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Commentary

Of Pens, Pizzas, and Pharmaceuticals

Peter J. Pitts
is President, Center for Medicine in the Public Interest.

ABSTRACT

Much ado about pharma freebies to physicians. Much ado about nothing medically and everything politically. A new study published by JAMA Internal Medicine (Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries) makes it sound (as Meagan McArdle has written for Bloomberg), that your doctor is "willing to sell you out for the price of a sandwich." It's not that simple … or true.

A valuable takeaway from the new JAMA study should be that wide adoption of Open Payments reporting has led to transparent interactions and value exchanges of education, money and meals between the pharmaceutical industry and prescribers. These data are now available to inform and improve educational efforts to meet the treatment needs of patients using the latest advances in medicine and science. However, such data must be cautiously interpreted with full acknowledgement of study limitations and author bias.

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Keywords: gifts to physicians, Interactions with pharma reps, normative bias

The truth is rarely pure and never simple.
— Oscar Wilde

Much ado about pharma freebies to physicians. Much ado about nothing medically and everything politically.

A new study published by JAMA Internal Medicine (*Pharmaceutical Industry–Sponsored Meals and Physician Prescribing Patterns for Medicare Beneficiaries)* makes it sound (as Meagan McArdle has written for Bloomberg), that your doctor is "willing to sell you out for the price of a sandwich." It's not that simple … or true.

The JAMA methodology:

- Cross-sectional study of 279,669 physicians that received industry-sponsored meals (retrieved from Open Payments program) and wrote Medicare part D prescriptions in any of four drug classes: statins, cardioselective blockers, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers (ACE inhibitors and ARBs) and selective serotonin reuptake inhibitors (SSRIs)/ serotonin norepinephrine reuptake inhibitors (SNRIs)
- Prescribing rates of promoted medicines were compared with in-class alternatives adjusted for volume, demographic characteristics, specialty and practice setting

It's important to note up front the JAMA conclusion stated that, "The findings represent an association and not a cause and effect relationship." But you won't find that in the media coverage. Also, the Open Payments data and Medicare Part D prescription data are not temporally linked. As John Adams points out, "Facts are pesky things."

Mechanism of association cannot be extrapolated from the methodology of the study; systematic confounding variables such as physician self-selection to attend the educational event and the effect of education itself obscure interpretation of the results. The study design is cross-sectional, only 5 months of payment data may not be representative of a full year and beyond. And, importantly, branded medicines that are often newer may represent advances over older generic agents with regard to efficacy and tolerability.

This is not a new debate nor is it new to the pages of the Journal of the American Medical Association. A widely cited 2000 JAMA article in summarized 29 published studies critiquing the interaction between

Correspondence:
Peter Pitts, Center for Medicine in the Public Interest, US. Email: ppitts@cmpi.org

doctors and drug reps. Notable feature of these articles, as quoted in the summary paper: "No study used patient outcome measures." Absent in 2000 and in 2016 was any discussion of how diagnostic and dispensing decisions are often influenced by external cost-control measures. Both JAMA articles allowed politics to trump the public health. The polite term for this is "normative bias."

Studies and commentary that discuss alternative findings are generally ignored. In the February 7, 2009 edition of The Lancet, Richard Horton points out that the battle lines being drawn and between clinicians, medical research and the pharmaceutical industry are artificial at best — and dangerous at worst. Dangerous, because all three constituencies are working towards the same goal — improved patient outcomes. His main point is that we must dismantle the battlements and embrace of philosophy of "symbiosis not schism." It's what's in the best interest of the patient.

Information is an important lubricant for markets and yields numerous benefits to market participants. Open, honest, and regular communication is critical for alerting both doctors and patients as to what medicines are available, and for what diseases. No single person, especially a general practitioner, can keep up with all of the information available on drugs, let alone health care. By one estimate every year some 1,700 articles are published in each of 325 professional journals on the 25 top medicines. Drug producers use a variety of promotional efforts to stand out in this information flood. One may like or hate the industry's tactics, but there is nothing illegitimate about them.

Per Dennis Ausiello and Thomas P. Stossel (both of Harvard Medical School):

> *The real intent of these critics goes far beyond food and trinkets, and its true purpose is to curtail strictly or even eliminate all contacts between physicians and private industry. We strongly oppose this agenda. Despite extensive training, physicians cannot know the details of all products, especially new ones. Therefore, company salespersons complement physicians' information derived from many sources. They tell physicians about a limited range of products about which their employers train them under strict FDA regulations. We believe that the best approach to optimize cost effectiveness of product prescribing is to promote more, not less, interaction among all stakeholders involved in health-care delivery, including company marketing reps.*

From a strictly free market perspective, if there were only one drug company, there would likely be an opportunity for that entity to speak regularly with physicians. But who marketed anything in the Soviet Union? Imperfect though the process might be, marketing promotes price competition and lowers prices.

According to Paul H, Rubin, Professor of Law and Economics at Emory University and former Chief Advertising Economist at the Federal Trade Commission and Chief Economist at the U.S. Consumer Product Safety Commission:

> *Drug company reps offer overworked doctors useful, lifesaving information in an efficient manner. The drug companies are of course motivated by profit, but economists have known since Adam Smith that the profit motive is the best way to induce someone to do something useful. Marketing and research are both information activities; they work together to get effective drugs to patients. The two activities are not in competition for resources. The denouncers of drug companies don't understand this. One of the senators sponsoring the bill suggests that "the millions of dollars these companies spend on marketing ... could be put into research." In fact, drug companies would not switch money from marketing to research. If they cannot market drugs in the best way, they will reduce spending on research. What's the point of inventing a new drug if doctors and patients don't know about it?*

This is crucial — in all of the medical literature on drug sales, there was no evidence of harm to patients caused by doctors and drug reps sharing a few slices of pizza. Physicians who, by their oaths, put patient welfare first wrote these articles. Yet they were critical of the industry based on analyses that totally ignore the only measure that really counts – patient outcomes.

"Good for sales" and "Good for the public health" are not mutually exclusive.

A valuable takeaway from the new JAMA study should be that wide adoption of Open Payments reporting has led to transparent interactions and value exchanges of education, money and meals between the pharmaceutical industry and prescribers. These data are now available to inform and improve educational efforts to meet the treatment needs of patients using the latest advances in medicine and science. However, such data must be cautiously interpreted with full acknowledgement of study limitations and author bias.

In summary, the new JAMA study is devoid of any data regarding patient outcomes; omits all the variables physicians consider when treating their patients; assumes pharmaceutical sponsored meals are purely

social gatherings in which no educational information is shared; and reduces complex prescribing decisions to a simple transaction.

"The best interest of the patient is the only interest to be considered."

— William Mayo, MD

Article

Intellectual Property Business Models Using Patent Acquisition: A Case Study of Royalty Pharma Inc.

Su Young Lim
is a Ph.D. Student in the Graduate School of Technology Management at Hanyang University and Manager, Product Development Department at LG Life Science.

Minsuk Suh
is Assistant Professor, Graduate School of Technology Management at Hanyang University.

ABSTRACT

In the pharmaceutical industry, companies are currently facing great challenges in developing new products due to patent expiration and decreasing profitability. In particular, the decrease in R&D productivity caused by the constant increase in the development period and cost of innovative new drugs means that the expectations of investors cannot be met. This study examined the successful case of Royalty Pharma's business model, which adopted securitization, a new investment method that makes advance payments of future profits in order to overcome the decline in R&D productivity and enables the pharmaceutical manufacturers (as patent owners) to resolve the issue of attracting investment funds, while also making these funds available for other development projects. It examined the role in the biopharmaceutical sector of patent aggregating companies in providing the competency to analyze patent technologies and to create investment megafunds, as well as the success factors that can lead to a virtuous cycle of product development. From this analysis, the application of a patent-based business model is proposed for small and mid-sized pharmaceutical industries.

