, can include not only patents owned by the RPS, but also those patents for which the RPS has been granted an exclusive license. 42 U.S.C. § 262(l)(3)(A)(i).

During this exchange, the RPS and biosimilar applicant also exchange contentions providing their positions regarding infringement and validity of the identified patents. 42 U.S.C. § 262(l)(3)(B)(ii)(l) and (C). Because the timeframes for providing these contentions are very short, advance preparation is important. For example, once the RPS receives the biosimilar application, the RPS has only sixty days to evaluate the application and identify a list of patents it believes can be asserted against the biosimilar applicant. 42 U.S.C. § 262(l)(3)(A)(i). Preparation is even more important for the biosimilar applicant. Once the RPS provides the biosimilar applicant with this patent list, the biosimilar applicant has only sixty days to list any other patents of the RPS that should be included in the pre-litigation exchange and to prepare its invalidity and non-infringement contentions for all claims of all listed patents. 42 U.S.C. § 262(l)(3)(B)(i)-(ii).

The exchange also contemplates a discussion of potential licenses. At the time the RPS identifies its list of patents that could be asserted, the RPS must also identify any patents it is willing to license to the biosimilar applicant. The biosimilar applicant must respond to the offer of license. 42 U.S.C. § 262(l)(3)(A)(ii) and (l)(3)(B)(iii).

After the parties have exchanged contentions, they are required to negotiate to identify which patents will be asserted in the first wave of litigation. The BPCIA allows the RPS to initiate the first wave of litigation even before the biosimilar applicant has launched any product. 42 U.S.C. § 262(l)(6).

If the RPS acquires and/or licenses additional patents once the patent exchange has started, the RPS must identify those patents to the biosimilar applicant within thirty days of issuance or licensing. 42 U.S.C. § 262(l)(7). The biosimilar applicant must provide contentions on these newly listed patents within thirty days of receiving notice from the RPS. 42 U.S.C. § 262(l)(7). In order to prepare for this expedited exchange, the biosimilar applicant should closely monitor any pending patent applications of the RPS or its licensors so that it can complete these contentions within the required time frame.

If the biosimilar applicant decides to commercially launch its product, it must provide notice of its

intent at least 180 days prior to marketing. 42 U.S.C. § 262(l)(8)(A). Once that notice has been provided, the RPS may institute preliminary injunction proceedings against the biosimilar applicant. 42 U.S.C. § 262(l)(8)(B).

Impact of the Pre-Litigation Patent Exchange

This pre-litigation exchange of the BPCIA creates some unique issues for licensees and patent owners. First, it encourages the RPS to maximize the number of patents it identifies to the biosimilar applicant, in order to preserve the ability to assert those patents against the biosimilar applicant in litigation. In addition, by allowing newly licensed patents to be part of the pre-litigation exchange, it also encourages the RPS to in-license additional technology.

At the same time, a third party patent owner who has exclusively licensed its technology to an RPS may want to exercise some control over how its patent is enforced. The patent owner's ability to exercise such control may be impacted by the compressed time frames of the BPCIA. As a result, both the RPS and patent owner need to consider the provisions of the BPCIA when negotiating a patent license.

Finally, while the BPCIA does not expressly apply to patents owned or licensed by the biosimilar applicant, there may be strategic reasons for a biosimilar applicant to develop or in-license its own patent portfolio. This technology could be of interest to the RPS and could be leveraged into a cross-license with the RPS. A biosimilar applicant may also be interested in acquiring patent rights for the purpose of enforcement against other biosimilar applicants. As a result, it is important for biosimilar applicants to be aware of issues that can arise in patent licenses.

With these considerations in mind, this article identifies several common provisions in patent licensing agreements that should be reviewed in light of the BPCIA.

LICENSING PROVISIONS IMPACTED BY THE BPCIA

Access to the Biosimilar Application and Confidentiality Provisions

The pre-litigation exchange of the BPCIA begins when the biosimilar applicant discloses its biosimilar application to the RPS. The information contained in the biosimilar application remains confidential and can only be accessed by the RPS's outside counsel and one in-house attorney. 42 U.S.C. § 262(l)(1)(B)(ii)(I)-(II). Furthermore, the attorneys who receive access to the Biosimilar Application cannot participate in patent prosecution relevant or related to the referenced biologic product. 42 U.S.C. § 262(l)(1)(B)(ii)(I)-(II). If the RPS wishes to share the biosimilar application with a third-party patent owner, it can do so only if (1) the RPS has an exclusive license to the patent; (2) the patent owner has retained a right to assert the patent or participate in litigation; and (3) the patent owner has agreed to the statute's confidentiality provisions, which include the restrictions on patent prosecution described above. 42 U.S.C. § 262(l)(1)(B)(iii).

In drafting patent licenses, the RPS should consider these restrictions and evaluate whether a third-party patent owner should be notified when the RPS receives a biosimilar application. If so, the license agreement should provide for notification periods that are consistent with the pre-litigation exchange deadlines. The parties should also consider whether the patent owner should have access to the biosimilar application. Given the complicated nature of biologic patents, it may be helpful to have input from the patent owner in evaluating potential infringement by the biosimilar applicant. The patent owner may also want access to the biosimilar application in order to assess the likelihood of success of any enforcement action.

In exchange for access to the biosimilar application, the patent owner must agree to the restrictions on use of the confidential information of the biosimilar applicant. In view of the compressed time frames of the BPCIA, the RPS may want to include a provision in which the patent owner agrees in advance to the BPCIA's confidentiality provisions.

If any of the confidentiality provisions are violated, the biosimilar applicant may pursue injunctive relief. 42 U.S.C. § 262(l)(1)(H). Accordingly, a biosimilar applicant should vigorously monitor disclosure of its biosimilar application and other confidential information, and should consider pursuing injunctive relief, if necessary. The RPS may also want to consider remedies and or indemnification provisions in its license agreements in the event of a confidentiality breach by the patent owner.

Disclosure of Patent Rights

After the RPS receives the biosimilar application, the RPS must identify to the biosimilar applicant any patents owned or exclusively licensed by the RPS that would be infringed by the acts of making, using, selling, offering to sell, or importing the biological product that is the subject of the biosimilar application within sixty days of receipt. 42 U.S.C. §262(l)(3)(A)(i) and (l)(2).

If an RPS plans to identify any exclusively licensed patents to the biosimilar applicant, it should confirm that its license allows for the disclosure of such patents. Many patent licenses contain a confidentiality clause that prohibits the disclosure of the license to third parties, absent notice to and/or approval from the patent owner.

Accordingly, in evaluating its portfolio for the pre-litigation exchange, the RPS should review its exclusive licenses to assess whether it has the flexibility to disclose such licenses in the exchange process. If disclosure is not permitted without prior approval, the RPS should consider securing such approvals in advance of any pre-litigation exchange with a biosimilar applicant.

Similarly, if a biosimilar applicant intends to use its patent portfolio as leverage during the pre-litigation exchange with the RPS, it should review its own license agreements to determine what portions of its portfolio can be disclosed to the RPS and to determine the extent of its ability to offer licenses to third parties.

Notice provisions for biosimilar application submission

Another issue to consider for both an RPS and a biosimilar applicant is whether it has any obligation to notify its licensors if it becomes aware of infringement by a third party. A patent owner will often include such a notice obligation in a license agreement so that it can be informed when its patented technology is being used by others.

For the RPS, these notice obligations could be triggered at several points during the pre-litigation exchange of the BPCIA. One trigger point could occur when the RPS receives the biosimilar application and process information. 42 U.S.C. §262(l)(2). Depending on the particular notice provision, the RPS may be required to disclose the existence of the biosimilar application to the patent owner at this time.

A second trigger point could occur when the RPS identifies the patents that would be infringed by the acts of making, using, selling, offering to sell, or importing the proposed biosimilar. *See* 42 U.S.C. §262(l)(3)(A)(i). Because the RPS is identifying patents that would be infringed, the RPS may have an obligation to notify the patent owner of this potential infringement as well. However, due to the confidentiality provisions of the BPCIA discussed above, the RPS may be restricted from disclosing this information to the patent owner. This could create a situation in which the notice obligations under an existing patent license may not be consistent with the confidential access provisions set forth in the BPCIA. To avoid any uncertainty regarding the issue, the RPS should review its existing licenses to determine (1) whether it has any notice obligations for patents that could be identified in the pre-litigation exchange; (2) when such obligations would arise; (3) whether the notice obligations are broader than what is permitted by the BPCIA. The RPS should also consider asking its licensors in advance to designate a "patent owner representative" who is willing to abide by the confidentiality obligations and prosecution bar provisions of the BPCIA.

A biosimilar applicant who has licensed-in technology may encounter similar notice issues, but they will likely arise at a later stage than the pre-litigation exchange of the BPCIA. For example, if the RPS and biosimilar applicant proceed to litigation, a biosimilar applicant may obtain confidential information about the RPS' approved biologic product during discovery that is relevant to infringement of a patent licensed-in by the biosimilar applicant. A biosimilar applicant may have an obligation under an existing license to notify the patent owner of such infringement, but may not be able to comply with that obligation if the information regarding the RPS product is confidential and governed by a protective order. As a result, a biosimilar applicant should evaluate its own notice obligations to assess if and how it can provide notice of infringement of in-licensed patents.

Consent to litigation/joinder in litigation

Another set of provisions in existing license agreements that may impact litigation under the BPCIA are clauses relating to control of the litigation by the patent owner. Patent licenses often include provisions requiring a licensee to obtain agreement from the patent owner before making an accusation of infringement. Such provisions frequently have timing requirements as well. For example, a licensee may need to give a patent owner a specific notice period prior to making an assertion of infringement, so that the patent owner can evaluate the issue and provide any necessary consent.

These consent provisions and timing requirements may not be consistent with the expedited pre-litigation exchanges of the BPCIA. For example, at the outset of the pre-litigation exchange, the RPS only has sixty days after receipt of the biosimilar application to identify patents that may be infringed. 42 U.S.C. § 262(l)(3)(A)(i). After the exchange of contentions, the parties have a fifteen-day period to agree on what patents will be included in the first wave of litigation. 42 U.S.C. § 262(l)(4). If agreement cannot be reached, the parties then have a five-day period to exchange lists of patents that could be litigated. 42 U.S.C. § 262(l)(5).

In view of these expedited procedures, the RPS should review its existing licenses for any provisions that require consent or approval by the patent owner for any enforcement activity. If the timing and procedures for such consent and approval are not consistent with the BPCIA, the RPS should consider modification of those provisions.

These types of provisions may also be relevant to patent licenses involving a biosimilar applicant. If a biosimilar applicant has patent rights that it wishes to assert against other competitors, it should make sure it has the ability to move quickly to enforce these patents when needed. For example, if a biosimilar applicant becomes aware of potential infringement by a competitor, it may want to quickly enforce its patents through a preliminary injunction proceeding. If it needs approval from a patent owner prior to such enforcement efforts, such procedures could hinder this strategy. Accordingly, biosimilar applicants should also be aware of these provisions when negotiating patent licenses.

Control of Litigation

Patent licenses may include provisions that allow a patent owner to participate in strategic decisions for the litigation. These provisions should be reviewed for their potential impact on any litigation under the BPCIA.

As an initial matter, if the patent owner and licensee engage in discussions regarding potential litigation or licensing strategies, the parties should consider entering into a common interest agreement to protect the confidentiality of such communications.

In addition, companies should consider whether and how to explicitly address the pre-litigation exchange of the BPCIA as well as the ensuing litigation. The following issues should be considered by the RPS:

- Should the patent owner have any role in approving the patents that will be initially identified by the RPS in the pre-litigation exchange?
- Should the patent owner have any role in approving licenses that the RPS may negotiate with the biosimilar applicant?
- Should the patent owner have any role in deciding what patents will be included in the first wave of litigation?
- Should the patent owner have any role in deciding whether to pursue a preliminary injunction?
- If a licensed patent is identified in the pre-litigation exchange, should the patent owner bear any of the costs of the pre-litigation exchange for that patent?

A biosimilar applicant should also consider provisions relating to control of litigation and evaluate the following:

- Should the patent owner have any role in approving the biosimilar applicant's cross-licensing offers?
- Should the patent owner have any input in developing the non-infringement or invalidity positions of the biosimilar applicant?
- Should the patent owner have any role in deciding whether to enforce patents against other biosimilar applicants?
- Should the patent owner bear any of the costs associated with defending the licensed patent?

It is helpful to consider and address these issues prior to initiation of activity under the BPCIA, in order to remove any uncertainty as to the roles of the patent owner and licensees in carrying out the statutory exchange as well as the post-exchange litigation.

Patent Enforcement by an Exclusive Licensee

After the parties have completed the pre-litigation exchange and identified the patents to be asserted in the first wave of litigation, the RPS must bring suit on these patents within thirty days, or it will lose the right to recover certain remedies against the biosimilar applicant. The BPCIA also allows the RPS to initiate preliminary injunction proceedings against a biosimilar applicant. In order to maintain either of these enforcement actions, the RPS must show that it has both constitutional and prudential standing to assert the patent against the biosimilar applicant. Likewise, a biosimilar applicant who is seeking to enforce its patents against others has the burden to show that it has the proper constitutional and prudential standing. In each of these situations, the party accused of infringement can use the discovery process to evaluate the relevant ownership and licensing documents and, if applicable, challenge standing. A successful standing challenge will reduce the number of patents asserted in the litigation. Accordingly, this section summarizes standing issues that can arise for exclusively licensed patents.

In general, if a company owns an asserted patent and has not granted any rights to third parties, it will be

able to establish standing. However, if a company seeks to enforce the patent as an exclusive licensee, the determination of standing is more complex. When determining whether or not a licensee has constitutional and prudential standing, the court will look not only to the rights that have been licensed to the licensee but also to the rights retained by the patent owner. Among the rights considered, are the right to exclude others from making, using, selling or importing a patented invention, the right to sublicense, and the right to assign. In general, the more rights retained by the patent owner, the more likely it is that the licensee will not have the necessary rights to meet the constitutional and/or prudential standing requirements.

Constitutional standing must be present on the date a suit is filed, and it requires a showing that the licensee has, at a minimum, the right to exclude others. If a licensee cannot establish constitutional standing, the suit must be dismissed. The right to exclude that is required for constitutional standing may be in the form of an exclusive license, or as part of an assignment of substantially all rights to the patent. In the context of an exclusive license, the right to exclude does not need to be a right to exclude everyone: It may be more limited, for example, a right to exclude others in a particular field of use. If a more limited right to exclude is granted, the parties should carefully consider who will be excluded and ensure that the excluded parties encompass any potential infringement targets. This will prevent a scenario in which an accused infringer obtains its own license under the relevant patent, thereby destroying constitutional standing for the licensee. Another option to ensure constitutional standing is to assign substantially all of the patent rights, including the right to exclude, to the licensee.

In addition to establishing constitutional standing, a licensee must also demonstrate that it has prudential standing. In patent cases, prudential standing typically requires that all co-owners of the patent be joined in a suit for infringement. When an exclusive licensee is seeking to enforce a patent, it will often need to join the patent owner to meet the prudential standing requirement. In contrast to constitutional standing, which must be present at the outset of litigation, a lack of prudential standing can be cured, for example, by adding, voluntarily or involuntarily, the patent owner, to a suit filed by the patent owner's exclusive licensee.

Because patent enforcement by an exclusive licensee may require joinder of the patent owner, both the RPS and the biosimilar applicant should consider this joinder issue in any license agreement. For example, the parties could include a provision requiring the patent owner to agree in advance to participate in litigation when needed. This will avoid any potential challenge to prudential standing when the patent is asserted. If joinder by the patent owner is required, the agreement should also include provisions discussing who will handle the costs of representing the patent owner and whether the patent owner and licensee will be represented by the same counsel.

However, there are circumstances in which a patent owner may not wish to participate in patent litigation brought by its exclusive licensee. In those situations, a licensee should seek to obtain an assignment from the patent owner of substantially all of the patent rights. This will increase the likelihood that the licensee has sufficient rights to satisfy the prudential standing requirements on its own, without joining the patent owner. This type of assignment may be particularly beneficial for licenses in which a state university is the patent owner. Many state universities are reluctant to participate in litigation and, more importantly, are not willing to waive sovereign immunity in order to join a patent lawsuit. To avoid any challenge to prudential standing when a patent owner is unwilling or unable to join a lawsuit, the license should structure the assignment of rights so that joinder by the patent owner is not required.

In view of the requirements for establishing constitutional and prudential standing by exclusive licensees, both the RPS and biosimilar applicant should consider which parties will be needed to enforce any in-licensed patents and determine if the license is appropriately structured.

CONCLUSION

Given the complexities and unique provisions of the BPCIA, both the RPS and the biosimilar applicant will be well served to consider the BPCIA's provisions discussed above when drafting and negotiating patent license agreements.

From the Board Room

The relevance and importance of business development and licensing in the biopharmaceutical industry

Received: November 19, 2012; Revised: June 5, 2013

Roger Davies
is a consultant working with Medius Associates who has spent the last 25 years in business development and licensing and has personally completed over 100 deals during that time. He is the former Chairman of the UK Pharmaceutical Licensing Group and is the Finance Module author and tutor for the MSc at the University of Manchester. Former roles include Director of Licensing and Business Development at Bioglan plc and Mundipharma and various financial and marketing roles in Fisons Pharmaceuticals and Rank Xerox. Roger has a Master's degree in Economics.

ABSTRACT

The importance of the business development and licensing (BD&L) function in the global biopharmaceutical industry has grown significantly over the past 20 years as pharmaceutical companies have sought to supplement their internal R&D with innovative products and technologies sourced from biotechnology and drug delivery companies. This has required companies to employ BD&L executives to search, evaluate, negotiate and alliance manage deals ranging from small biotechnology companies to the largest of the Big Pharma companies. Nowadays all the large companies have BD&L teams, sometimes in excess of 100 people. To inform new BD&L entrants and to improve the professionalism of the experienced BD&L executives, various training courses are offered by not-for-profit associations and commercial organisations. The leading not-for-profit association in Europe for biopharmaceutical executives is the Pharmaceutical Licensing Group and in the US it is the Licensing Executive Society. Both organisations offer basic training courses but as far as is known, the only university accredited Master's degree qualification in BD&L is the distance learning MSc offered by the University of Manchester. The dissemination of specialist knowledge and best practice is through the journals and conferences of the professional associations. The need for well-qualified BD&L executives in the biopharmaceutical industry is demonstrated by the fact that 25% or more of Big Pharma sales come from third party products and the cost of licensing deals alone is over $200m on average.

Journal of Commercial Biotechnology (2013) 19(3), 49–56. doi: 10.5912/jcb.592
Keywords: business development; licensing; deals; biopharmaceutical; training

SYNOPSIS

The importance of the business development and licensing (BD&L) function in the global biopharmaceutical industry has grown significantly over the past 20 years as pharmaceutical companies have sought to supplement their internal R&D with innovative products and technologies sourced from biotechnology and drug delivery companies. This has required companies to employ BD&L executives to search, evaluate, negotiate and alliance manage deals ranging from small biotechnology companies to the largest of the Big Pharma companies. Nowadays all the large companies have BD&L teams, sometimes in excess of 100 people. To inform new BD&L entrants and to improve the professionalism of the experienced BD&L executives, various training courses are offered by not-for-profit associations and commercial organisations. The leading not-for-profit association in Europe for biopharmaceutical executives is the Pharmaceutical Licensing Group and in the US it is the Licensing Executive Society. Both organisations offer basic training courses but as far as is known, the only university accredited Master's degree qualification in BD&L is the distance learning MSc offered by the University of Manchester. The dissemination of specialist knowledge and best practice is through

Correspondence: Roger Davies, Medius Associates, UK.
Email: linda@medius-associates.com

the journals and conferences of the professional associations. The need for well-qualified BD&L executives in the biopharmaceutical industry is demonstrated by the fact that 25% or more of Big Pharma sales come from third party products and the cost of licensing deals alone is over $200m on average.

THE RELEVANCE AND IMPORTANCE OF BUSINESS DEVELOPMENT AND LICENSING IN THE BIOPHARMACEUTICAL INDUSTRY

One of the most interesting and fun jobs in any industry must be one where there is the opportunity to meet people, to travel, to get involved in all aspects of the business, to negotiate deals (which can be exciting or stressful or both) and to have the satisfaction of completing projects. In the biopharmaceutical industry this describes the job undertaken by executives who are responsible for partnering new products and technologies from other companies. These people are called licensing and business development (BD&L) executives/managers/directors. The types of deals they undertake range from simple patent licences to complex co-development and commercialisation deals. They are often, but not always, separate from corporate development executives who are mostly involved with corporate strategy and company acquisitions. A third group of executives involved in BD&L is technology transfer executives whose main work is with early stage technologies and products and who are located in or linked to universities. A fourth group of executives who are often part of the BD&L team are alliance managers who are responsible for managing the relationship between the partner companies post deal signature. It should also be noted that the term "business development" in this article does not include selling activities by salesmen, major account managers, etc. and the plethora of titles given to sales people that disguises the fact that their primary role is involved with selling products.

This article is focussed on BD&L executives but recognises that there is considerable overlap with corporate development and technology transfer executives and alliance managers. It examines the role and responsibilities of BD&L executives in finding, evaluating and negotiating such deals and the importance and contribution of partnering deals in the biopharmaceutical industry.

By the end of the article it is anticipated that the reader will have a deeper insight into the role of BD&L executives, what type of skills and experience they need and the vitally important contribution they make to the industry.

WHY DO DEALS HAPPEN?

The reason deals happen is because two parties identify an opportunity to achieve a greater success (or a reduced risk) from collaboration with a partner than by working alone. The identification of the opportunity usually arises from a strategic review by one or both companies. The strategic review by a potential acquirer or licensee may have identified a product or technology gap from internal R&D that could be filled by a third party product. The strategic review by a biotechnology company may have identified that the cost and risk of clinical development is too high to be undertaken without a partner company. There are many other reasons for deals such as negotiating freedom to operate for blocking patents, licensing a screening technology, acquisition of a regulatory dossier for a generic product, appointing a co-promotion partner to increase marketing power, appointing a distributor to obtain marketing coverage in distant markets. The range of deals over the life of a product is illustrated in Table 1.

BD&L executives are usually involved in all these deals and often instigate and manage the deal from start to finish.

THE NEED FOR PARTNERING PRODUCTS AND TECHNOLOGIES

The opportunity to achieve a greater success by collaboration with a partner than by a company working alone most frequently involves new products and technologies. These deals range from new molecules to generics and where the stage of development ranges from discovery to post launch. The reason for partnering is driven by the pharmaceutical industry's need for a constant flow of innovative new products and these new products are often developed, not by the pharmaceutical companies, but by small entrepreneurial biotechnology and other product development companies or academic institutions. Overall R&D productivity has been declining as costs have been inexorably rising, often driven by new regulatory requirements, while the number of new molecules gaining approval has been declining or at best has been static. This is reflected in the chart below presented by Evaluate Pharma at the European Pharmaceutical Licensing Group meeting in Budapest in September this year. It shows a continual increase in R&D costs from the early 1990 to today with R&D spending now over $130bn while the number of new molecular entities obtaining approval has declined or at

Table 1: The range of deals over the life of a product

	EARLY STAGE DEALS			MID TERM DEALS			MARKETING DEALS			
	Research	Pre-Clinical	Phase I	Phase II	Phase III	Pre registration	Launch	Post launch	Patent expiry	Post patent expiry
Confidentiality	■	■	■	■	■	■	■	■	■	■
Material Transfers	■	■	■							
Options		■	■	■						
Evaluations	■	■	■	■						
Screening	■	■								
Research alliances	■	■								
Contract research		■	■	■	■					
Co-development		■	■	■	■					
Patent licensing	■	■	■	■	■	■	■	■	■	■
Product licensing		■	■	■	■	■				
Co-marketing							■	■		
Co-promotion							■	■		
Product							■	■	■	
Distribution							■	■	■	
Supply			■	■	■	■	■	■	■	■

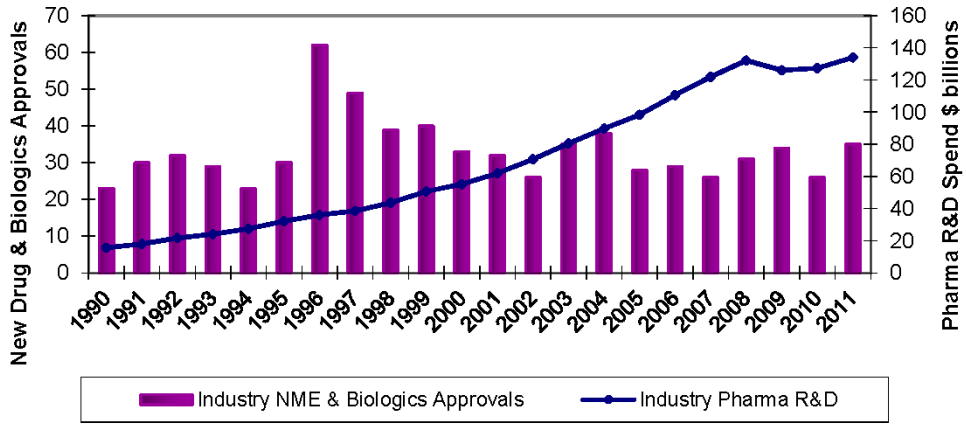


Figure 1: R&D costs and NME launches

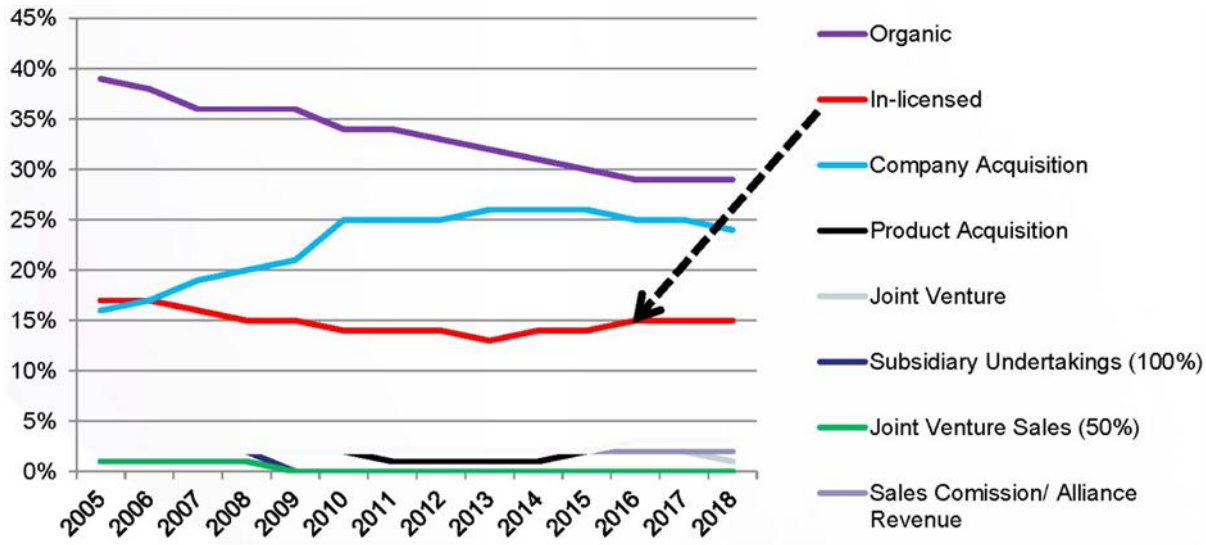


Figure 2: Aggregate sales by strategy (top 500 companies)

best has remained static (Figure 1). As a result the productivity of R&D in the top 20 companies has declined by 60% as the ratio of new product sales to R&D spend has slumped from nearly $2.50 in the period 1996 to 2005 to less than $1 in the period 2006 to 2015.

The decline of internal R&D productivity has been an acute problem for many Big Pharma companies and as a result these companies have increasingly sought to obtain innovative new products from other companies. An analysis by Evaluate Pharma of the top 500 pharmaceutical companies for the period from 2005 to 2018 (forecast) shows significantly declining share of company sales from organic R&D, stable share of sales from licensed products accounting for 15% of sales plus a 25% share from company acquisitions (Figure 2).

THE DEVELOPMENT OF BD&L

The sales contribution from third party projects compared to internal R&D is difficult to measure especially as a pre-registration product sourced from a third party requires substantial development support from internal R&D to get to market. However the overall picture is clear, all pharmaceutical companies these days require external collaborations to obtain products to supplement internal R&D. It was not always so, in the 1980s, when pharmaceutical companies internal R&D was able to regularly develop and launch new products, the need to source new products from third parties was limited or non-existent. In addition commercialisation deals were usually confined to appointing distributors in export markets or, for example, co-marketing deals in Southern Europe. If a BD&L manager existed the typical profile was a person who was nearing the end

of their career with a commercial background, usually sitting in a small office in the basement! In the last 25 years as pharmaceutical companies internal R&D departments have struggled to develop new innovative medicines and in parallel the biotechnology and drug delivery industry has grown based on innovation, there has been an increasing trend to in-license or acquire technologies and products from other companies. This has spurred the creation of BD&L jobs and in the bigger companies there are teams in excess of 100 people worldwide to facilitate partnering deals. In many of these companies the BD&L roles are separated into "silos". For example in the first silo there are scouts who search for new opportunities and make initial contact. The second silo may consist of evaluators, the third silo negotiators and the fourth silo alliance management. In contrast in small companies the BD&L executive is expected to undertake all the roles.