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Keywords: royalty pharma, translational research, patent aggregation, patent broker

INTRODUCTION

The pharmaceutical industry is facing considerable challenges with its existing new drug development models due to patent expiration, decreases in R&D productivity, and a general decline in profitability. Various methods have been presented to resolve these issues, such as open innovation, drug repositioning, securing new drug candidates through M&A, and translational research. Translational research transforms the results of basic research in order to create new drugs that are viable in clinical practice.[1] Basic research is highly important in developing innovative new drugs, but it is also significant in increasing translatability for commercialization. One of the factors that causes lower productivity in the pharmaceutical industry, despite recent developments in medicine and the life sciences, is the lack of such translational research.[1] In particular, the cost to pharmaceutical companies of gaining new drug approvals/releases worldwide increased from $2.3 billion in 2004 to $3.9 billion in 2013, while the time required until the release also increased by approximately four years during the same period (see Table 1).[2]

The increase in the development period results in further costs, while also reducing the term from the release of a product to the expiration of any patents granted during the development phase, thereby cutting the period in which these products can maintain the status of being original drugs. This sustained productivity decrease in new drug development further increases the risks in developing innovative new drugs, thereby reducing investment incentives. This may lead to a deterioration of competency in the development of new drugs essential for improvements in healthcare.

To overcome these risks and develop innovative new drugs, constant capital investment is indispensable. Accordingly, securitization has been suggested, which is a new investment method that makes advanced payment

Correspondence:
Minsuk Suh, Hanyang University, Korea. Email: mssuh@hanyang.ac.kr

Table 1: R&D Expenditure of Pharmaceutical Companies Worldwide: Development Cost per New Drug[2]

Year	`04	`05	`06	`07	`08	`09	`10	`11	`12	`13
Number of new drugs	38	28	29	26	31	34	26	35	43	35
Development cost per new drug ($billion)	23	34	37	46	42	37	49	39	31	39

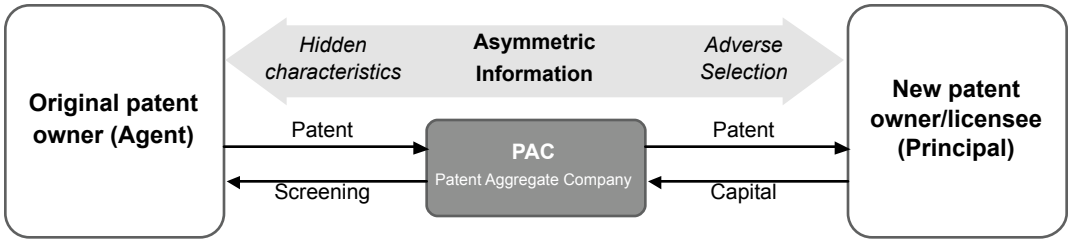

Figure 1: Players and Relationships in the Patent Aggregating Ecosystem[4–6]

of future profits in order to overcome the decline in R&D productivity and to enable the pharmaceutical manufacturers (patent owners) to resolve the issue of attracting investible funds, while also being able to use these funds for other development projects. Conventional funding methods have been dependent on investments from various venture capital sources, hedge funds, colleges, and pharmaceutical companies. However, the productivity of pharmaceutical companies is rapidly decreasing, with biotechnology venture capital showing an internal rate of return of approximately –1% for the 10 years from 2001 to 2010.[3] Royalty Pharma is a typical case of success in securing funds with bond issues, using patents as security through debt financing. This study examines the business model of Royalty Pharma, which presented new ways of patent management and investment for drug development; based on this analysis, it provides direction for the application of a patent-based business model in the bio/pharmaceutical industry.

PATENT AGGREGATING COMPANIES (PAC)

Advanced technologies and inventions, which constantly become more complicated and demand greater expertise to understand, easily result in information asymmetry between the companies or people that participated in the development process and those that did not. Here, the information concerns the economic value of the relevant technology or patent; such information asymmetry therefore prevents interested parties from determining the potential of the technology or patent, thereby causing adverse selection by the patent acquirer. A patent aggregating company (PAC) refers to a firm that focuses on acquiring patents without placing its core competency in R&D and producing/manufacturing physical products.[4] As shown in Figure 1, a PAC arranges the sale of patents or license transfers and gains profits accordingly by acquiring the commercialization rights from the patent owner, thus reducing the information asymmetry between the patent owner and the buyer. In other words, the PAC generates a market by finding the means to resolve information asymmetries between the patent owner and the acquirer; it thus creates value by analyzing, inspecting, and buying patents to resolve such asymmetries.

A non-practicing entity (NPE)—which differs in its use of intellectual property compared with a PAC—refers to a business that generates profits through patent sales or litigation by purchasing and managing the patent rights of other companies or individuals, rather than through technological development or manufacturing. The NPE is conceptually subordinate to the PAC in terms of its purpose in buying patents and its methods of generating profits.[4] The term NPE also has a more neutral meaning than does the negative expression "patent troll," but the literature thus far has not clearly distinguished patent trolls from NPEs; and Magliocca claims in his journal that the NPE is indeed a patent troll.[7] This study used the PAC as a criterion for analysis, using this term to refer to all companies that aggregate patents.

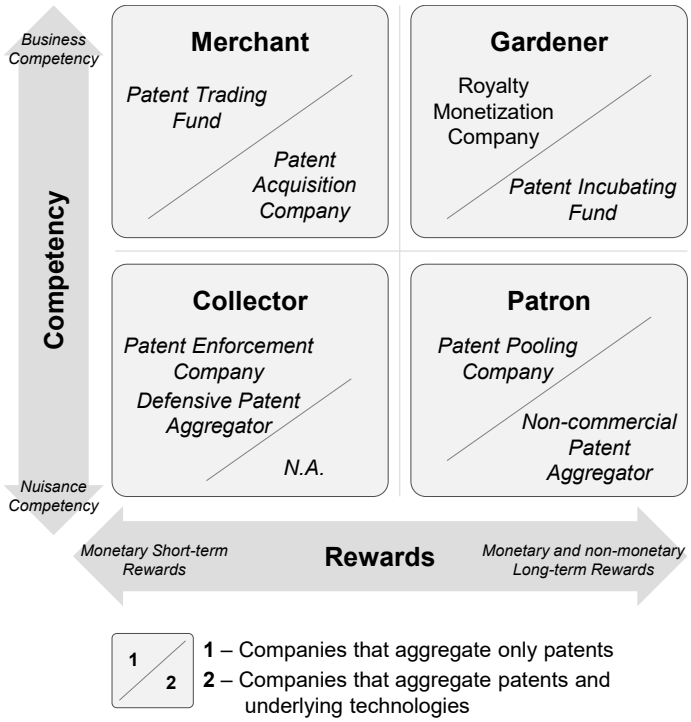

Figure 2: Typology of Patent Aggregating Companies[4]

TYPES OF PAC

Rüther categorized PACs into four types based on competency and reward in his 2013 book *Patent Aggregating Companies*.[4] Competency can be divided into business and nuisance competency. Based on its business competency, a PAC understands the development process and future value of a patent, based on detailed information about the technology and knowledge it represents. Nuisance competency is the judgmental ability to acquire patents in order to bring infringement lawsuits against third parties, based on knowledge and experience of using legal force. The rewards include not only cash flows, but also long-term and short-term strategic advantages. From these perspectives, a PAC can be classified as a merchant, collector, gardener, or patron, as shown in Figure 2. Studies on NPEs have been focused mostly on merchant and collector competencies and cash flow rewards; however, this investigation used a more comprehensive definition.