HOW DO DEALS HAPPEN – RESOURCES

Once the strategic objective to partner has been agreed the next step is to secure the BD&L resource and set direction to ensure the objective can be met.

Finding potential partners can be done either using external or internal resource. The external resource may be a consultancy that has contacts in target companies or it may be an investment bank especially if a company divestment is planned. The internal resource is the BD&L executive or equivalent resource. In small biotechnology companies the CEO, COO or CFO may act as the BD&L representative. Most companies, particularly the larger companies, use internal BD&L resources especially where the company's product or technology requires specialist scientific knowledge or it is a country specific commercial deal.

HOW DO DEALS HAPPEN – SEARCHING AND INITIAL CONTACT

Whatever the reason for seeking a partner, one or both companies have to put in place a process to find, evaluate, negotiate and complete a deal. The first stage is to search for companies that have the target product, technology or development and commercialisation capability. This involves searching databases containing company, patent and product development information and also making other companies aware of your requirements via websites and contacts.

Once the target companies have been identified the next step is to make contact. The preferred approach is by personal contact especially where the contacts know each other. These personal contacts can be obtained by company visits or via industry or professional associations' (PLG, LES) conferences. Alternatively there are partnering conferences such as BIO/BioEurope that provide an electronic appointment system between companies and provide facilities for short meetings. After a dozen half hour meetings in a day this can be very tiring and boring … it is like speed dating without the excitement!

The task of searching for opportunities already starts to define the profile of the ideal BD&L executive, namely, knowledgeable about products/technologies and companies, good contacts in other companies, good interpersonal skills, patience and stamina.

HOW DO DEALS HAPPEN – EVALUATION AND DUE DILIGENCE

Once the initial contact has been made and information exchanged the BD&L executive will arrange the internal company evaluation of the opportunity. This requires input from many of the company functions including patents, R&D, medical, regulatory, manufacturing and marketing. A team may be established once the project has reached an advanced stage. In this situation the BD&L executive needs to be able to persuade or cajole specialist colleagues who have a full time job within their respective function e.g. medical, to devote time to reviewing the new product while still having to achieve their functional objectives. In addition the BD&L executive needs to have sufficient knowledge of each functional area to ensure the review undertaken by the specialist is both comprehensive and addresses the key issues. So, while the BD&L executive almost certainly will have joined BD&L after working in a specialist function such as R&D, regulatory or marketing, it is important that during their career they have gained awareness of the challenges facing other functions.

So the second dimension of the profile of the ideal BD&L executive is to be both a generalist, that is someone who has a broad knowledge of the business, and to be a good at organising and managing a team of specialists.

HOW DO DEALS HAPPEN – NEGOTIATION

Once two companies have established there is sufficient technical or commercial interest for a deal, the next step is to negotiate a formal agreement. There is likely to be a number of steps such as an initial meeting,

preparation of a term sheet, preparation of a draft agreement and further negotiations until the final agreement is signed.

So the third and perhaps the most important feature of the ideal BD&L executive's profile is the ability to negotiate. This means not only the ability to negotiate with other companies but also internally. The internal negotiation is often more difficult than the external one particularly where the top management have to be persuaded that the commercial terms of the deal make sense in comparison to internal and external benchmarks. It has been reported that in one Big Pharma company more than 20 signatures are required from different stakeholders to complete a deal!

WHAT IS THE IDEAL BD&L EXECUTIVE PROFILE?

In summary the profile of the ideal BD&L executive who is involved in all aspects of business development and licensing includes good interpersonal skills and ability to negotiate, excellent team organisation and management skills, a general knowledge of products and companies, good contacts in many companies and plenty of patience and stamina. In fact these attributes are very similar to those of a CEO and as a result there are many cases where a BD&L director in a biotechnology company is appointed to a CEO role.

Not all BD&L executives are able to develop the complete range of skills needed for their role. For example, negotiating requires a certain type of interpersonal behaviour that can be trained but if the executive is not comfortable negotiating, it is unlikely they will be good in this aspect of the role. This is why the larger companies organise BD&L executives in silos where each person's strength in each skill can be maximised.

Whatever the organisational structure, a word of warning is appropriate: the success rate of in-licensed product opportunities is very low. The number of opportunities reviewed by Merck & Co in 2011 is shown below. Less than 1% of the in-license opportunities received and 4% of the opportunities reviewed resulted in deals.

	Number	% of received	% of reviewed
Opportunities received	8672	100%	
Opportunities reviewed at committee	1290	15%	100%
Opportunities where CDAs signed	697	8%	54%
Alliances signed	52	<1%	4%

Similar statistics were presented by Roche some years ago where the number of alliances signed as a percentage of new opportunities was less than 2%.

A BD&L executive who closes more than 2 in-licensing deals a year is doing well. Out-licensing has a higher success rate particularly with platform technologies and product divestments but if a biotechnology company has only one lead product and a year or two year gap until the next one reaches proof of concept, the BD&L executive may only have one deal to close every two or three years. In this biotechnology situation the BD&L executive may find their work mainly consists of alliance management once the deal has been completed.

HOW DOES THE BD&L EXECUTIVE OBTAIN THE NECESSARY SKILLS AND KNOWLEDGE?

Very few executives enter the BD&L profession direct from university. Most new BD&L executives have begun their career in some other function. In biotechnology companies most come from R&D or have a scientific background as the BD&L role requires detailed knowledge of the technology/product. In pharmaceutical companies most BD&L executives have a scientific or marketing background depending on the types of deals to be achieved. There are also some entrants from finance, legal or patents. Whatever their background, new BD&L entrants need some form of training to enhance or develop their skills and knowledge. In addition there is increasing demand for training from executives in other functions who interact with BD&L.

Training courses in BD&L are offered by non-profit making associations and commercial organisations. These vary from introductory courses for new entrants to specialist courses in say, negotiation or valuation. The top non-profit making organisations in BD&L are the Pharmaceutical Licensing Group (PLG) which is the leading professional association for biopharmaceutical BD&L executives in Europe and the Licensing Executives Society (LES) which leads in the US. Both these organisations offer basic courses in BD&L. These organisations also offer their members the opportunity to network at association conferences, access to other member contact details and a regular peer-reviewed journal.

The quality of the courses varies substantially partly depending on the target audience but most of the basic

training courses cover most of the knowledge aspects of BD&L. To assess the quality of a training course it is important for the potential delegate to understand the scope of the course and how it will meet their needs and to critically assess the number and quality of the specialist speakers and the number of delegates allowed to attend. For example a basic training course delivered by one or two speakers to 50 delegates, depending on the delegate's requirements, is likely to be of less interest and less interactive than one where there are 10 specialist speakers presenting to a maximum of 20 delegates.

In addition to the introductory courses, there are more advanced courses for experienced BD&L executives and there are specialist courses that not only cover knowledge but also skills such as negotiation. There is, to the author's knowledge, only one University accredited course that is focussed on all aspects of BD&L and that leads to a Master's degree qualification and that is the distance learning MSc in BD&L offered by the University of Manchester in conjunction with the Pharmaceutical Licensing Group. In practice it has been found that many students choose to take one module in a specialist subject such as Legal or Finance rather than to apply for the full MSc. Also it has been found that many of the modules are taken by non-BD&L executives such as lawyers, project and regulatory executives.

In addition to the knowledge that can be gained from training courses, membership of the professional associations such as PLG and LES can provide valuable information, as well as contacts. For example, imagine a scenario where a US biotechnology company with a primary care product in Phase 2 is seeking a 20% royalty rate. The company has also calculated that the cost of goods will be 20% of the target ex company selling price. So if the licensee company agreed to these terms their gross margin would be 60%. Would this be acceptable to a licensee pharmaceutical company? The answer is probably not according to a survey undertaken amongst European PLG members. According to the respondents, over 50% of branded and generic companies have internal guidelines regarding minimum gross margins. The median minimum gross margin guideline for a prescription speciality product in Europe was in the range 60% to 70% but nearly 20% of companies reported that their minimum was over 70%. Based on this information the US company BD&L executive would be better equipped to understand and negotiate a deal with a European company. Similarly the LES in their journal Les Nouvelles from time to time report results of royalty surveys they have undertaken that provide BD&L executives with benchmark data.

THE IMPORTANCE OF BD&L TO ACHIEVING SALES GROWTH

The contribution of third party collaboration projects to overall sales and growth of a company is very difficult to assess. Part of the reason is the time lag between signing a deal and the product reaching peak sales. It is even more difficult to assess the profit impact of such deals. Over the years some estimates have been made and even allowing for the error in the data, the conclusion is that BD&L projects are a major contributor to sales and profit in most biopharmaceutical companies. In the extreme case, biotechnology companies would not survive without a collaboration not least of all because their business model assumes its products will be licensed out at some stage of development. At the other end of the product spectrum, the generic companies buy regulatory dossiers from third parties to obtain access to products and manufacturing they do not possess or cannot develop. Co-promotion deals provide a useful contribution to sales and profit for one partner and profit for another.

The data showing the contribution of BD&L projects to overall company sales varies enormously. In 2003 Boehringer Ingelheim presented data showing that over two thirds of sales of three of the top 15 pharmaceutical companies were from in-licensed products. 10 companies had an average in-licensed sales of 22% of the total and only two companies sales were entirely from own R&D products. Since 2003 much has changed three of the companies have merged and today not one of the Big Pharma companies has sales solely from own R&D. For example, nearly a third of Abbott's pharmaceutical sales in 2009 (prior to the Solvay acquisition) were from one in-licensed product, Humira (adalimumab) from Cambridge Antibody Technologies. At the European Pharmaceutical Licensing Group meeting in September, Merck & Co reported that 25% of their sales were from in-licensed products.

In many cases the new product sales have come from acquisition of biotechnology and product development companies. For example, AstraZeneca acquired Medimmune in 2007 for over $15bn and in August GSK acquired Human Genome Sciences for over $3bn. On a broader basis, over the period from January to September 2012 the aggregate value of biopharmaceutical deals reported in the Deal Watch articles published by Medius was nearly $77bn. Three quarters of that value was accounted for by company and product acquisitions with an average deal value of $650m but with an enormous range from GSK's $3bn acquisition of Human Genome Sciences to $8m for the acquisition by Alliance Pharma of three products in the UK. In-licensing deal values over the period averaged $225m, about one third the value of

acquisitions, with a range from $1bn for a global deal to $8m for a one country deal. Although pharmaceutical companies now, and perhaps in the future, increasingly depend on collaborations with third parties, the licensing deals are not cheap.

In conclusion, third party collaborations are now an essential part of biopharmaceutical companies' strategy to supplement product pipelines and to maximise revenues using commercial deals. The need for all types of deals and the high cost of such deals has driven the need for more professional BD&L managers. This in turn has created the provision of training courses to improve knowledge and skills and in parallel the professional associations have provided dissemination of knowledge and best practice to increase the level of professionalism. The contribution to companies' growth of partnered projects and the BD&L executives are fundamental to that success.

Legal & Regulatory Update

Evergreening patents: The Indian Supreme Court rejects patenting of incremental improvements

Received: May 14, 2013

Joanna T. Brougher
is Senior Counsel at Vaccinex, Inc. and Adjunct Lecturer, Harvard School of Public Health

ABSTRACT

On April 1, 2013, the Supreme Court in India handed down its decision to dismiss Swiss drug maker Novartis AG's attempt to win patent protection for its cancer drug Glivec. In doing so, the Supreme Court held that incremental improvements or modifications to an existing drug are not patentable under India's patent laws. While the ruling may have allowed India to maintain its ability to manufacture generic drugs, the ruling has increased the challenges that pharmaceutical and biotechnology companies face in obtaining patent protection in India. In the long term, these challenges may prove to have far greater implications for the biotechnology industry that go beyond merely the patentability of one drug product. In view of this recent decision, pharmaceutical and biotechnology companies are undoubtedly re-evaluating their foreign patent strategies.

Journal of Commercial Biotechnology (2013) 19(3), 57–61. doi: 10.5912/jcb.614

INTRODUCTION

On April 1, 2013, the Supreme Court in India handed down its decision to dismiss Swiss drug maker Novartis AG's attempt to win patent protection for its cancer drug Glivec. In doing so, the Supreme Court held that incremental improvements or modifications to an existing drug are not patentable under India's patent laws. While the ruling may be a victory for Indian companies manufacturing cheap generics, the ruling presents significant hurdles to Western pharmaceutical companies trying to market their products in India.

AGREEMENT ON TRADE RELATED ASPECTS OF INTELLECTUAL PROPERTY RIGHTS (TRIPS AGREEMENT)

The dispute surrounding the patentability of incremental improvements to a drug in India finds its origins in several sources, namely the Agreement on Trade Related Aspects of Intellectual Property Rights, or TRIPS Agreement, the Patents Act 1970 (India) and Patents (Amendment) Act 2005 (India).

Upon joining the WTO, each country must ratify a number of Agreements, including the TRIPS Agreement. The TRIPS Agreement was negotiated in 1994 to establish minimum standards for protecting and enforcing intellectual property rights for all WTO member countries. Prior to the TRIPS Agreement, patent laws varied across countries, and in many, including India, patent protection for pharmaceutical drugs was not permitted.

To harmonize patent laws across countries, the TRIPS Agreement established certain minimum standards that must be adhered to by each member nation. Among these basic standards are that patents must be available for inventions that are "new", involve "an inventive step" and are "capable of industrial application."[1] Additionally, patents must exist for twenty years and must confer the exclusive right to prevent others from making, using or selling the claimed invention. Furthermore, member nations are prohibited from discriminating by field of

Correspondence: Joanna T. Brougher, Vaccinex Inc., US.
Email: joannabrougher@gmail.com

1 TRIPS Agreement, Article 27(1).

technology or place of innovation. These basic standards mean that under the TRIPS Agreement, all member nations are required to provide patent protection for pharmaceutical drug products for twenty years. Although developed countries were required to implement TRIPS in 1995, developing countries, such as India, were given until 2005 to implement these new laws. This decade long extension was intended to allow developing countries more time to establish the necessary infrastructure to develop and carry out the new patent laws.

INDIA'S PATENT LAWS

While the requirements under TRIPS appear as a one size fits all type system, countries were afforded some flexibility with how to apply those requirements. For instance, the TRIPS Agreement does not define how high the inventive step must be, what kind of industrial application is required, or what constitutes making, using or selling. Accordingly, the TRIPS Agreement leaves ample room for countries to design a patent system tailored to their specific needs.

An example of the leniency allotted under the TRIPS Agreement is found in India's amendment to its patent laws.[2] Prior to the TRIPS Agreement, India, like many developing countries, denied patent protection for pharmaceutical drug products. In the context of food and medicine, India's patent laws stated that "no patent shall be granted in respect of claim for the substances themselves, but claims for the method of manufacture shall be patentable."[3] In other words, India permitted patents to methods of manufacturing a drug but not to the drug itself.