First, the "merchant" type can be divided into "patent trading fund" and "patent acquisition company." Patent companies in the merchant type acquire patents by assessing their market potential and the possibility of infringement lawsuits, as well as the provision of short-term monetary rewards. Of the two business models, the patent trading fund owns only the legal rights, while the patent acquisition company owns the general background knowledge and technology as well. The "collector" type is more in line with the concept of a patent troll and is classified further into "patent enforcement company" and "defensive patent aggregator." Both business models generate profits by winning actions involving patent fees and infringements; they therefore focus on the possibility of patent infringement lawsuits when reviewing a patent. These companies basically have an obstructive competency and provide short-term monetary rewards to patent owners. The "gardener" type, which is the case covered in this study, is further classified into "royalty monetization company" and "patent incubating fund," both of which assess patents based on technology and potential markets and their ability to provide long-term monetary rewards. By combining with a company of the gardener type, the patent-owning company can promote innovation and achieve business growth. A patent-incubating fund mostly obtains patents for technology transfers, while a royalty monetization company focuses on royalty income that can be obtained by acquiring the legal rights to patents. Finally, the "patron" type consists of "patent pooling companies" and "non-commercial patent aggregators," both of which resolve licensing issues and provide patents for many users, while also possessing obstructive competencies. The patron type mostly provides humanitarian licenses for the general public in order to improve a company's reputation and to create indirect R&D opportunities. One example is Golden Rice PDP, stemming from

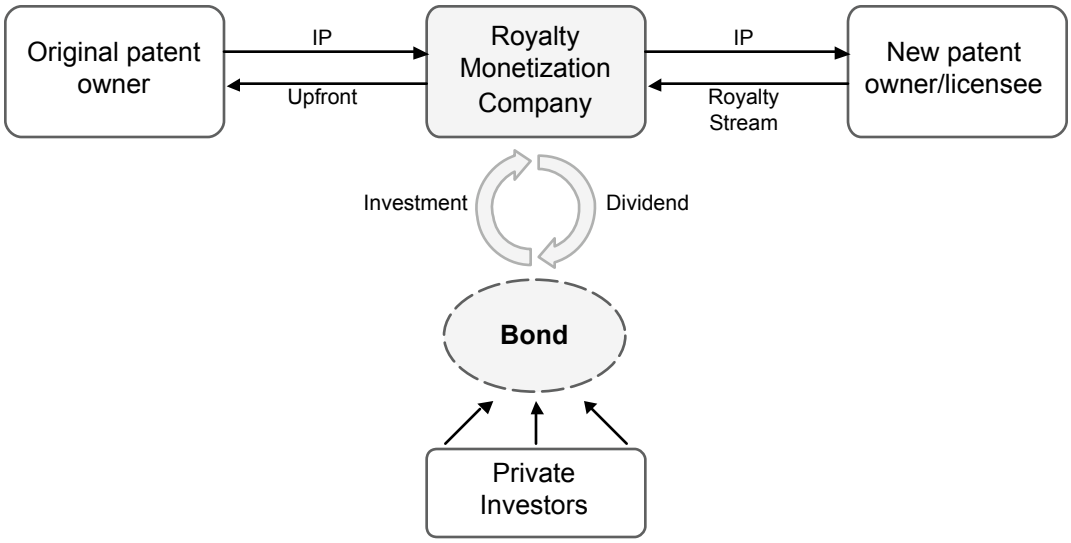

Figure 3: Cash Flows and Transaction Structure of a Royalty Monetization Company

the Rockefeller Foundation, which purchased a patent to resolve the issue of diseases caused by a lack of vitamin A.

CHARACTERISTICS OF ROYALTY MONETIZATION COMPANIES

A royalty monetization company, which is the business model of this case study, is one of the gardener type companies. The gardener type improves the financial condition of the patent-owning company, provides learning opportunities, and protects it from commercialization risks by providing long-term funds to patent owners. A royalty monetization company acquires patents as security for the capital provided for the patent owner; this capital serves as security again when it is collected from individuals or corporate investors.

A royalty monetization company is based on the fact that there is an agreement between the patent owner (owner) and another company (licensee) and that predictable cash flows are created. When the licensee tries to use the patent, an agreement can be made with the royalty monetization company through a proposal for royalty streams. The royalty monetization company makes available a special means of financial payment such as bonds; it then provides dividends to investors and funds to owners through the royalty stream obtained from the licensee. The royalty monetization company mostly trades with research institutes and small and mid-sized biotech or biopharmaceutical companies, taking on the risks of their license transfers and R&D. It provides capital for the patent owner to reinvest in new R&D projects while waiting for the royalties. Here, the capital provided is a lump sum payment in the form of a royalty stream that will be generated by the relevant patent in the future, rather than in the form of a loan. If there are no royalty incomes, the royalty monetization company covers the loss. Ultimately, the patent owner gains in advance the profits for the patent that it expects. In trading with investors, the royalty monetization company designs financial products such as bonds and sells them to investors based on patents, allocating the royalty incomes to the investors again (see Figure 3).[8]

A few examples of companies that use royalty monetization as a business model include AlseT, Capital Royalty, Pete Invest Med Tech, and finally Royalty Pharma, which will be examined in this study.[4] The fundamental strategy of a royalty monetization company is to provide an alternative source of capital to the patent owner, obtaining the patent as security; and indirectly using the patent through refinancing in the capital market by creating and marketing a financial product. Through this capital and knowledge management process, the company provides a means of investment for investors in the capital market, while providing stable cash flows in the pharmaceutical industry.

ROYALTY PHARMA'S BUSINESS MODEL

Founded in 1996, Royalty Pharma is a patent-based business focusing on royalty stream investments in the medical industry. It is an unlisted company located in New York, US, with 21 employees as of 2015, but its profitability is remarkably high, with a royalty income as high as $800 million. The main investment goal of Royalty Pharma is biopharmaceutical royalty income and it has a portfolio of 26 types of FDA/EMA-approved products

and two types of products currently under development. Among its product lines in about 12 areas, such as anticancer drugs, antidiabetics, and antirheumatic drugs, six products—including Humira®, which showed the world's biggest sales in 2014—are ranked within the top 20 in sales rankings, with a total of seven products within the top 50 in sales rankings.[9]

We selected Royalty Pharma, a royalty monetization company, as a case study because it is the first company in the biopharmaceutical industry to implement an innovative business model that reduces various risks in development and creates opportunities by providing patent owners with reasonable payments. Royalty Pharma is known to be a leading company that first introduced this business model before competitors like Cowen Healthcare or Paul Capital, putting six of its products among the ranks of the top 20 biopharmaceutical products in sales.[8] Moreover, Royalty Pharma developed the guidelines for the successful commercialization of pharmaceutical patent transfers. It captured an opportunity in the system of capital flows that had been overlooked in the drug development process, creating financial instruments that allowed it to generate an annual income of $800 million while also enabling patent developers, license acquirers, and investors all to make profits, thereby forming a new market structure in the biopharmaceutical industry.