To be compliant with the TRIPS Agreement, but also to protect its public interest in developing generic drugs, India included a provision in its amendment that sought to limit the patenting of modifications to the already existing drug compounds, a practice also known as evergreening. Evergreening, in general, allows drug companies to extend the market exclusivity of a drug beyond the life of its original patent by obtaining multiple patents that cover different aspects of that drug, including the active ingredient, formulations, methods of manufacturing, chemical intermediates, mechanisms of actions, packaging, screening methods, and biological targets.

The provision, referred to as Section 3(d), was thus designed to prohibit the patenting of incremental improvements or slight variations to the existing compound. There are two main ways that Section 3(d) accomplishes this task. First, Section 3(d) interprets "invention" and "inventive step" in such a way that renders any "new form of a known substance which does not result in the enhancement of the known efficacy of that substance" as well as any "new use of a known substance" unpatentable. Second, Section 3(d) provides that "salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy." In this manner, Section 3(d) substantially hinders the practice of evergreening in India, while still allowing India to comply with its obligations of providing patent protection for pharmaceutical drugs under TRIPS.

Since its enactment, the Indian Patent Office has implemented a narrow and strict interpretation of Section 3(d). In 2008, for instance, the Indian Patent Office rejected a patent application for Viramune Suspension (nevirapine hemihydrates), a syrup form of Viramune (nevirapine), which is important for children living with HIV who are unable to swallow tablets, as a "new form" of a "known substance".[4] In 2009, likewise, the Indian Patent Office rejected patent applications on two ARVs, Viread (tenofovir) and Prezista (darunavir), despite arguments that the drugs, which consist of previously known compounds, demonstrated enhanced efficacy.[5] In 2010, the Indian Patent Office set aside the patent for Roche's drug Valcyte (valganciclovir hydrochloride) as lacking an inventive step and not showing increased therapeutic efficacy.[6] Valcyte is a modification of an existing drug, Cytovene (gancyclvoir), which is used to treat a common opportunistic infection associated with HIV called cytomegalovirus. More recently, the India Patent Office rejected an application filed by Abbott Laboratories for Aluvia (lopinavir and ritonavir), a heat stable version of Abbott's earlier drug. The patent office concluded that the drug was not a new invention, and thus not eligible for patent protection.[7]

2 Patents (Amendment) Act 2005 (India).

3 Section 5 of Patents Act 1970 (India).

4 http://www.twnside.org.sg/title2/intellectual_property/info.service/2008/twn.ipr.info.080610.htm

5 http://www.thehindu.com/health/article15145.ece

6 Victory for access to medicine as Valganciclovir patent rejected in India 06/05/2010; Why Roche lost a patent battle in India http://business.rediff.com/column/2010/may/13/guest-why-roche-lost-a-patent-battle-in-india.html May 13, 2010.

7 Intellectual Property Watch. Patent on AIDS Medicine Denied in India. 4 January 2011.

THE BATTLE OVER GLIVEC

With its narrow and strict interpretation of Section 3(d), India has experienced backlash from companies trying to obtain patent protection in India. One company, Novartis, has challenged India's laws and Section 3(d) in particular. Norvartis' case has garnered a great deal of attention around the globe because it has challenged how far countries can go to protect their own interests while still complying with the requirements of TRIPS.

The controversy involves Novartis' cancer drug, called Glivec (imatinib mesylate) or Gleevec, which is used to prolong the life of patients suffering from chronic myeloid leukemia. The price of Glivec ranges from about US$25,000 to about US$50,000 per patient per year. Generic versions of the drug, however, are available from several different Indian generic drug manufacturers for about US$2,100 per patient per year, a more than ten-fold price reduction. Glivec is an important drug for Novartis, bringing in about US$4.72 billion in global sales in 2012 alone.[8]

The dispute over Glivec revolves around a modification to an existing drug. The patent covering the active ingredient, imatinib, was filed in the US and certain other countries in 1993.[9] This patent was directed to imatinib as a "free base" molecule and disclosed the salt as imatinib mesylate. This first patent was never filed in India because India's patent laws at the time did not permit the patenting of drug compounds. In 1998, however, Novartis discovered a new application for a beta crystalline form of imatinib mesylate and filed a patent application directed to this new salt, which was a beta isomer of the already disclosed imatinib mesylate.[10] Unlike the first application, this second patent application was filed in India. When the application finally came up for examination in 2005, a pre-grant opposition was filed by several organizations, including Natco Pharmaceuticals, Alternative Law Forum, and Lawyers Collective on behalf of the Cancer Patients Aid Association. The opposition challenged the new Glivec application under Section 3(d), claiming that the application only concerned a modification of an already existing drug and did not improve its efficacy.

To overcome the patentability issue under Section 3(d), Novartis had to show that Glivec differed significantly over the existing drug with regard to efficacy. Under India's patent laws, isomers, such as the new form of Glivec, are generally considered to be the same substance as the original unless they differed significantly in properties with regard to efficacy. In its attempt to establish efficacy, therefore, Novartis demonstrated that the new form had enhanced bioavailability of thirty percent in studies conducted on rats. Novartis, however, was unable to demonstrate how the enhancement in efficacy was critical in the performance of the drug or what difference it made compared to the known efficacy. Unconvinced by Novartis' arguments, the patent office found Glivec to be unpatentable under Section 3(d).

Following the rejection, Novartis filed two cases, one challenging Section 3(d) of India's patent laws as violating both India's obligations under TRIPS and also Article 14 of India's Constitution, and another challenging the patent office's rejection of the Glivec patent application. The dispute over Glivec accordingly was thus divided into three components: (1) the compliance of Indian patent law with TRIPS, (2) the constitutional validity of the Section 3(d), and (3) the patentability of Glivec.

COMPLIANCE WITH TRIPS

The first component of the dispute involved compliance of Indian patent laws with the TRIPS Agreement. In its argument, Novartis claimed that Section 3(d) was in violation of India's obligations to the WTO. The Madras High Court, however, refused to hear the argument saying that domestic courts could not issue an opinion on matters dealing with international treaties and obligations and deferred the question to the WTO. To settle his dispute, Novartis would likely have to submit the case to the WTO. The issue remains unresolved.

CONSTITUTIONAL VALIDITY OF THE SECTION 3(D)

Novartis also challenged the constitutional validity of Section 3(d) under Article 14 of India's Constitution arguing that Section 3(d) discriminates against the pharmaceutical sector. With regard to this issue, the Madras High Court upheld the constitutional validity of Section 3(d), saying:

> *"India, being a welfare and a developing country, which is predominantly occupied by people below poverty line, has a constitutional duty to provide good health care to its citizens by giving them easy access to life saving drugs. In so doing, the Union of India would be right, it is argued, to take into account the various factual aspects prevailing*

8 http://www.fiercepharma.com/special-reports/gleevec

9 U.S. Patent Number 5,521,184

10 U.S. Patent Number 6,894,051

in this big country and prevent 'evergreening' by allowing generic medicine to be available in the market."[11]

The Court further added that Section 3(d) sets an obviousness standard which member states are free to define in a manner consistent with their national policy. The Court further upheld the constitutionality of Section 3(d) because it did not "discriminate" against the pharmaceutical sector, but only makes a justified differentiation given the specificity of salt forms. Other technology sectors, according to the Court, do not face issues arising from "different salt forms."

PATENTABILITY OF GLIVEC UNDER SECTION 3(D)

The patentability of Glivec under Section 3(d) thus rested with the Intellectual Property Appellate Board ("IPAB"). To win, Novartis had to show that the thirty percent increase in bioavailability was an enhanced efficacy, and that the beta crystalline form of the mesylate salt was not an obvious form of the free base form. After seven years of fighting over Glivec, however, the Supreme Court on April 1, 2013 found that Glivec did not show enhanced efficacy under Section 3(d), and thus did not meet India's requirements for patentability.

THE IMPORTANCE OF THE GLIVEC DECISION

The Supreme Court's decision in the Glivec case is importance for several reasons. First, the decision is important because it has solidified India's role in providing access to affordable medicines. India's generic drug industry has prospered into a $26 billion industry which has allowed India to become the leading supplier of generic drugs to developing countries. In fact, India is often referred to as the "pharmacy to the developing world", with about 67 percent of drugs produced in India being exported to developing countries, and about 80 percent of all medicines distributed by the International Dispensary Association to developing countries being manufactured in India. India is also the dominant supplier of HIV/AIDS drugs to developing countries with approximately 80 percent of ARVs used by Medicins San Frontiers ("MSF") being purchased in India, and in some African nations, like Zimbabwe, about 90 percent of its HIV/AIDS generic drugs being imported from India. India's continued ability to produce and distribute generic drugs to the developing world is protected following the Supreme Court's interpretation of TRIPS's flexible provisions.

The decision is also important because it has profound effects for pharmaceutical companies looking to patent products in India. The most obvious effect is that it prevents evergreening and the possibility of extending patent life for incremental improvements to existing drugs, meaning that a pharmaceutical company will not be able to extend the patent protected life of a drug simply by tweaking an old drug or if the drug is subsequently found to treat diseases besides those initially listed. Furthermore, depending on how the Indian courts interpret "efficacy", it may not be possible to patent formulations that merely reduce the need for refrigeration or offer easier methods of administration. Thus, once the original patent on a drug expires, the drug will no longer belong to the company. Instead, it will belong to the public domain. Overall, India's application of the TRIPS Agreement appears to eliminate ways of extending the patent protected life of a drug beyond the twenty years provided for by the initial drug patent.

While is still too early to determine the full impact of the Glivec decision in the pharmaceutical and biotechnology industries, it is almost certain that companies will re-evaluate the value of pursuing patent protection in India all together. Obtaining patent protection is costly, and with little chance to successfully obtain a patent, companies may choose to forgo filing in India.

There is also a chance that countries may impose certain trade restrictions on India. In response to Thailand's issuance of a compulsory license for Abbott's HIV/AIDS drug, Kaletra (lopinavir/ritonavir) in 2007, Abbott withdrew all of its new products from Thailand. The United States and the European Union both objected to Thailand's actions with the U.S. placing Thailand on its Priority Watch List as a trading partner and the EU Trade Commission voicing that such a practice will be detrimental to new pharmaceutical innovation.

This last point, that ignoring patent rights will hurt future pharmaceutical innovation, is very important. The patent system is designed to accomplish two goals, namely to promote the development of new medicines that are important to the public's health, and to allow the public to access the medicines once they are developed. A system that only achieves one of these objectives may be ineffective in continually improving the health of the general population. For instance, a system that promotes low drug prices does little to improve the population's

11 *Novartis AG and another v. Union of India and others* (6 August 2007, High Court of Judicature at Madras for W.P. Nos. 24759 and 24760 of 2006).

health because it fails to encourage development of other drugs that can be used to treat more diseases. By failing to provide adequate patent protection for pharmaceutical drugs, India may risk harming future development of new medicines.

CONCLUSION

The Supreme Court decision in the Glivec dispute has increased the challenges that pharmaceutical and biotechnology companies face in obtaining patent protection in India. By raising the threshold for obtaining a patent, India has maintained a strong generic drug industry that is the source of lower cost medicines to most of the developing world. At the same time, however, the long term consequences of this decision may prove to have far greater implications for the biotechnology industry that go beyond merely the patentability of one drug product. In view of this recent decision, pharmaceutical and biotechnology companies are undoubtedly re-evaluating their foreign patent strategies.

Legal & Regulatory Update

The life sciences industry and the changing IP landscape

Received: May 24, 2013

Dr Gareth Williams
is a Chartered (UK) Patent Attorney and European Patent Attorney specialising in biotechnology-related patent work, with particular expertise in genomics and peptides. He is a partner in the Cambridge (UK)-office of Marks & Clerk Patent and Trade Mark Attorneys. As well as filing and prosecution of patent applications worldwide, Gareth has extensive experience of hearings at the European Patent Office. He was the editor of the 2013 Marks & Clerk Life Sciences Report.

ABSTRACT

This article looks at the findings of Marks & Clerk's 2013 Life Sciences Report, launched in April 2013. Of interest to both R&D/IP experts and professionals in strategic positions within biotechnology companies, it explores many of the issues facing the biotechnology industry and is informed by an industry survey of over 330 international life sciences professionals. Topics explored include the financial climate, growing markets in Asia, IP reforms in the US and Europe, biosimilars and personalised medicine.

Journal of Commercial Biotechnology (2013) 19(3), 62–68. doi: 10.5912/jcb.618

As the life sciences industry continues to adapt to the ongoing challenges forced upon it by multiple factors, it is finding new ways to survive and, in the case of certain organisations, to thrive. The continued economic troubles in Europe, the long-anticipated, but nonetheless calamitous patent cliff and the continued variability in regulatory and IP regimes across different territories have all given rise to distressing headlines in the life sciences press, and widespread headaches in the boardroom. Meanwhile, in Asia, the booming economies of China and south east Asia are causing both excitement and angst for biotechnology strategists traditionally focussed on the European and North American consumer markets.

It is against this backdrop that Marks & Clerk produced its 2013 Life Sciences Report. With this report, we aimed to explore the issues facing the industry and provide insight from IP professionals. Our analysis has not only been informed by the many different biotechnology and pharma companies and associates that we work with the world over, but also by a targeted research survey of over 330 life sciences sector representatives that we conducted in March 2013.

For this study, we asked for opinions, predictions and first-hand experiences of the issues addressed in our report. Survey responses came from the US, Europe, China, South East Asia and other regions. Participants informed us that they worked for biotechnology, pharmaceutical (both originator and generic), academic, financial and other organisations, with the size of the organisations ranging from less than 10 employees to more than 10,000. As such, the views expressed are, we hope, indicative of those of the whole industry, and provide great insight into the realities faced by this diverse sector.

Correspondence: Dr Gareth Williams, Marks & Clerk LLP, Cambridge, UK. Email: gwilliams@marks-clerk.com

2012/2013 IN REVIEW

In order to measure the pulse of the industry as a whole, we were keen to better understand the general background against which our report was produced. When asked about the overall financial climate that respondents had encountered over the preceding twelve months, views were somewhat negative, with nearly four in five (77 per cent) respondents stating that the overall financial climate had either stayed the same or deteriorated. Only 20 per cent believed it had improved.

Although in our 2010 study, nearly two thirds (63 per cent) of participants felt there had been an improvement in economic landscape over the preceding twelve months, the disastrous immediate effects of the economic contraction resulting from the financial crisis meant that the economic bar was at that point much lower. The decrease, therefore, in the proportion of respondents citing an improvement this year is more a sign of stagnation than one of tougher times.