Basically, Royalty Pharma does not develop or manufacture products, but makes profits through potential royalty income by acquiring royalty agreements that colleges and venture businesses made with pharmaceutical companies and providing capital for these colleges and venture businesses. It acts as a patent broker between colleges/venture businesses and major pharmaceutical companies. Typical examples include Abbott's Humira®,

Table 2: Top 20 Selling Products in the World[2,10]

	Product	Company	WW Product Sales ($bn)
1	Humira	AbbVie+Eisai	12,890
2	Sovaldi	Gilead Sciences	10,283
3	Enbrel	Amgen+Pfizer+Takeda	8,915
4	Remicade	JNJ+Merck & Co+Mitsubishi Tanabe	8,807
5	Lantus	Sanofi	8,428
6	Rituxan	Roche	7,547
7	Seretide/Advair	GlaxoSmithKline+Almirall+Faes	7,058
8	Avastin	Roche	7,018
9	Herceptin	Roche	6,863
10	Januvia/Janumet	Merck&Co+Daewoong+Ono+Almirall	6,358
11	Crestor	AstraZeneca+Shionogi+Chiesi	5,987
12	Lyrica	Pfizer+Jeil	5,209
13	Revlimid	Celgene	4,980
14	Gleevec	Novartis	4,746
15	Abilify	Otsuka Holdings	4,638
16	Neulasta	Amgen+Kyowa Hakko	4,599
17	Nexium	AstraZeneca+DaiichiSankyo+Daewoong	4,325
18	Lucentis	Novartis+Roche	4,301
19	Spiriva	Boehringer Ingelheim	4,300
20	Prevnar 13	Pfizer+Daewoong	4,297

J&J/Centocor's Remicade®, Pfizer's Lyrica®, Amgen's Neupogen/Neulasta®, and Genentech's Rituxan®; the scale of the resulting profits is shown in Table 2.[10]

CHARACTERISTICS AND RISKS OF EACH STEP OF PHARMACEUTICAL INVESTMENTS

The existing value chain of new drug development includes the R&D process from basic research to obtaining approval for market sales. Over the course from basic research to drug development (clinical trials), the risk of a product's market failure decreases, and the value of a new drug candidate increases rapidly along the value chain, as shown in Figure 4. However, for a drug candidate to be approved and commercialized as a new product on the market, costs are required at each step, requiring cooperation and coordination among agencies that can cover these costs and carry the trials forward.

The value chain of new drug development covers the entire process of drug development, from basic research to marketing.[11] As shown in Table 3, the period from basic research to preclinical trials included in the value chain of Figure 4 is three to 10 years, which is half the entire development period; however, the dropout rate is 99%. In other words, most candidates drop out before the clinical trials. Thus, 10 years of research and investments of $280 million result in almost no increase of value. However, once clinical trials have started, the dropout rates of candidates rapidly decrease to 70%, 20%, and 8% over the three respective trial phases. The cost for each product increases progressively when compared with the basic research phase, but in proportion to the lower dropout rates, the value of the candidates increases in the value chain. Candidates that have successfully completed the three phases of clinical trials are, in many cases, successfully approved by the authorities like the FDA and EMA, based on extensive discussions and negotiations.

Industry-academic cooperation occurs in each phase of the development process, starting with unofficial links like networking within the basic research cluster and then later, in the clinical trials, forming horizontal relationships in which the players share one another's technology and information. Ultimately, however, drugs can only reach patients after they are acquired by bio/pharmaceutical companies with competencies in mass production and marketing. Here, cooperation includes not only industry-academic cooperation, but also investors and financing methods to cover the astronomical development costs.[12] Many studies thus far consider drug development to be

Table 3: Characteristics of Drug Development Phases [12,14]

	Scientific research: chemistry and pharmacology	Development: medical testing and clinical trial			Marketing
Timing	~10 year	3-10 year			3 year
		Phase I	Phase II	Phase III & Registration	Phase IV
Rate of dropout	99%	70%	20%	5~8%	
Cost per drug	$2.8 billion	$1.3 billion	$1.9 billion	$2.8 billion	
Level of Risk	High	Medium		Low	
Dimensions of Cooperation	Networks/informal cooperation with clusters (University-industry linkages)	Horizontal alliances for product development (University-industry partnership)		Acquisitions by larger biopharma firms	

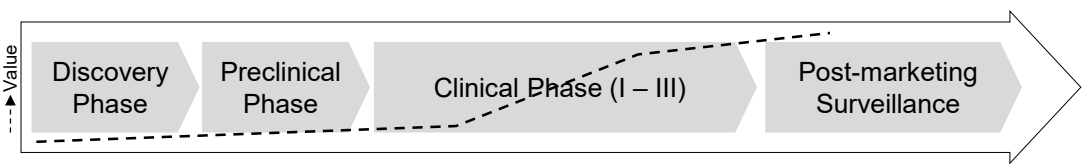

Figure 4: Value Chain of New Drug Development[11]

over once the drug completes Phase 3 of the clinical trial and is approved by the FDA or EMA. However, costs are still needed for Phase 4 to check optimal treatment regimes and side effects, which is part of translational research. According to recent studies, the biopharmaceutical industry requires active product and process innovations even after approval has been granted.[13]

TRANSLATIONAL RESEARCH

The concept of translational research first began to be used in the 1990s to emphasize the importance of translating the results of basic research to clinical trials. The main goal of translational research is bench-to-bedside, that is, integrating the basic research results studied in the lab with the development of clinical trials and delivering the final products to patients.[15] Molecular information obtained from various experiment techniques such as microarray analysis, genome sequencing, and proteomics must be shared between research centers and clinical hospitals.[16] In the 1990s, when the concept of bench-to-bedside was coined as a term, translational research implied the linking of basic research results to the development of new therapeutic measures (T1), perceived as an operation that could only be conducted by major pharmaceutical companies. As shown in Figure 5, various issues in clinical infrastructure, subjects, related regulations, and research costs that serve as translational blocks appeared in the development processes of new therapeutic measures. Since the 2000s, however, the concept of translational research has expanded to include the selection of optimal therapies after the developmental phase and supplying these to the medical field (T2).[1,16] Therefore, translational blocks still exist even after the authorization of products. However, the predominant view is that such bench-to-bedside processes have been interrupted, resulting in the currently existing business model being incomplete.[17,18] For example, while a huge budget is invested in T1 by the National Institutes of Health (NIH), only 1.5% is invested in T2.[1] Royalty Pharma has established a business model implementing a new financing method to facilitate T2 that has been overlooked by the NIH, despite the enormous expenses involved.[8]

BUSINESS FINANCING MODEL

Patent financing is a business model in which a patent-based business does not own a patent itself, but invests capital in another company that owns the patent in order to secure it as a subject for consultation, after which it shares the profits from the patent itself or from the sale of products protected by that patent. This can be defined as patent financing, as the patent-based business provides financial services. Royalty Pharma can be included in this type.

The basic model can be subdivided into IP-based financing, investment in IP-intensive companies, and IP-backed lending.[20] Royalty Pharma's operations can be classified as IP-based financing, which is a business model that provides capital for patent-owning companies in return for the rights to future royalty income of patent rights that are currently making profits. In other words, IP-based financing is a method that forecasts the royalty income that will be generated by patent rights

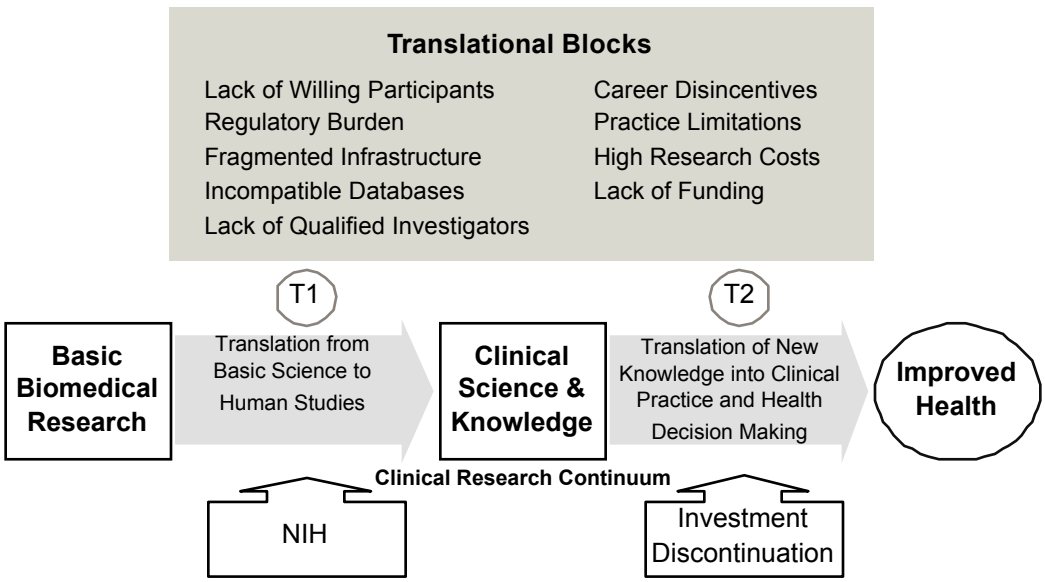

Figure 5: Translational Blocks in the Clinical Research Continuum [19]