Looking at this assessment of the financial context in more detail, there was a little more positivity from those that identified as being involved in biotechnology (29 per cent improved) and being involved in investment (33 per cent improved). Readers may take heart from both of these figures, and particularly the latter, as the climate for investment is a key concern for the industry. Indeed, digging down into the individual issues influencing this relatively downcast view of 2012/2013, investment is the area considered to have deteriorated most over the past twelve months, with 40 per cent of participants in our research reporting that smaller ventures' access to funding has declined, and nearly one third (31 per cent) feeling that investor appetite for the sector has deteriorated.

Several other key areas appear to be eliciting the industry's concern. Half of all respondents (50 per cent) affirmed that the appetite for partnerships and strategic alliances had improved and less than one in ten believed it had deteriorated. Just over a third (34 per cent) reported similar improvement as regards mergers and acquisitions. The recently expanded partnership between the Scripps Research Institute and Takeda Pharmaceutical Co and Pathwork Diagnostics's recent collaboration with Kindstar Global in China both bear witness to this shift. This also confirms the predictions made in our 2010 survey, in which three quarters of participants looked ahead to an improvement in conditions for acquisitions and collaborations over a two year timescale. Of course, these are only signs that biotechnology and pharma companies are looking to other sources of growth, where core activities cease to generate sufficient levels of revenue.

FORECASTS FOR 2013/2014

Following questions on areas of disquiet in the sector over the last twelve months, we asked how respondents thought things may change over the coming year. In slight contrast to the assessments of the previous year, the sector showed a small increase in optimism, with 30 per cent predicting an improvement in the general financial climate, the investment community once again being the most hopeful of some kind of improvement (67 per cent). However, one quarter of respondents (24 per cent) felt that smaller ventures' access to funding and R&D pipelines will further deteriorate, and 21 per cent were pessimistic as to investor appetite for the sector over the coming twelve months. Unsurprisingly, just under half (49 per cent) predicted further improvement in the appetite for partnerships and strategic alliances, and 40 per cent were optimistic regarding mergers and acquisitions.

The conclusion that we would draw from the consistency between the evaluations of the preceding twelve months and forecasts for the next twelve is that the industry is not hopeful of an economic shift any time soon. This is not an insignificant concern – when asked how significant a problem the global economic climate will be for the life sciences sector over the next five years, an overwhelming 88 per cent answered that it would be either significant or very significant. Only three per cent thought it not very significant or not significant at all.

In addition, around two thirds (ranging from 62 per cent to 68 per cent) of respondents suggest each of the "patent cliff", variability in patent and regulatory protection across territories, and increasing regulatory barriers to market as being key concerns.

ASIAN PROMISE

With the misgivings of the European and, to a lesser extent, the North American biotechnology industries, it might be tempting to overlook that, in another part of the world, the industry is seeing huge growth. For the last ten years or so, European and North American industries have been waking up to the possibilities offered by the growth economies of Asia. The rapidly growing middle class consumer market, the increasingly skilled workforce and the various reforms being brought in by Asian governments are increasing the potential opportunities, and opening up the market.

And the industry is excited. For the first time in our series of Life Sciences Reports, respondents to our survey found China to be a more attractive territory in terms of market opportunities than Europe. With 76 per cent finding it an attractive or very attractive market and just seven per cent considering it unattractive or very unattractive, it is hot on the heels of the US (84 per cent attractive or very attractive, and 3 per cent unattractive or very unattractive). Meanwhile, Europe's comparatively mediocre result, with only 65 per cent deeming it attractive or very attractive in terms of market opportunities, was comparable to the 65 and 63 per cent that found India and South East Asia to be attractive or very attractive. Whilst not completely surprising, this should surely ring alarm bells for those of us serving the European market and for European policymakers.

Reflecting the enthusiasm for Asian markets, the life sciences industry is already forecast to increase its investment in the continent over the next five years. A significant majority of participants in our study predicted an increase in Asian marketing, sales and advertising spend (84 per cent) and Asian production capability

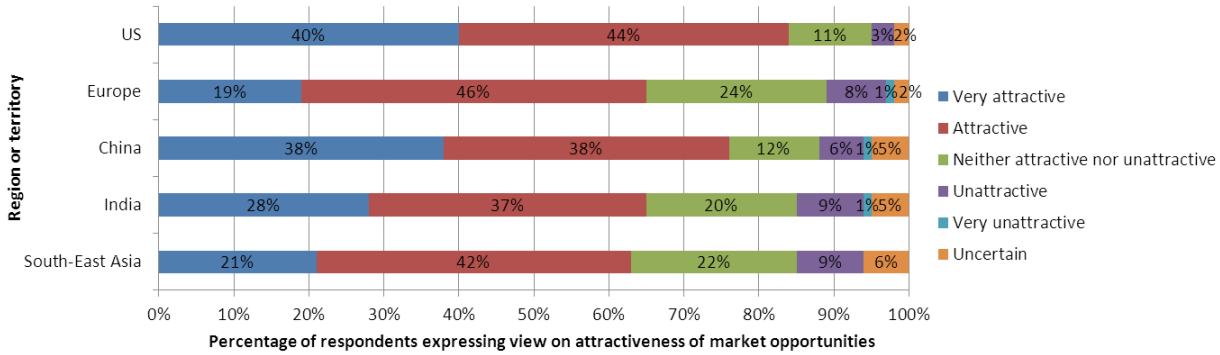


Figure 1: Respondents' views on the attractiveness of the market opportunities of different territories or regions

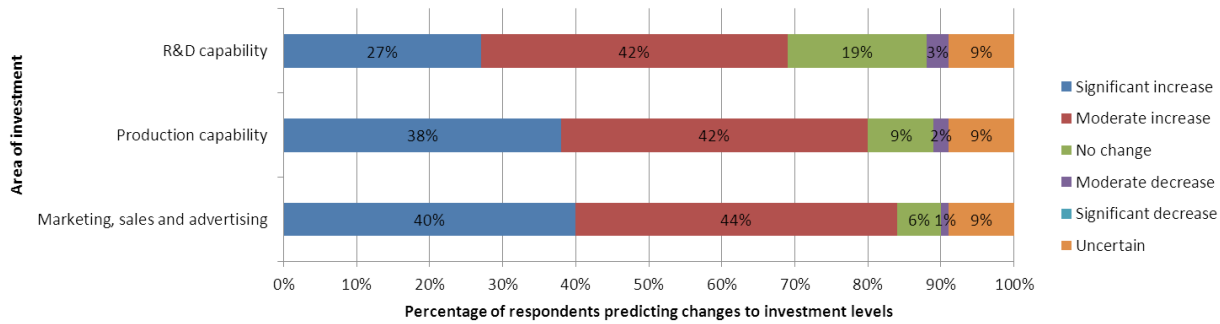


Figure 2: Respondents' predictions around the life sciences sector's adjustments to its investment over the next five years in Asian marketing, sales and advertising; Asian production capability; and Asian R&D capability

(80 per cent) over the coming half-decade. However, the investment in Asian R&D capability is forecast to lag behind marketing and production investment, with a slightly lower 69 per cent predicting an increase over the next five years. This will allow life sciences companies to tap into the skills and expertise of the workforce in these territories, potentially leading to greater knowledge transfer to the rest of the world, and more innovations coming out of China and south east Asia.

Further down the line, with a workforce over twice the size of Europe's and the US's combined, China is likely to become a key global R&D centre, and, in turn, it may even lose its status as a global manufacturing hub, with the development of manufacturing centres in countries like Malaysia, Vietnam, India and Indonesia.

As a consequence of the steps China is taking towards becoming an international R&D hub, it is not surprising that the explosion in patent filings in China in recent years, not just in biotechnology, but in almost all industries, has been widely discussed and debated. A booming patent office is a sign, albeit a delayed one, of a booming research economy.

Analysis of World Intellectual Property Organisation (WIPO) statistics for 2011 shows that although the number of Chinese IP applications is increasing rapidly, the number of Chinese-originating IP filed abroad is quite low. Specifically, the percentage of patents, utility models, designs and trade marks of Chinese origin which are being filed internationally appear to be modest at 3.8 per cent, 0.1 per cent, 11 per cent, and 11.8 per cent, respectively. It seems that the direction of investment in Chinese R&D is predominantly inward (from overseas into China) and domestic (Chinese companies investing in their own territory), with any expectation of a wave of Chinese IP filing overseas unfulfilled. As China's R&D capacity grows, these figures will no doubt begin to tell a different story. If the huge potential for knowledge creation and innovation is to be realised, both Chinese and foreign organisations and governments will have to improve the climate for joint ventures and knowledge transfer; otherwise the untapped R&D potential of China will remain so.

Despite China's undeniable allure, questions of training levels, infrastructure and, perhaps more fundamentally, regulatory regimes mean that Asian states, including China, have quite some way to go before they catch the two traditionally most important biotechnology markets up. When we asked survey participants

about the attractiveness of territories specifically in terms of their regulatory regimes, while no country performed particularly well (the US gained the highest level of approval, with 47 per cent considering it attractive or very attractive), China fell back behind Europe, with just 38 per cent finding the regulatory regime of the world's most populous country attractive or very attractive and 25 per cent (the highest of all scores) finding it unattractive or very unattractive.

Despite or perhaps because of its clear disadvantage on the regulatory front, more of the industry is seeing improvement in China's regulatory system than is seeing deterioration, with just 11 per cent of survey respondents considering it has gone downhill in the last half-decade, compared to 38 per cent believing it had improved (to varying extents). Meanwhile, 20 per cent considered Europe's regime had deteriorated and 14 per cent for the US.

Perhaps bad news for other Asian economies, however, is the low scores that South East Asia (as a whole) and India achieved in terms of regulatory improvement. Many Asian countries are implementing significant reforms in their regulatory and IP systems in order to attract inward investment. In particular, Singapore and Malaysia have instituted organisations and reforms, similar to moves in Hong Kong, to encourage the development of "IP hubs". However, as noted in the Report's summary of changes to the IP systems in various Asian and Australasian countries, some territories, such as India and Indonesia, have made generics-friendly decisions to open the way for cheap versions of drugs. Such steps need to be balanced with investor-friendly moves to reassure originator companies that there is room for them to operate in these markets too.

IP REFORM ON BOTH SIDES OF THE ATLANTIC

Both the European and US markets have historically faced challenges thanks to the set-up of their IP systems. The fragmentation of the European market with the current European patent system and the divergence of the US patent system from others worldwide, have often increased uncertainty for those responsible for patent protection and those engaging in patent litigation in those regions.

The last year has seen unprecedented progress towards a true single patent system in Europe, and the implementation of the most significant amendment to patent law since 1952 in the United States.

As many readers will know, organisations seeking patent protection for their inventions currently need to file one patent application at the European Patent Office (EPO), which is then validated individually in different countries. A European patent is, therefore, effectively a bundle of individual national patents (up to 40, depending on the states in which the patentee chooses to validate their patent), which must be enforced on a national basis. This fragmentation leads to increased uncertainty as court decisions on patent cases have been known to differ between European Patent Convention (EPC) contracting states, and a win in one country is by no means the end of litigation, nor even assurance of the outcome elsewhere. Accordingly, the costs of fighting litigation or insuring against the risk of having to do so are significant.

For decades now, European regulators and legislators have been working towards a single European (unitary) patent, which would mean one patent to protect inventions across all of Europe, with which one action could stop infringement Europe-wide. For biotechnology companies, this would not only reduce the uncertainty of inconsistent court decisions, but ensure protection in territories where organisations do not tend to file for patent protection; many companies tend to validate their European patents only in the Big 3 (the UK, France and Germany) and one or two other jurisdictions, as the costs of seeking pan-European protection under the current system can be prohibitive for smaller companies.

19th February 2013 marked a major milestone for the Unitary Patent system, as almost all of the European Union member states signed an international agreement for the creation of the Unified Patent Court (UPC). Assuming all the current signatories ratify the agreement, this means a unitary patent will span the whole of the European Union, save for Poland and Spain, and a decision from the UPC will be binding across all participating jurisdictions, whether it be an injunction or a revocation.

In our survey, just under half of respondents felt the UPC will improve commercial certainty and make it easier to enforce/defend against pan-European injunctions (46 per cent and 45 per cent respectively). Ultimately the Unitary Patent and UPC should indeed bring greater certainty for litigants and the possibility of resolving disputes through one set of proceedings, rather than many, should reduce litigation costs. In the short term there may in fact be greater uncertainty, as the new court gets up to speed and litigants explore and learn the approaches taken by the various local, regional and central divisions to the exercise of their new powers.

Encouragingly, nearly two thirds (64 per cent) of respondents expect the European reforms will have a positive impact on the European life sciences industry. Two thirds (67 per cent) feel the changes will go some

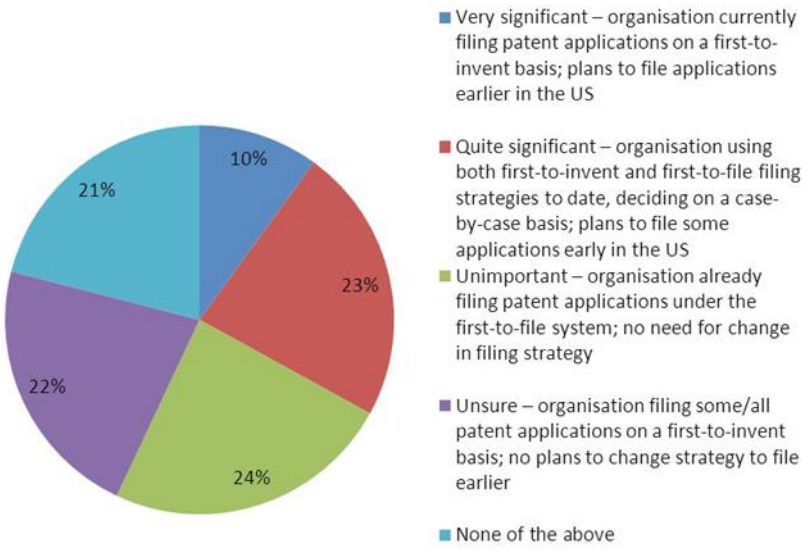


Figure 3: The AIA's impact on respondents' business's filing strategies in light of the move to FITF

way to addressing the historical problem of a fragmented marketplace.

Less positive, however, was the reaction of our research participants to the recent reforms undergone by the US patent system. The provisions of the America Invents Act (AIA) brought in during the course of 2012 and the first months of 2013 include the introduction of a first-inventor-to-file (FITF) system for patent protection, the elimination of interference proceedings and the introduction of new post-grant opposition procedures. In addition, the Act expands the definition of prior art, notably to include foreign offers for sale and public uses, and to bring in more foreign patent applications, previously excluded under the old law. Thanks to these, and the European developments summarised above, the US and European patent systems are becoming more and more similar in nature, although some important conceptual differences still exist.