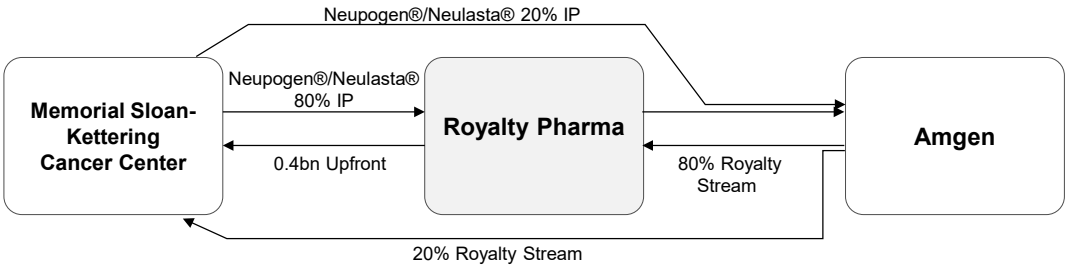

Figure 6: Example of Cash Flows and Transaction Structure of Royalty Pharma and MSK

that are currently making profits, based on which a certain amount of funds is provided to the patent-owning company in advance. In terms of royalty income structure, Royalty Pharma can also be referred to as a royalty monetization company. In this business model, it is more appropriate to say that capital is invested in the patent rights owned by the company rather than in the company itself. In other words, the company owns the patent rights in return for providing a stable capital base for the patent owner. In many cases, this upfront is provided in the form of bonds, converting the royalty income into securities and selling them on the capital market.

The executives of a royalty monetization company generally have financial or scientific backgrounds, as is the case with Royalty Pharma. Royalty monetization transactions evaluate the cash flows of products based on a patent, rather than evaluating the patent itself. For legal evaluations of patents, external resources are used, such as patent attorneys or patent evaluation service companies. Legal and financial advisers then design securities that can be sold. However, since long-term cash flows are essential for investments in patent royalties, it is difficult to create revenue streams in sectors other than the pharmaceutical industry.[4] A royalty monetization company mostly focuses on products at the FDA authorization/approval stage or Phase 3 of clinical trials among patents in the pharmaceutical industry. Major pharmaceutical companies that invested in initial products of the biopharmaceutical industry such as Humira® and Remicade® selected these products when it was difficult to determine their success or failure; they ended up achieving great success as brokers. By creating bond-type financial products for patent owners and connecting them to investor capital, they acted as coordinators to ensure that drugs could successfully reach patients.

ROYALTY PHARMA'S SUCCESSFUL TRANSACTION: NEUPOGEN/NEULASTA®

Neupogen (filgrastim) and Neulasta (prefilgrastim) are used to treat neutropenia, which promotes leukocytopoiesis; they were developed by Memorial Sloan Kettering Cancer Center (MSK) from 1970 and are FDA approved and sold by Amgen. They are used to prevent infections of patients in chemotherapy and patients receiving bone marrow transplants. These drugs recorded worldwide sales of $460 million in 2009 and $1.049 billion in 2015. Royalty Pharma engaged in transactions with MSK from the late 1990s and paid an upfront of $400 million twice in January 2004 and August 2005, acquiring 80% of the royalty agreement with Amgen (valuated as $500 million) from MSK. Following the royalty sale, MSK held financial assets totaling $2.1 billion by adding $400 million, which is approximately 25% of its current financial assets ($1.6 billion). This enabled MSK to build a new research facility and use its budget more effectively (see Figure 6).[21]

ROYALTY PHARMA'S INTELLECTUAL PROPERTY BUSINESS PROSPECTS

Major pharmaceutical companies have assessed the potential of the biopharmaceutical industry and are transforming into biopharmaceutical companies like Novartis. They will be making investments either into directly studying the candidate ingredients of biopharmaceuticals, such as synthetic drugs, or through the aggregation of findings from research institutes; these activities will be an obstacle for intellectual property brokers like Royalty Pharma. As a countermeasure, Royalty Pharma could only create new business opportunities by taking risks in fields other than biopharmaceuticals, where it initially made profits by covering the risks of drug development.

Table 4: Royalty Pharma's Portfolio[10]

Product	Acquisition Date:	Technology
Rituxan – US	Jan-98	Monoclonal Antibody
TOBI	Jan-99	Small molecule chemistry
Thalomid	Aug-01	Small molecule chemistry
Viviant	Mar-02	Small molecule chemistry
Neupogen/Neulasta	Jan-04	Recombinant product
Atripla/Truvada/Emtriva/Complera	Jul-05	Small molecule chemistry
Humira	Oct-06	Monoclonal Antibody
Remicade	May-07	Monoclonal Antibody
Prezista	May-07	Small molecule chemistry
Lyrica	Dec-07	Small molecule chemistry
RotaTeq	Apr-08	Vaccine
Letairis/Volibris	Dec-09	Small molecule chemistry
Savella	Dec-10	Small molecule chemistry
Myozyme/Lumizyme	Jan-11	Recombinant product
Cimzia	Feb-11	Recombinant product
Mircera	Feb-11	Recombinant product
Cubicin	Mar-11	Small molecule chemistry
Lexiscan	Mar-11	Small molecule chemistry
Januvia/Janumet	Jun-11	Small molecule chemistry
Onglyza/Kombiglyze	Jun-11	Small molecule chemistry
Galvus/Eucreas	Jun-11	Small molecule chemistry
Nesina	Jun-11	Small molecule chemistry
Tradjenta	Jun-11	Small molecule chemistry
Tecfidera	May-12	Small molecule chemistry
Imbruvica	Jul-13	Small molecule chemistry
Priligy	Jul-14	Small molecule chemistry

Biopharmaceuticals currently owned by Royalty Pharma did not face risks in regulatory approval and verification of clinical effects during acquisition, but at the time there were risks regarding the receptivity of these products by doctors and patients. Thus, the company needs to make a royalty income of 1–4% of the amount in the present while covering these risks and the costs in the treatment optimization (T2) step. However, with high biopharmaceutical receptivity of doctors and patients having been achieved, big pharmaceutical companies will no longer provide astronomical royalty income for patent brokers, but would rather make direct investments. As a response, Royalty Pharma acquired patents in synthetic drugs that have not yet been fully developed by big pharmaceutical companies and included them as a major part of its portfolio, as can be seen in Table 4. Moreover, the company will take on risk by acquiring candidates in earlier clinical stages rather than in post-approval products,

Table 5: Current Status of New Drug Development in Korea[24]

No.	Products	Company	KFDA Approved Date	Indication	R&D (yr)	R&D Cost (Government Investment, $ million)	2013 Sales ($ million)
1	Sunpla	SK chemicals	1999.7	Gastric cancer	10	6.8(16%)	0
2	Easyef	Daewoong	2001.5	Diabetic foot ulcers	8	4.2(3%)	1.2
3	Joins	SK chemicals	2001.7	Antiarthritis	9	5(5%)	13.5
4	Milican	Dong Wha Pharm.	2001.7	Anti-Liver Cancer	8	3.6(0%)	0
5	Q-roxin	JW Pharmaceuticals	2001.12	Antibiotic	10	4.2(6%)	-
6	Stillen	Dong-A	2002.6	Gastritis	9	15(5%)	20.8
7	Factive	LG Life Sciences	2002.12 (KFDA) 2003.4 (FDA)	Antibiotic	11	250 *GSK:83%	1.9
8	Camtobell	Chong Kun Dang	2003.10	Anticancer	11	125(13%)	2.1
9	Maxmarvil	Yuyu	2004.1	Osteoporosis	7	2(6%)	-
10	Revanex	YUHAN	2005.9	Antiulcer	15	33(7%)	2.1
11	Zydena	Dong-A	2005.11	Erectile Dysfunction	9	17(11%)	9.8
12	Levovir	Bukwang Pharm	2006.11	Hepatitis B	11	93(1.5%)	2.9
13	Mvix	SK chemicals	2007.7	Erectile Dysfunction	10	12.5(10%)	7.5
14	Noltec	Ilyang	2008.10	Antiulcer	22	25(37%)	11.3
15	Kanarb	Boryung	2010.09	Hypertension	13	24(11%)	17.4
16	Pyramax	Shin Poong	2011.08	Malaria	12	58(0%)	0
17	Zepeed	JW Pharmaceuticals	2011.08	Erectile Dysfunction	6	2.1(0%)	-
18	Supect	Ilyang	2012.01	Leukemia	12	25(14%)	0.7
19	Zemiglo	LG Life Sciences	2012.06	Diabetes	10	39(11%)	4.4
20	Duvie	Chong Kun Dang	`13.07	Diabetes	14	21(18%)	-

as it gains more experience and knowledge in technical analysis, thereby maintaining its current business structure for the present.

CHARACTERISTICS OF THE KOREAN PHARMACEUTICAL INDUSTRY

According to the Korea Pharmaceutical Manufacturers Association, the market size for 2014 is approximately $16 billion;[22] and there is only one Korean pharmaceutical company, Yuhan, with more than $880 million in annual sales as of 2014. The current condition of the market in Korea can be pointed out as an issue, since it falls far short of the critical mass required for new drug development in terms of the R&D resources of Korean pharmaceutical companies. Drews estimates that the critical mass of global pharmaceutical companies for new drug development is annual sales of $6-8 billion;[23] as shown in Table 3, the cost required for new drug development is approximately $880 million. There is not enough capacity to nurture Korea-based pharmaceutical companies into major global pharmaceutical enterprises. Likewise, the size of

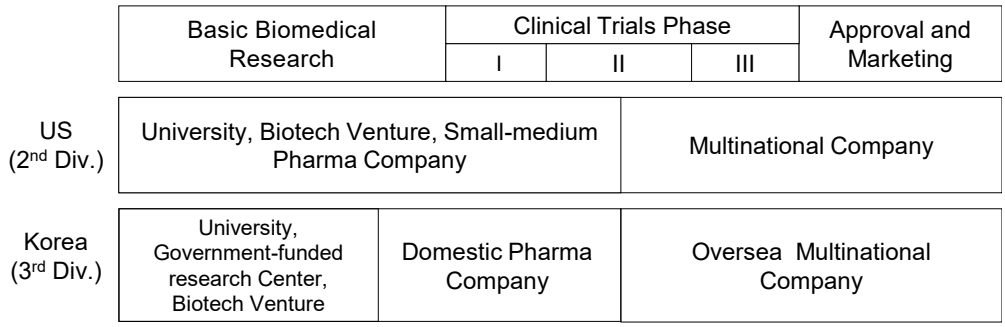

Figure 7: Divisional Structure of New Drug Development in Korea and US[25]

Korean pharmaceutical companies in the Korean market falls short of the minimum critical mass for them to compete as global operators, yet they will be unable to reach this critical mass without considering the global market.

CURRENT STATUS OF NEW DRUG DEVELOPMENT IN KOREA

According to recent data on the current status of new drug development in Korea by the Korea Drug Research Association, new drug development in Korea is led by pharmaceutical companies on the basis of 20 products that succeeded in gaining approval from the Ministry of Food and Drug Safety. The average development cost of these 20 new drugs in Korea is $32 million, but considering that 83% of the development costs of Factive® by LG Life Sciences were covered by GlaxoSmithKline (GSK), the average is actually less than $22 million.[22] Moreover, as can be seen from the current status of new drug development in Korea in Table 5, the level of government investment for authorized new drugs is less than 9% on average, while most R&D funds are direct investments from the sales of pharmaceutical companies. More importantly, most drugs, even after they have with difficulty been finally authorized, show poor sales of less than $8 million.[24]

To overcome the limitations of the current industrial structure and new drug development processes, the Korean pharmaceutical industry has adopted a three-party structure that out-licenses operations to major pharmaceutical companies in Phase 2 of clinical trials, as shown in Figure 7.[25] In contrast with the two-party industry structure in the US, Korean pharmaceutical companies are serving as venture enterprises in terms of size and role. As of 2014, only 11 companies in Korea spend more than $15 million annually in R&D, which is the scale of venture businesses in advanced countries.[25] In fact, LG Life Sciences developed Factive®, was the first to succeed in gaining FDA approval, and has the highest ratio of R&D investment to sales, yet its asset size is $500 million in 2014. Meanwhile, MSK, which was mentioned as a successful case of transaction by Royalty Pharma, has assets of $5.365 billion.[26,27] In 2005, when the royalty translation took place, the assets of MSK were $2.1 billion.[21] Such clear disparities in size have led to the differences in R&D investments, resulting in remarkable gaps in terms of the project size of new drug development in Korea.

CONCLUSIONS AND IMPLICATIONS

This study examined Royalty Pharma, which led the virtuous cycle of product development in the biopharmaceutical field with its competencies in patent analysis and the creation of financial products to attract investments in the tough environment of the pharmaceutical industry. This company accurately perceived the fact that while the goal of developers is focused on authorization, there are still many steps required in order even for fully developed drugs to reach patients; moreover, it served as a broker by capturing the needs of developers and investors. The company also took on the risks of developers in the process of acting as a broker, as well as the risks of investors such as adverse selection, thereby creating a virtuous cycle of development.

Those industries where advanced technologies like bio, nano, and alternative energy form the foundation tend to actively implement and combine different technologies, most of which face difficulties in overcoming barriers such as risks in successful development or immense R&D costs. Royalty Pharma's business model is differentiated from that of the patent troll (NPE), which focuses on making profits through patent ownership and litigation. Rather, its operations result in fulfilling the needs of both patent owners and acquirers, bringing innovative biopharmaceuticals to the market and providing new opportunities not only for patients, but also for many researchers and research centers previously blocked by the entry barriers mentioned.

However, major pharmaceutical companies began to seek change following their business successes, to which

Royalty Pharma is also showing signs of responding. Currently, it seems that Royalty Pharma's biopharmaceutical range will sustain its present earnings rate until 2020, but the company is taking more risks in development by shifting its portfolio—which had been focused on approved biopharmaceutical products—to those in Phase 3 of clinical trials or before. In other words, with the stabilization of the business model that targeted profits as brokers taking on the risk of product receptivity by doctors and patients, those pharmaceutical companies based on R&D and production of synthetic drugs, as well as PACs based on developing intellectual property and securing competencies, have come to face direct competition.

The Korean pharmaceutical industry should use Royalty Pharma's business model as a strategy to overcome the size variance and the limitations of a small and mid-sized bio/pharmaceutical industry. Domestic markets and direct governmental support in most countries apart from the US have clear limitations in supporting projects for pharmaceutical companies based on making new global drugs for massive markets like the US or Europe. In a similar manner to the way that private investors of Royalty Pharma receive dividends later, it is necessary to increase the size of investment funds with government and private investments, using marketable patents as security, and pay the upfront to colleges, research centers and companies conducting basic research so that they can invest in various products that are likely to succeed. Then it will be possible to set the direction to overcome most of the difficulties faced by small and mid-sized pharmaceutical industries like Korea.