The principal effect of the AIA on biotechnology organisations will be a shift in filing strategy. Of course, for applicants with a filing strategy based on a European model, the implementation of FITF will have little or no impact, but for the rest, significant adjustments to strategies may need to be implemented. Our survey indicated that more than half of respondents already filed at least some patent applications on a first-to-invent basis. Surprisingly, however, some 26 per cent of US-headquartered respondents indicated that, although they used to base their filings on the first-to-invent system, they still had to consider how to change their filing strategy.

When asked about the impact of the AIA, just under half of respondents (47 per cent) thought that the AIA would be positive for the US life sciences market. This means that more than half of respondents were either uncertain what the changes would mean for the market (31 per cent) or felt that the AIA would have a neutral or negative effect (21 per cent). Proportions of each type of response were remarkably consistent across company type and geographical split, suggesting that these views are broadly shared across the industry.

The lukewarm reception of the AIA can be attributed to many individual aspects of the change, but perhaps most telling is the opinion of respondents on the principal beneficiaries of the Act: 41 per cent believe the main beneficiaries will be large corporations, perhaps with the resources to defend their patents under the new post-grant review procedures, and only one in five answered that the entire sector would benefit.

ONGOING UNCERTAINTY AROUND SPCS

A further aspect of fragmentation within the European market, the Supplementary Protection Certificate (SPC) system, has also given rise to uncertainty in this traditionally central biotechnology market. SPCs are intended to compensate owners of patents for medicinal products for the erosion of patent term caused by the lengthy periods required to obtain regulatory approval to put the product on the market. Although the defining legislation is intended to be harmonised across Europe, SPCs are applied for and granted on a national basis. In practice this has resulted in local patent offices and courts differing in their interpretation of the legislation.

The importance of SPCs to the industry is clear, with over 50 per cent of participants in our study agreeing that dwindling pipelines will increase reliance on

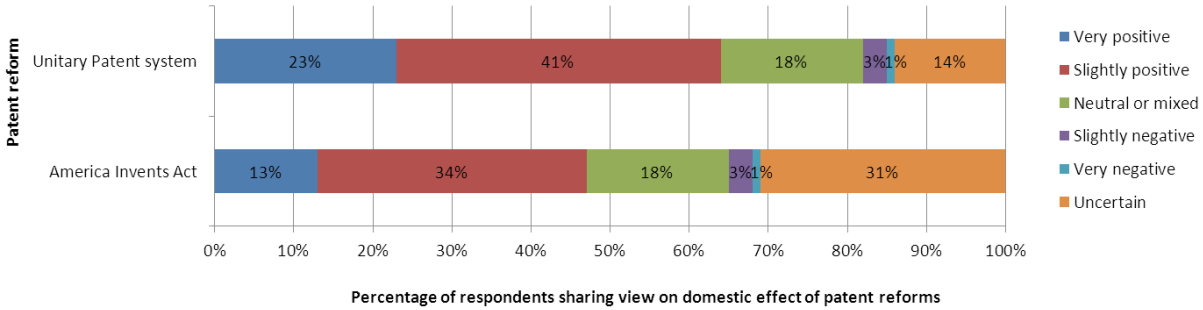


Figure 4: Respondents' views on the impact of US and European patent reform on the US and European life sciences sectors (respectively)

SPCs going forward. However, recent case law coming out of Europe's highest court, the Court of Justice of the European Union (CJEU), which has responsibility for clarifying questions of European law when national courts request explanations, has only served to confuse this already complex area.

For example, the court's decision on the *Medeva* case in 2011 on whether SPCs should be granted for combination vaccines dismayed many in the industry. Taking a narrow view and ruling that the active ingredients concerned should be "specified or identified in the wording of the claims of the basic patent", the CJEU failed to explain the actual test to be applied in such cases. What is more, the decision also appeared to interpret a 1997 decision (*Biogen*) to mean that only one SPC could be granted per patent. Previously, it had been understood that more than one SPC could be granted per patent if multiple products used the patented invention.

Reactions across Europe have differed, leading to further divergence in the application of the SPC legislation. For example, the UK IPO and Swedish Patent Office have indicated that their practice will not change and that they will continue to permit the granting of one SPC per product per patent. However, the Dutch IPO has refused to issue multiple SPCs on a single patent following *Medeva*.

In view of this unresolved incoherence and other concerns, the question remains as to whether the SPC regime should be replaced by something that is better fit for purpose. 87 per cent of respondents to our survey think that consideration should be given to whether the system should be rewritten to more closely reflect the US system of patent term extensions.

THE RISE OF BIOSIMILARS

Although biosimilar therapeutics are nothing new in Europe, the phenomenal success of monoclonal antibody therapeutics makes the expectation of biosimilar antibody products all the more significant. There are currently two biosimilar monoclonal antibody therapeutics under consideration by the EMA; Europe is far ahead of the US in progress towards entry of biosimilars to the market. Indeed, this may be a further reason for the decline in perceived European attractiveness as a market. However, our survey highlighted that there is generally very little awareness of the status of biosimilars. There is a fairly even divide between those who are aware and unaware of the progress that is being made towards biosimilar monoclonal antibody products in both Europe and USA. 38 per cent consider themselves aware of the progress in Europe whereas 40 per cent are unaware; 42 per cent said they aware of the progress in the US compared to 39 per cent who are not aware.

Furthermore, there is concern about whether biosimilar monoclonal antibodies that have not gone through the raft of clinical studies that the referenced product did will perform and be safe in patients. There is a real need for regulators to establish clearly defined boundaries for what will and what will not fall on the right side of the line when it comes to bioequivalence, even at this early stage in the development of this kind of drug. 84 per cent of our respondents feel it is important to the life sciences industry that regulatory regimes establish clarity with regard to biosimilars — as always, certainty is desirable for the industry.

PERSONALISING MEDICINE FOR PATIENTS

Personalised medicine, being the identification of individuals responsive to certain treatments or at risk of developing certain disease conditions, is one of the most exciting and fast-developing fields in the life sciences. Patent claims have tended to be directed towards isolated or purified DNA, or methods and kits based around biomarkers. In Europe, the patent position is fairly clear with respect to methods in personalised medicine, such

as those for determining the likelihood of a patient being responsive to a particular drug for rheumatoid arthritis. However, in the US, recent case law (*Prometheus* and *Classen*) has forced patent applicants to limit their claims.

The ongoing saga of the Myriad patents has also thrown into doubt the patentability of isolated (or purified) DNA despite the USPTO having sanctioned the patentability of isolated/purified DNA for over a decade. At the time of writing, the US Supreme Court recently ruled that isolated DNA is unpatentable. The impact of this significant change on the industry remains to be seen.

The corresponding position in Europe for DNA claims is that DNA is not excluded from patentability, although the body of prior art is now much fuller following the publication of the Human Genome and subsequent investigations. Further, the EPC requires that the industrial application of a gene must be disclosed in the patent application.

The position on both sides of the Atlantic with respect to stem cells is even more complicated. Within Europe, the UK and Sweden are strongly in favour of research into therapeutic cloning, whilst Germany has a much stricter regulatory approach. In addition to this, the highest court in Europe (the CJEU) has ruled in the recent Brüstle case that stem cell lines that were created involving the destruction of human embryos are excluded from patentability. The majority of respondents to our survey think that the CJEU decision on the patentability on human embryonic stem cells (hES cells) is likely to have a negative impact on levels of research and investment in the stem cell community, with 29 per cent going as far as saying it will force R&D abroad.

Following President Obama's reversal of President Bush's blanket ban on the Federal funding of stem cell research, things are now looking more positive in the US, although certain states still retain bans on any research into therapeutic cloning. To date, however, the debate in the US has seemed to focus more on the political side (funding or regulation) than the judicial (patentability).

CONCLUSION

As Marks & Clerk's 2013 Life Sciences Report explores, Europe's continued problems from the aftermath of the financial crisis and Asia's increased speed of development have led biotechnology organisations to re-evaluate their business models and deal with the pressing challenges of dwindling pipelines and overwhelming pressure on their balance sheets in a whole new way. The potential of China remains huge, and industry is clearly ready to engage with the market, but some caution remains over the regulatory regime, and knowledge transfer of Chinese-originating IP remains lacking. Meanwhile, the fundamentals of the IP system itself are changing, with patent reform in the United States underwhelming the industry and the introduction of a new unitary patent system in Europe providing hope, but not (yet) certainty to patentees and claimants.

Legal developments in other fields are also influencing the mood of the sector. Biosimilars and personalised medicine continue to hold great promise for future therapies, but recent developments regarding patentability of genes, diagnostic methods, and stem cells have created uncertainty and confusion. This is only exacerbated by the continued lack of clarity from the CJEU on the requirements for obtaining SPCs to prolong protection for medicinal products. The sector continues to wait for decisive action from policy makers and the judiciary, which of course needs to be balanced by forethought and a long-term assessment of the consequences of any immediate moves.

The questions faced by the biotechnology sector need tangible answers. This is an industry with a heightened sensitivity to outside economic and regulatory changes. Consequently, for many, the increasingly pressing question is how to adapt to the new world order; it's becoming more and more obvious that any expectations that the global conditions under which the biotechnology industry is used to operating will return to a twentieth century-norm will be frustrated.

EU Legal & Regulatory Update — May 2013

Received: May 29, 2013

ABSTRACT

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

- licensing intellectual property and know-how
- R&D agreements and other commercial contracts
- clinical trials
- regulatory issues
- risk management
- private equity, venture capital, joint ventures, strategic alliances, mergers & acquisitions and stock exchange listings
- patent & trade mark litigation
- data protection
- EU & competition law
- product liability

Bird & Bird has offices in Beijing, Bratislava, Brussels, Budapest, Düsseldorf, Frankfurt, The Hague, Helsinki, Hong Kong, London, Lyon, Madrid, Milan, Munich, Paris, Prague, Rome, Shanghai, Singapore, Stockholm and Warsaw and close ties with firms in other key centres in Europe, Asia and the United States.

This section is intended to be a synopsis of recent legal developments and is not intended to be exhaustive. If any issue referred to in this section is to be relied on, specific advice should be sought.

Journal of Commercial Biotechnology (2013) 19(3), 69–75. doi: 10.5912/jcb.620

EU: INTERIM MEASURES AWARDED AGAINST THE EUROPEAN MEDICINES AGENCY PREVENTING IT, PENDING FULL HEARING, FROM DISCLOSING CLINICAL TRIAL DATA TO THIRD PARTIES

On 25 April 2013 the President of the General Court of the EU Court of Justice made an order granting interim measures in favour of AbbVie and InterMune against the European Medicines Agency which prevent the Agency from disclosing to third parties certain clinical data that these companies had filed relating to already authorised medicinal products (respectively Humira (INN adalimumab) and Esbriet (INN pirfenidone)) before the two companies' respective challenges to the Agency's proposed actions have been fully examined by the Court. The President considered that both companies had mounted a prima facie case that the EMA's decisions to disclose such documents were in breach of Article 4(2) of Regulation (EC) No 1049/2001 regarding public access to European Parliament, Council and Commission documents, of the fundamental right to the protection of information covered by business secrets and being of a confidential nature under Article 7 of the EU Charter of Fundamental Rights, and of the obligation on the part of EU institutions under Article 339 of the Treaty on the Functioning of the EU not to disclose information of the kind covered by the obligation of professional secrecy. Given the prima facie case, and the fact that premature disclosure would do irreparable harm to the companies if their substantive challenge proved to be well founded, the President regarded the requirement of

Correspondence: Ewan Grist, Bird & Bird LLP, UK.
Email: Ewan.Grist@twobirds.com

urgency to be met and ordered the interim measures that the companies had sought. The grant of interim measures by the Court is rare but the orders in this case recognise that if the data in issue were to be released the substantive challenges to such action would be deprived of any real purpose.

Article 4(2) of Regulation (EC) No 1049/2001 requires that institutions such as the Agency refuse access to a document where disclosure would "undermine the commercial interests of a natural or legal person, including intellectual property … unless there is an overriding public interest in disclosure." The Agency's new guidelines, which have been in place since 2010, treat the following as commercially confidential information: detailed information concerning the quality and manufacturing of the medicinal products; information concerning the development of the product, including detailed information on the synthesis and manufacturing of the active substance; formulation, test procedures, validation, as well as manufacturers and suppliers of the active substance and excipients; and detailed descriptions of the manufacturing and control processes for the finished product. In contrast, information encompassing clinical and non-clinical development of a medicinal product is not regarded as per se commercially confidential, and thus as a rule the Agency regard data included in clinical trial reports as data that can be disclosed.

However, the President observed that it was not obvious from the documents before him that, following the necessary weighing up of interests that the Court would have to undertake when hearing the substantive challenges, the balance would clearly be in favour of the public interest defended by the Agency. He noted however that there is no case-law enabling an answer to be given easily to the question which the Court will have to determine, which is whether the contested decisions, based on the Agency's new disclosure policy, infringes the companies' rights on the ground that the information at issue is confidential in nature and must therefore be protected against any disclosure, and this involved "a question of principle affecting the functioning of the pharmaceuticals and biotechnology sector in Europe and worldwide." The wider significance of the substantive challenge is reflected in the applications to intervene in the cases that have been made by pharmaceutical industry associations, medical publishers and the European Ombudsman (whose recommendations in 2010 had led to the Agency's change in approach to freedom of information requests under which clinical trial data such as that in issue here was, along with non-clinical information, to be disclosed).

In both cases the clinical trial data that the Agency proposed disclosing had initially been sought by commercial competitors, although in the AbbVie case this was then followed by a request by a university science student in connection with the preparation of a master's thesis. Moreover, InterMune had when notified of the request for its clinical data provided the Agency with a copy of the documentation sought which it had redacted to remove information that it regarded as confidential, a constructive approach on the part of the company which the Agency appears to have disregarded, and the order made by the President allows this redacted version only to be disclosed.

The substantive challenges to the Agency's actions as to which the General Court will now in due course have to determine take place against a background of a controversial trend on the part of the Agency in recent years to grant under freedom of information legislation an increasing amount of access to the data that is filed with it. This is not just a question of the trend towards increasing transparency in relation to clinical trials, although a major concern with these is, unlike these cases, those trials which never lead to the authorisation of a medicinal product. But where, as here, the clinical trials in issue have led to the authorisation of a medicinal product (or an authorisation for a new indication of an already authorised product) even though, within Europe, data as to these disclosed for reasons of transparency cannot be relied on to undermine the regulatory data protection afforded such products by supporting applications by third parties seeking abridged marketing authorisations for generic or biosimilar products, there can of course be nothing under European law which could prevent such data, once disclosed, from being so used in non-European jurisdictions.

UPCOMING AMENDMENTS TO THE POLISH PHARMACEUTICAL LAW

The Polish Ministry of Health has recently published two draft amendments to the Act on Pharmaceutical Law. They implement the EU directives with regard to the prevention of the entry into the legal supply chain of falsified medicinal products (Directive 2011/62/EU) and pharmacovigilance (Directive 2010/84/EU).