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*Su Young Lim
Lim graduated from the University of Rochester and earned a master's degree at Johns Hopkins University, after which she completed the doctoral program at the Graduate School of Technology & Innovation Management of Hanyang University. Currently she is serving as Project Leader/Manager of Product Development Center at LG Life Sciences. Her main areas of interest are technical innovation, biopharmaceutics, intellectual property, and business strategies.

**Minsuk Suh
Suh earned a bachelor's degree in mechanical engineering and a master's degree in mechanical design engineering at Yonsei University, and a master's and Ph.D. in industrial engineering at the University of Michigan. Currently he is a professor at the Graduate School of Technology & Innovation Management of Hanyang University, and his main areas of study are knowledge management, new product development, and technology commercialization.

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Article

Manage Complexity and Uncertainty in Biotechnological Innovations: Converting Theoretical Advances Into Opportunities

Jonathan Baert
holds a master in bioingeneering from Université Libre de Bruxelles (ULB) and a master in management from the Solvay Business School Economics and Management (SBEM). He is currently working on bioporcesses optimization and completing his PhD thesis at Gembloux Agro-Bio Tech (GxABT).

ABSTRACT

The recent development of synthetic biology and system genomic open a new promising dimension for bioprocesses optimization. This induces an increasing complexity of applications in the biotechnology industry. Moreover, profitable bioprocesses design requires close collaboration between specialists as biologist, geneticist, or process engineer. As a consequence, the theoretic complexity of bioprocesses development steps is hardly increased. The implementations of efficient collaboration structures allowing to take profit from external opportunities are at the basis of strong competitive advantages for technological companies. Additionally, the uncertainty of technological innovations in live science is the second constraint to solve for allowing novelty emergence in biotechnology. This paper develops an organization and strategic framework which encompasses both industry and universities or public research centers. It highlights several keys aspects to cope efficiently with complexity and uncertainty. More precisely, this article suggests the interest to implement an efficient technological innovation framework considering three main dimensions: an appropriate human recourses management, a rational technological innovation strategy and an efficient collaborative network.

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Keywords: Industrial microbiology, technological collaboration, innovation strategy, complexity management, uncertainty mitigation, value capturing

INTRODUCTION: THE BIOTECHNOLOGY INDUSTRY'S EMERGENCE AND CONSTRAINS

Microbial biotechnologies encompass all applications based on the exploitation of microorganisms or a functional part of them for synthesizing a wide range of bio-molecules or functional ingredients (1). The exploitation of living microorganisms as "cell factories" provides the advantage to benefit from their metabolic and physiologic complexity, giving access to a broad range of bio-reactions of interests (2). The emergence of this industry generated 91,9 billions of Euro sales in 2010 and should generate about 515,1 billions Euro in 2020 (3). Despite the undeniable interests of bio-products for industrial applications, these increased sales are also enhanced by evidences towards climate changes and the necessity to find new sustainable production pathways. Indeed, while traditional chemical industry commonly builds complex compounds from simple chemical units mainly coming from fossil resources, biotechnology have the advantage to allow the valorization of inexpensive and renewable carbon sources. Therefore, it gives promising alternatives toward use to fossil resources as raw material (4). Furthermore, the emergence of environmental concerns is driven by the necessity to avoid damaging "green" corporate reputations. Therefore, developments of green-labeled processes or products become more and more a marketing positioning and are commonly at the basis of industrial marketing strategies.

Correspondence:
Jonathan Baert, Gembloux Agro-Bio Tech, Belgium.
Email: jbaert@ulg.ac.be

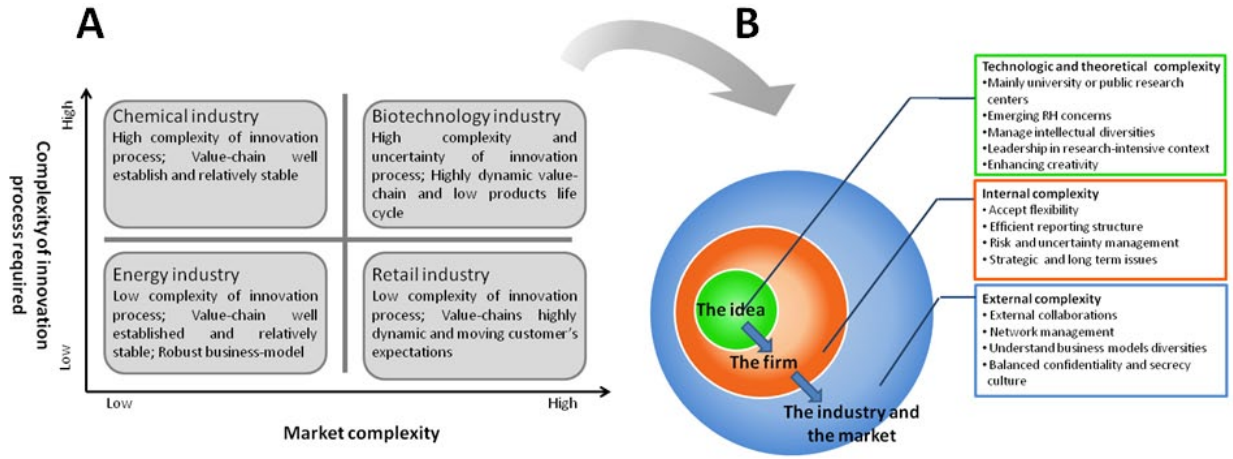

Figure 1: A. Positioning of different industries according to their respective market and innovation requirement complexity; B. Description of the different level of complexity include within the biotechnology industry from the emergence of an innovative idea to the availability of a novel product on the market.

These high incentives for the development of biotechnology industry have encouraged the investigation of new approaches for bioprocesses optimization. Therefore, a major part of recently designed microbial cell-factories include a genetic engineering component. These genomic considerations for designing efficient bioprocesses give access to a very wide range of targets for improving the profitability of industrial applications (5,6). But, the counterparty of these genomic approaches is the strong increasing in complexity of research and development (R&D) investigations involved with biotechnology innovations (See Figure 1). By this way, complexity and uncertainty regarding technological innovations in live sciences are the two major aspects threatening the successful completion of a project linked to novelty emergence. Mitigate these limitations is the main challenge to solve for ensuring the efficient biotechnology industry development but required organizational, strategic and collaboration ability of both public and private organizations.

Biotechnologies are undeniably one of the more intensively scientific and research driven industry (7) but efforts have to be done for improving the ability to turn technical or theoretical opportunities into profitable businesses. This paper highlights several keys aspect in technological innovation management in live science and highlights some key aspects involved in complex innovation process, commonly encountered in biotechnology bioprocesses development. Furthermore, the discussion of these aspects has been realized considering the necessity of enhancing close collaborations between universities or public research centers and companies in order to reconcile their divergent business models and create strong synergies. Plenty of opportunities can emerge from this collaborative approach while management of technological innovation are commonly discussed without considering the general intellectual context (i.e. research hot topics in universities; emergence of new theoretic or technical trends) in which there are involved and may miss promising competitive advantages for supporting innovation in live science.

MANAGE THEORETICAL COMPLEXITY: THE RISING HUMAN RESOURCE CONCERNS FOR ACADEMICS

Universities are at the origin of many major theoretical or fundamental discoveries. Inside these academic organizations, the manifestation of complexity in link with biotechnological innovations is mainly related to the theoretical ambiguity of scientific discoveries. Live science and biotechnology required indeed different complementary knowledge to allow a deep understanding of living-systems. As a consequence, many technologic or scientific innovations emerge from collaborations between different research teams sharing their own knowledge. Together, they are able to solve problems, integrate the emergence of new technological tools and conduct experiments in order to create value in accordance with the *raison d´être* of public organizations as universities. As an example, Craig Venter, a major pioneer in genomic, announced in 2001 the fully sequencing of the human genome. The related paper published in science the same year included no less than 200 co-authors coming from different specialties all over

the world (8). Nevertheless, a majority of these contributors came from the academic area, which simplifies the structural context of collaborations as they are all mainly focused on basis research and priorities are given to recognition by peers through publications in international journals.