Falsified medicinal products

The first amendment introduces to the Polish Pharmaceutical Law the requirements set out in the Directive 2011/62/EU concerning falsified medicinal products. In particular it adds to the glossary the definitions of "falsified medicinal product", "active substance" and "excipient".

According to the amendment, manufacturers, importers and distributors of active substances will be obliged to comply with Good Manufacturing and Good Distribution Practices. The conformity of manufacturing and distribution of active substances with these practices will be verified not only by the Pharmaceutical Inspection, but also by obligatory audits conducted by manufacturers and distributors of medicinal products. Any instance or suspicion of falsified medicinal product will have to be reported to the Pharmaceutical Inspection as well as to the marketing authorization holder.

Definition of brokers

In light of an increasingly complex distribution network for medicinal products, the amendment follows Directive 2011/62/EU in addressing a new category of actors in the supply chain, i.e. brokers of medicinal products. According to Directive 2011/62/EU, brokers are the persons involved in the sale or purchase of medicinal products without selling or purchasing those products themselves, and without owning and physically handling the medicinal products. This meaning of brokers is hardly reflected in the Polish implementation which states that: brokering are activities in relation to the sale and purchase of medicinal products, except for wholesale distribution and physical possession or supply, consisting in independently negotiating on behalf of another legal or natural person.

Firstly, the Polish definition seems to be self-contradictory as it is impossible to act independently and on behalf of another person at the same time. Secondly, and most importantly, the definition may be interpreted to cover persons who are not brokers of medicinal products within the meaning of Directive 2011/62/EU, e.g. external attorneys at law acting on behalf of pharmaceutical distributors and negotiating distribution agreements.

This could lead to absurd consequences in practice. According to the amendment every broker will be obliged to fulfil specific requirements. Hence, provided that the wording of the definition is not changed in the legislation process, an attorney at law representing a pharmaceutical company in negotiations concerning sale or purchase of medicinal products would have to register with the competent authorities, comply with the Good Distribution Practice, inform the Pharmaceutical Inspection on falsified products, etc.

Moreover, the pharmaceutical distributors could appoint only those attorneys at law who would fulfil the requirements set out by pharmaceutical regulations for brokers. It seems that in order to prevent such situations, the wording of the Polish definition of brokering should be corrected.

Sale of medicinal products on the Internet

Considering that the majority of falsified medicinal products are sold to the public via the Internet, the amendment addresses also the retail supply of medicinal products offered through distant selling by means of electronic communication.

Accordingly, pharmacies intending to sell medicinal products via the Internet will be obliged to notify the Pharmaceutical Inspection at least 14 days prior to the commencement of such activity. This requirement already exists in the Polish pharmaceutical regulations. However, so far, it was solely contained in the executive act that is the Ordinance of the Minister of Health and not in the Act on Pharmaceutical Law itself. Any modification of the data provided in such notification will have to be communicated without undue delay to the Pharmaceutical Inspection. A failure to satisfy the notification requirements as well as selling via the Internet prescription products might be sanctioned with revocation of the authorisation for retail distribution.

The minimum information standards for the Internet pharmacy website will be specified by the Minister of Health in a separate executive act. They should provide for the requirement to use a common logo identifying websites which are legally offering medicinal products to the public through distant selling.

Pharmacovigilance

The second amendment regards pharmacovigilance issues. The major changes concern the obligation of the marketing authorisation holders to report the suspected adverse reactions to the EU-wide pharmacovigilance database, known as "Eudravigilance".

The amendment facilitates the reporting of suspected adverse reactions directly by patients or their representatives. They will be able to communicate suspected adverse reactions both to the marketing authorisation holders and to the Drug Registration Office. On the other hand healthcare professionals will still be obliged to report suspected adverse reactions directly to the Drug Registration Office.

Following the amendment, an appropriately qualified person responsible for pharmacovigilance will have to be at the disposal of parallel importers on a permanent and continuous basis. So far this requirement concerned exclusively marketing authorisation holders.

The Drug Registration Office will gain new competences with regard to pharmacovigilance. This includes the possibility of imposing financial penalties of up to PLN 50.000 (ca. EUR 12.500) and suspending or even revoking a marketing authorisation in case of failure to report an adverse reaction.

Additional fee for marketing authorisation

Apart from implementing the provisions of Directive 2010/84/EU, the second amendment also introduces an additional fee for marketing authorisation holders for the activities related to pharmacovigilance.

The fee will amount to up to PLN 3.000 (EUR 750) (the exact amount will be specified by the Minister of Health in a separate executive act) and will be levied on an annual basis for each marketing authorisation held by the given holder. It will constitute an additional income source for the national budget.

Both drafts are currently forwarded to the Permanent Committee of the Council of Ministers and will be probably soon be sent to the Polish Parliament for enactment.

The drafts can be found here:

http://bip.mz.gov.pl/index?mr=m12091&ms=&ml=pl&mi=209&mx=0&mt=&my=749&ma=31653
http://www.mz.gov.pl/wwwfiles/ma_struktura/docs/projustprfarm_20130219.pdf

UK: DO PARTHENOTES FALL WITHIN THE TERM "HUMAN EMBRYO"?

The English High Court referred a question to the CJEU on the interpretation of Article 6(2)(c) of Directive 98/44/EC on the legal protection of biotechnological inventions. The question asked whether a parthenote, which only contained pluripotent cells and was incapable of developing into a human being, was included in the term "human embryo" under Article 6(2)(c) of the Directive.

International Stem Cell Corporation ("ISCC") had applied for patent protection for methods of producing and isolating pluripotent human stem cell-lines from parthenogentically activated oocytes. On the evidence before it, the Court found that parthenogenesis referred to the initiation of embryogenesis of an oocyte, i.e., cell division leading to the formation of blastocyst, without the involvement of sperm. Although the initial stages of development of a parthenote is similar to that of fertilised ova, they are not identical at any stage. The parthenote's lack of paternal DNA affects genomic imprinting, which means it can never develop into a viable human being and does not contain any totipotent cells.

In case C-34/10 (*Oliver Brüstle v Greenpeace eV [2012]*), Advocate-General Bot had differentiated between totipotent cells, which have the capacity to develop into a full human being and pluripotent cells which do not. However, in *Brüstle*, there was no consensus in the written observations on the subject of the development potential of parthenotes. In *Brüstle*, the CJEU held that the concept of "human embryo" under Article 6(2)(c) must be understood in a wide sense and held that "a non-fertilised human ovum whose division and further development have been stimulated by parthenogenesis" should be regarded as a human embryo. Although not fertilised, the CJEU stated that on the evidence before it, it was apparent that a parthenote was "capable of commencing the process of development of a human being just as an embryo created by fertilisation of an ovum can do so" (see paragraphs 32 to 38).

The Judge agreed with ISCC's submission that if the process of development was incapable of leading to a human being, which the English Court had found in this case in relation to parthenotes, then it should not be excluded from patentability as a "human embryo". Noting that a balance needed to be struck between the encouragement of potentially life-saving and revolutionary stem cell research and the need to respect the fundamental principles of safeguarding the dignity and integrity of the person, the Judge expressed his view that excluding processes of development which were incapable of leading to a human being did not strike that balance.

COURT CONFIRMS THAT A PRESS RELEASE TO JOURNALISTS AMOUNTS TO PROHIBITED ADVERTISING OF PHARMACEUTICALS

The decision by the MPA was appealed to the Administrative Court of Uppsala, which rendered its judgment on 18 February 2013, rejecting the appeal. Boehringer is thus prohibited from using the relevant press release or a similar statement, under the penalty of a fine amounting to SEK 750.000.

The press release at issue was released in Swedish and concerned the prescription drug "Pradaxa". It was published on the web site www.mynewsdesk.com/se/pressroom on 5 May 2011.

The decision of the MPA was based on the prohibition on advertising of prescription medicines in the

Swedish Medicinal Products Act, which is based on EU Directive 2001/83:

> *"Member States shall prohibit the advertising to the general public of medicinal products which are available on medical prescription only."*

According to the MPA, the purpose of the message is decisive as to whether it is deemed to be advertising (i.e. falling within the scope of the prohibition) or pure information (i.e. falling outside the scope of the prohibition). The latter is usually limited to information on the product package and in the leaflet. According to the MPA the text in the press release clearly displayed advertising character, inter alia, mentioning only positive aspects of the product.

Boehringer rebutted that (i) the press release in itself was not to be considered as advertising, and (ii) it was not targeted to the general public. In addition, Boehringer claimed that the release was protected by the constitution, relying on the freedom of speech argument.

In respect of the substance of the press release, the Court found that it lacked objectivity, as it did not state any potential adverse effects of the product. It was neither a reproduction of the leaflet or the product summary of the MPA.

The release also coincided with the expected approval of a new indication for the product. The Court also considered that the press release was available to the general public (there were no technical obstacles to access the press release), albeit that it was stated in connection with the release that it was intended for journalists only. Overall, the Court found that the release was designed to promote the prescription, supply, sale or consumption of medicinal products, and thus that it was to be considered as constituting advertising.

In respect of the relevant public, the Court found that it was targeted to the general public, the other possible category being persons qualified to prescribe or supply medicinal products. As journalists cannot be deemed to fall within the latter category, they therefore belong to the "general public" category.

Finally, in respect of the freedom of speech arguments raised, the Court found that, on the basis that the press release constituted pure advertising, the prohibition was compatible with the constitution. Furthermore, the prohibition was deemed reasonable and proportional.

This is an interesting case, and appears to be the first of its kind in Sweden.

As for any potential implications, it may be that the circumstances of this particular case, such as the timing of the press release and the nature of the press release itself, tipped the scales. There is cause for prudence when communicating on a platform which is available to and accessible by everyone (the outcome may have been different had the press release only been made available to a limited number of people e.g. by means of a password).

In essence, the MPA wishes to limit information disseminated publicly concerning prescription-based pharmaceuticals to what is available on the packaging, the leaflet and in the product summary.

The judgment of the Court has been appealed to the Administrative Court of Appeal of Stockholm.

NO UNLIMITED PATENTABILITY OF NEURAL PROGENITOR CELLS DERIVING FROM HUMAN EMBRYONIC STEM CELLS – GERMAN FEDERAL SUPREME COURT, NEURAL PROGENITOR CELLS II ("BRÜSTLE")

Recently, the German Federal Supreme Court decided on a nullity action on the patentability of progenitor cells extracted from human embryonic stem cells under s 2 (2) sentence 1 no 3 of the German Patent Act.

S 2 (2) sentence 1 no 3 of the German Patent Act (PatG) implements Article 6 (2) (c) of the European Directive 98/44 and reads:

> *"In particular, patents shall not be awarded for: [...] uses of human embryos for industrial or commercial purposes;"*

The nullity defendant is the proprietor of the German Patent number 197 56 864 directed at isolated and purified neural progenitor cells (including but not limited to human cells), methods for its manufacturing from embryonic stem cells and the use of the neural progenitor cells for the therapy of neural defects.

The nullity plaintiff had applied for the patent to be declared null and void in as far as progenitor cells are comprised which are derived from human embryonic stem cells for lack of patentability under s 2 (2) sentence 1 no 3 PatG.

At first instance, the German Federal Patent Court had declared the patent to be null and void in as far as it relates to progenitor cells and the manufacturing thereof from embryonic stem cells from human embryos. The patent proprietor appealed against this decision and motioned for the patent to be upheld as granted or, by way of auxiliary request, to uphold the patent with the claims phrased such as to exclude progenitor cells which have been derived from human embryonic stem cells, the

production of which included the destruction of human embryos.

The Federal Supreme Court in a decision of 17 December 2009 (docket no Xa ZR 58/07) decided to refer some questions to the CJEU regarding the interpretation of Article 6 of Directive 98/44 on which the latter issued a widely noted judgment on 18 October 2011 (docket no C-34/10 – Brüstle). Briefly summarized, the CJEU inter alia defined the term "human embryo". It found that Article 6 (2)(c) of Directive (EC) 98/44 also covered the use of human embryos for scientific research and held that it "excludes an invention from patentability where the technical teaching […] requires the prior destruction of human embryos or their use as base material […] even if the technical teaching claimed does not refer to the use of human embryos." Following this decision, the German Federal Supreme Court recently issued its decision in the case at hand.

The German Federal Supreme Court found that the patent was not patentable as granted under s 2 (2) (c) PatG but was patentable as applied for in the aforementioned auxiliary request. The Court explicitly differentiated between progenitor cells derived from stem cells which were obtained in a way involving the destruction of a human embryo and progenitor cells derived from stem cells which were obtained in a way which did not involve the destruction of human embryos. On the basis of the above mentioned CJEU decision, the German Court found that the patent as granted violated human dignity because although it did not expressly relate to the destruction of human embryos, the patent claims also included a technical teaching presupposing the destruction of human embryos. At the priority date, according to the understanding of the skilled person, the obtaining of stem cells typically involved the destruction of embryos. In light of s 2 (2) sentence 1 no 3 PatG this aspect was found to lack patentability and that it had to be excluded from the claims.

The patent as upheld by the Federal Supreme Court has a broader scope compared to the version as previously upheld by the Federal Patent Court. This was because the latter generally excluded from the patent progenitor cells derived from embryonic stem cells from human embryos without limiting these to the destruction of the human embryos. The Federal Supreme Court therefore found the aforementioned auxiliary request to be admissible and further to be disclosed such that a skilled person was able to implement the invention. In addition, it pointed out that it did not find it necessary that a specific way of obtaining progenitor cells without involving the destruction of human embryos was disclosed in the patent specification. Also, publications had been presented to the Court describing the obtaining of stem cells without requiring the destruction of human embryos. Moreover, the Court stated that human stem cells as such which have been obtained without involving the destruction of a human embryo did not classify as embryos. The Court found that it was not sufficient that these could – in combination with other, namely tetraploid, cells – potentially lead to a viable embryo for the stem cell in itself was not an organism having the capability of initiating the process of the development of a human being.

The Federal Supreme Court finally rejected a further reference to the CJEU on the question of the interpretation of the CJEU of Article 6 (2) (c) of Directive 98/44 contradicted Article 27 TRIPS since there was no indication that the CJEU had ignored Article 27 (2) TRIPS. The Court pointed out that the CJEU had cited this provision in the Brüstle-decision and applied the principles of the dignity and integrity of human beings set out therein.

After all, the Federal Supreme Court has drawn an interesting line regarding the applicability of s 2 (2) sentence 1 no 3 PatG which at the same time acknowledges and respects the findings of the CJEU and takes into account scientific developments which allow for obtaining stem cells without involving the destruction of human embryos.

CZECH REPUBLIC: UPCOMING CHANGES IN THE MEDICINE'S LEGISLATION

A new bill amending the Czech Medicines Act has recently been one of the most debated legislative pieces in the Czech Parliament. For the medicines' distributers and pharmacies, it brings two important changes.

Re-export policy on a straighter line

First of all, the requirements for reexport are envisaged to be stricter. A pharmacy which holds an authorization to distribute medicines shall not use the medicines that were obtained for its "pharmacy" business activities for further redistribution. The authors of the amendment argue that such practices can lead to unpredictability and unexpected market drop-outs of medicines. Also, there is a greater risk that copycats would enter the market due to the non-transparent distribution chain. The authorized pharmacy shall specifically determine which medicines are intended for further redistribution and which to be dispensed directly to the patients. Pharmacists opposing the proposed bill suggested that it

will do little to help the situation when dozens of medicines are no longer available in the Czech Republic.

Prescription drugs' obligatory authenticity features

Furthermore, new protective measures for identification of medicines (except for the radiopharmaceuticals) are being introduced which transposes into Czech law the European Directive on the Community Code relating to medicinal products for human use. The new bill aims at fighting counterfeits' spreading in the distribution chain. The obligatory authenticity features on the outer or inner packaging of prescription drugs should help to verify the product's authenticity and identify each package of medicine. The specific technical requirements for the authenticity features (e.g. the common logo) will be adopted by the Commission in the near future. Distributors shall perform a thorough control of these protective features on all received medicinal products and verify their authenticity. Any suspicion that a medicine has been counterfeited must be immediately reported to the Czech State Institute for Drug Control.

The Czech State Institute for Drug Control – extended competence

The Czech State Institute for Drug Control will likely gain more competence. The new bill proposes that the Institute can assess if the product name is appropriate with regard to public health and patients protection. According to travaux préparatoires, for instance the word "rapid" can no longer be used in the name if the product does not have significantly different characteristics from its counterparts and does not provide a faster effect to the patients. Any distributor, producer or importer that would like to have a permanent establishment or a place business in the Czech Republic shall report his intention at least 60 days before he starts his business activities in the country. The Institute will further obtain a competence to impose an obligation to perform post-authorization and safety studies on a marketing authorization holder if it finds it suitable.

Pharmacovigilance – new challenges

Overall, the pharmacovigilance rules will be much stricter. A principal change in the definition of adverse effect of medicinal products for human use is proposed. A mere suspicion that an adverse effect occurred will be sufficient for being reported to the Czech State Institute for Drug Control. At the same time, cases when a medicine was incorrectly used due to prescription mistakes, applications in contrary to the marketing authorization or misuses of the medical products will be also covered by the definition. The Institute is able to block the whole batch of the competitor's medicinal products. Some fear that this can be easily abused in the tough competitive pharmaceutical industry.

Book Review

Book review: The crowdfunding revolution: how to raise venture capital using social media

Received: June 3, 2013

Steven S. Ma
is a biomedical research associate based in Maryland, USA. He is interested in bioentrepreneurship and will be attending Duke University to earn his MBA (class of 2015). He received a B.S. in biology from Oregon State University in 2010.

Journal of Commercial Biotechnology (2013) 19(3), 76–77. doi: 10.5912/jcb.621

The crowdfunding revolution: how to raise venture capital using social media
Kevin Lawton and Dan Marom
McGraw-Hill, New York, 2013, 224pp., $35.00
ISBN: 9780071790451

Funding is a perpetual topic for life sciences start-ups. Historically, venture capital (VC) funding for this sector has been among the highest of all industries. In both 2011 and 2012, VC funding for biotechnology companies ranked second after funding for software.[1] However, VC funding for the sector has been on the decline since its peak in 2007, measured both in dollar amounts and in number of firms participating in biotech financings.[2,3] It is under such financing circumstances that the authors Kevin Lawton and Dan Marom argue the merit of crowdfunding.

In the book an introduction to crowdfunding was not given, and it is not needed. Crowdfunding platforms, such as Kickstarter and Indiegogo, have already made headlines by helping entrepreneurs raise millions of dollars in funds.[4] In 2012, congress passed the JOBS Act which included a provision for equity-based crowdfunding.[5] There is no doubt that a potential disruptive force in startup financing is building up in the U.S. Despite this excitement, there are key issues specific to the life sciences industry that may impede the widespread use of crowdfunding. First, can it raise sufficient funds to satisfy the intensive capital needs for drug and device development? Second, will regulatory requirements make it difficult for crowdfunded startups to obtain follow-on investment from VCs and institutional investors?

Lawton and Marom's goal is to convince the reader that crowdfunding will displace VC in the early stage financing of startups. Their argument lies on the observation that increased rate of technology turnover has led to a shorter technology generation-resulting in less time on market. The authors assert that the VC industry is inefficient at the early stage because firms rely on the knowledge of an exclusive group of individuals and thus are ill-equipped to handle the rapid pace of change. This reason is used to explain the observation that VC firms have shifted toward less volatile later-stage deals. On the other hand, the authors claim, due to the rise of the internet as a communication medium, individuals can connect and contribute their expertise as part of the crowd. The authors go on to explain terms such as "the collective IQ" and other reasons why crowdfunding will overtake VC funding by being more efficient in identifying the best ideas and allocating capital. This is what the word *revolution* is referring to in the book's title.

Lawton and Marom's revolutionary ideas are surely intriguing for entrepreneurs who have been following recent trends of the VC industry. Their argument on the evolution of innovation development extends beyond the uses for crowdfunding, and further toward the crowdsourced execution of ideas. The shrinking role of experts and the rising significance of collective wisdom brings to light a new, and perhaps inevitable, way of human innovation. In future workgroups and product development teams, efficiencies created by increased connectivity due to the internet must be utilized. The authors offer a compelling argument for this shift.

However, the book does not discuss how to actually raise VC funding via social media, as suggested by its subtitle. VC funding implies equity crowdfunding, and the Security and Exchange Commission (SEC) rules on this matter have yet to be finalized as of this writing. Instead, Lawton and Marom discuss tips on how to successfully start and run a campaign on leading donation-based crowdfunding websites, such as Kickstarter. Readers who were expecting details on

how to actually raise equity financing may be left disappointed. However, the goal behind cultivating a loyal supporter group should apply to equity crowdfunding once SEC rules are finalized. Lawton and Marom do touch briefly on regulatory aspects at the end-but more as evidence to oppose the restrictions within the JOBS Act. This is nonetheless informative from a policy standpoint.

Now onto the book's relevance for the life sciences. Biotechnology and medical devices are characterized by long development cycles and appear to be exempt from such ideas, if only for the time being. The authors identified such capital intensive projects as being beyond the scope of current crowdfunding platforms. The patent system is also briefly discussed, another potential roadblock for biotechnology crowdfunding. While the book is currently more relevant for less capital intensive projects, it would be prudent to keep an open mind and an eye out for changing models. There is already a trend in more patient-driven drug development and the FDA has recently launched the FDA Patient Network to stoke participation from patients.[6,7]

What the book lacks in the "how" of crowdfunding in the present, it makes up for in the "what" of crowd-based innovation of the future. While prospects remain uncertain for crowdfunding in the capital and regulation intensive life sciences industry, Lawton and Marom's book serves as an effective primer-or vaccine-and prepares the mind for the next disruptive model of early stage financing.

REFERENCES

1. PricewaterhouseCoopers and National Venture Capital Association. MoneyTree Report. New York: PricewaterhouseCoopers, 2013. [Online]. Available at: https://www.pwcmoneytree.com (accessed 27/05/13).
2. Rockoff, J.D. and Tam P. (2012) Biotech Funding Gets Harder to Find. The Wall Street Journal, 16 Mar, http://online.wsj.com/article/SB10001424052970203961204577267814201399918.html, accessed June 2, 2013.
3. Booth, B. (2012) Where is Everyone? Biotech's Dwindling Number of Venture Firms. Forbes, 23 Jul, http://www.forbes.com/sites/brucebooth/2012/07/23/where-is-everyone-biotechs-dwindling-number-of-venture-firms/, accessed 2 June 2013.
4. Kain, E. (2012) On Kickstarter Two Projects Pass the $1 Million Mark in a Single Day. Forbes, 13 Feb, http://www.forbes.com/sites/erikkain/2012/02/13/on-kickstarter-two-projects-pass-the-1-million-mark-in-a-single-day/, accessed 27 May 2013.
5. Colao J.J. (2012) Breaking Down the JOBS Act: Inside the Bill that would Transform American Business. Forbes, 21 Mar, http://www.forbes.com/sites/jjcolao/2012/03/21/jobs-act/, accessed 27 May 2013.
6. Swan, M. (2009) Emerging Patient-Driven Health Care Models: An Examination of Health Social Networks, Consumer Personalized Medicine and Quantified Self-Tracking. International Journal of Environmental Research and Public Health 6(2): 492-525.
7. U.S. Food and Drug Administration. The FDA Patient Network. Silver Spring: U.S. Food and Drug Administration, 2013. [Online]. Available at: http://patientnetwork.fda.gov (accessed 03/06/13).

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

PUBLISHER

Journal of Commercial Biotechnology is published quarterly in Washington, DC by thinkBiotech LLC.

Journal of Commercial Biotechnology is available online at *http://CommercialBiotechnology.com*. Visit the journal's website for focus, scope, and policies; submission guidelines; sample papers; and staff contacts. The website may also be used to order subscriptions.

CORRESPONDENCE

Business correspondence and inquiries should be addressed to *editor@CommercialBiotechnology.com* or to thinkBiotech LLC, 3909 Witmer Rd Box 416, Niagara Falls, NY 14305.

CUSTOMER SERVICE AND SUBSCRIPTION INQUIRIES

Susbcription policies and rates are posted at *http://CommercialBiotechnology.com/about/subscriptions*.

Subscriptions may be purchased by following the above link, or by sending a check, money order, or credit card details to the correspondence address above. Purchase orders, invoice requests, and additional questions may be directed to *editor@CommercialBiotechnology.com*.

2013 Subscriptions		
Student	Digital	US$169
Individual	Digital	US$225
	Print + Digital	US$280
Small company < 100 employees	Digital	US$560
Institutional	Digital	US$1060
	Print + Digital	US$1120

ADVERTISING

A media kit with advertising rates is posted at *http://CommercialBiotechnology.com/JCB-mediakit.pdf*. Additional questions may be directed to *editor@CommercialBiotechnology.com*.

REPRINTS

For reprints of this journal please contact the publisher at the address above or at *editor@CommercialBiotechnology.com*.

PERMISSIONS

For queries relating to reproduction rights please contact the publisher at the address above or at *editor@CommercialBiotechnology.com*.

COPYRIGHT

Print ISSN: 1462-8732
Online ISSN: 1478-565X

SEPTEMBER 17-18

PHARMA CI CONFERENCE & EXHIBITION USA 2013

HILTON EAST BRUNSWICK HOTEL
EAST BRUNSWICK, NEW JERSEY

The Best and Largest Assembly of Biotechnology and Pharmaceutical Competitive Intelligence Executives!

2012 Featured an Unprecedented
75+ Expert Speakers & 50+ Sessions

300+ Attendees

See Last Year's Sold Out Attendee List at
www.pharmaciconference.com/attendees

We Have a New Venue for 2013: Join Us at the Hilton East Brunswick Hotel in East Brunswick, New Jersey!

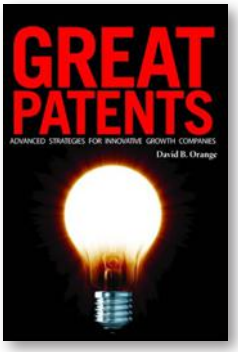
"Most influential global gathering of pharma/biotech competitive intelligence executives."
Actelion Pharmaceuticals Ltd

"Extremely interesting conference, very relevant for CI professionals and a great opportunity to exchange ideas and challenges."
Sanofi-Aventis

"It was a real pleasure to participate at the Pharma CI Conference & Exhibition. The event was so well attended and provided a great forum for CI Healthcare professionals to discuss and debate the value of CI and how it can continue to flourish going forward. The huge attendance was a testimony to a well organised and engaging event."
Bayer HealthCare Pharmaceuticals Inc.

Register at www.pharmaciconference.com

Books on the Busine



Great Patents

Advanced Strategies for Innovative Growth Companies

David Orange, editor

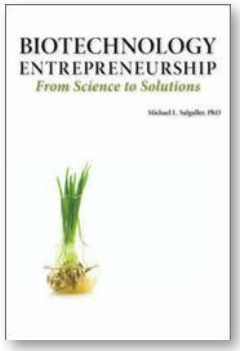
Softcover: 978-1-934899-18-2 - $74.95
Hardcover: 978-1-934899-17-5 - $89.95

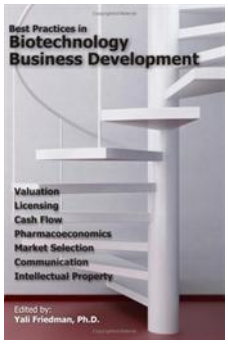
Biotechnology Entrepreneurship

From Science to Solutions

Michael L. Salgaller, Ph.D., editor

Softcover: 978-1-934899-14-4 - $64.95
Hardcover: 978-1-934899-13-7 - $79.97





Best Practices in Biotechnology Business Development

Valuation, Licensing, Cash Flow, Pharmacoeconomics, Market Selection, Communication, and Intellectual Property

Yali Friedman, Ph.D., editor

ISBN: 978-09734676-0-4 - $67.95

Building the Case for Biotechnology

Management Case Studies in Science, Laws, Regulations, Politics, and Business

Mark J. Ahn, Michael A. Alvarez, Arlen D. Meyers, Anne York, editors

Softcover: 978-1-934899-15-1 - $79.95
Hardcover: 978-1-934899-16-8 - $99.95

ess of Biotechnology

Get to Market Now!

Turn FDA Compliance into a Competitive Edge in the Era of Personalized Medicine

John Avellanet

Softcover: 978-1-934899-12-0 - $64.95

Building Biotechnology: Business, Regulations, Patents, Law, Politics, Science

The definitive biotechnology industry primer

Yali Friedman, Ph.D.

Softcover: 978-09734676-6-6 - $64.95

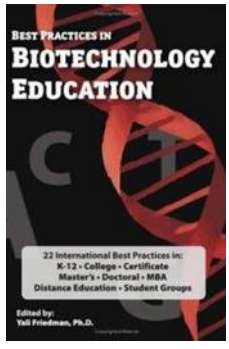
Hardcover: 978-09734676-5-9 - $89.95

Best Practices in Biotechnology Education

22 International Best Practices in K-12, College, Certificate, Master's, Doctoral, MBA, Distance Education Programs and Student Groups

Yali Friedman, Ph.D., editor

ISBN: 978-09734676-7-3 - $74.95



Logos Press

thought plus action

Books available at http://www.Logos-Press.com/books

or via:

Amazon, Ingram, Baker & Taylor, NACSCORP, Bertrans, Blackwell, Coutts, Gardners, Mallory, and others

LOGOS PRESS