Nonetheless, even if contributors follow the same final goal, manage such a diversity of knowledge remain a huge organizational challenge for academic structure. The ability to communicate clearly between partners will determine the success of technological collaborations. All the scientists have not the same specialty, they use specific terminologies and vocabularies and they deal with different kind of experimental and theoretical constraints. Furthermore, academics are for the majority intellectuals-intensive people adopting a reasoning boarded by theoretical constraints an sometime without considering the industrial or economical limitations of their work. As a consequence, their creativity and their frames of way of thinking are largely extensive and increase the risk of divergence toward the initial project objective or miss-alignment problems during collaborative works. In such complex human organizations, the decisive capacity to reach objectives is personified by leaders who have the capacity to communicate simply and clearly about expected final goals in order to realign the different work-teams in the good direction. An effective management of both theoretic complexity and intellectual diversity in live-science are keys of success and require as well human, theoretic and technical capabilities (9).

This effective communication is quite sensitive, given the very flat organization of such working groups in academic environments. The leader or the project investigator has to organize tasks and give a clear vision about the context and the desired target. But unfortunately, there are no clear hierarchical relations for supporting a well-established leadership in university. The succession of experimentations and activities emerge step by step through reasoned debates and negotiations rationally data-based. As a consequence, the direction taken by an innovation project is not directly linked with the willingness of the leader. This deeply collaborative process is largely time consuming but insures the adhesion and the active participation of each team during the project. To solve a complex issue, many advantages emerge from diversity and the ability to cope with this diversity is not an option even for universities (10).

To solve this diversity challenge, the personality of academic leaders is a critical point (11). They need to have the sensibility and the perspicacity to detect malfunctions inside the global team's framework before it could badly impact the performances of the group. Actually, the role of the leader in life science or in bioengineering is not linked with his ability to give technical advices on all issues faced during an innovation project. Instead, he has more to accept the limitation of his personal knowledge and experience. The acceptation of the unknown and the ability to admit mistakes represent valuable skills which will induce a modern working environment, open to questioning, enhancing innovating ideas and promoting creative approaches for solving technical key problems. Leaders have to be aware about serendipity and should know that mistakes or unsolved problems can provide unexpected opportunities. And last but not least, they need to efficiently decrypt scientists' personality in order to successfully deal with human diversity and bring out the best in individuals.

Unfortunately, these human considerations are often underestimated in an environment in which performances are mainly evaluated through the originality and the excellence of the researches as universities or public research centers. Nonetheless, modern research teams have to be more focused towards human resources (HR) since the quality of their results is deeply dependents with the quality of the interaction between scientists (12). A stimulating work environment is at the basis of creativity and novelty emergence. In most of complex problems, the ability to face difficulties with creativity could provide an incredible source of ideas, motivation and forge cohesive spirit in a high-collaborative working group. While HR management is a major preoccupation in industry, the universities or public research centers are widely not familiarized with this concept. Motivation, peer-recognition, personal evaluation or reward of creativity and excellence should be implemented through public organizations since these considerations play a major role in the successful of high-tech live science innovations for supporting industrial biotechnology novelty.

FROM ACADEMIA TO INDUSTRIAL COMPANIES: RECONCILE THE MULTIDISCIPLINARY OF CORPORATE FUNCTIONS IN THE INDUSTRY

Despite the necessity to face theoretical constrains mainly located at the academic level, the innovation process need to cope with another level of complexity mainly linked with the financial profitability constrains of industrial companies. As previously discussed, universities or public research centers perform experimental or theoretical investigations which are not necessarily tailored for a given application. However, these researches represent an incredible pool of knowledge for supporting

industrial innovations but require an important step of knowledge transfer to allow their valorization toward industrial applications (13). This transfer step remains particularly limiting and will be efficient only after the reconciliation between universities and industrial companies *raison d´être* divergences.

More precisely, one of the main differences between universities and companies is laid in their performances control mode. If firms are evaluated on the basis of their profitability and their ability to deliver value for customers, universities enhance excellence and originality of researches without any direct financial objectives. Nevertheless, in a context of rapid technological innovation and products obsolescence, competitive advantages are mainly driven by the emergence of novelty and are strongly supported by an efficient technology transfer capability. Despite their divergences, innovation course lets appear strong complementarities between universities and industrial companies. From this point of view, one of the challenges that industrials need to solve is directly linked with the way to manage the transfer and the integration of knowledge developed by other into their own products.

The first dilemma is to select the innovation project according to the market and the industry dynamic in order to clearly identify the basis knowledge that need to be transferred inside the company for creating strong competitive advantages (14). This choice should encompassed the entire operational, financial, human, and market corporate constrains or opportunities. Maximizing financial outcome of technological innovation projects will be achieved only through a profound understanding of uncertainties and remain one of the main challenge for biotechnology companies (15). But uncertainty mitigation requires interconnection and communication between the different level of the company organizational structure and all the company departments don't have the same objective or the same time horizon for forecasting. For example the strategy department is focus on the long term while the manufacturing department deals with the day to day production program. Furthermore their respective performances evaluations are profoundly divergent. In consequence, innovation projects in the pipe should stay simply describe, comprehensible by all the parties and focus on a few sound parameters for helping department's directors to take a fast decision. Furthermore, according to the financial risk and the operational long-term consequences of an innovation project failure, the decision to inject technological novelty in the company should be collective and required the interconnection of the major company's departments (16). This interconnected organizational structure will improve the technological transferability of an external knowledge and ensure its efficient integration into pre-existing processes.

COLLABORATION BETWEEN EXTERNAL STAKEHOLDERS WITH COMPLEMENTARY EXPERTISE: SHARING RISK AND KNOW-HOW

The notions of risk and uncertainty are fundamental in the bio-technological innovation context and are directly linked with the ability to appraise innovation outcomes and costs. In this context, external collaborations and creation of networks outside of the firms can provide a wide range of possibilities for improving risks and uncertainties management. As discussed, the emergence of new technologies leading to new or improved products requires the integration of diversity of knowledge coming from inside and outside the firm. The current rapid innovation dynamic in the biotechnology industry selects companies with advanced knowledge focusing on specific specialties. Given the theoretical and technological high level challenges in life science, collaborations with external organizations provide the ability for a company to solve constrains primary out of its scope by sharing different but complementary knowledge. These external collaborations have another major advantage mainly related with uncertainty mitigation ensuring that companies involved in a collaborative network are exposed to the risks in relation with their business model and specific know-how. Efficient collaborations can provide decisive competitive advantages towards several key aspects of the technological innovation as uncertainty and risk mitigations.

Generally, from basis researches toward final products, the underlying knowledge involved shift progressively from basic knowledge, provided by academics, toward applied and corporate knowledge, provided by corporate R&D. This dynamic knowledge switch needs to be tightly considered when external collaborations are designed. Consequently, risk and uncertainty of the different steps which succeed each other along a technological innovation project are not the same, and the way to get returns from them is fundamentally different. Indeed, while academics have not financial based objectives, companies need to cope with the monetary expectation of the shareholder board. Therefore, how they are eager to risk strongly diverges and has to be considered when tasks are split between collaborating organizations.

Furthermore several papers stated that technological start-ups able to set up a network and collaborations with external stockholders as universities are more able to survive than start-ups without any external contacts (17). In risks and uncertainty management, the main

interest for companies to collaborate with universities or organizations that so much differ in terms of business model and know-how, is the possibility of sharing risk and remain focus on the part of the project directly in relation with their respective strategy. Basically, collaborations on innovation issues suggest to outsourcing fundamental aspects of a project toward universities while its applied aspects should stay in the competence of the companies. Obviously, it requires that all the parts understand and accept the way following which the collaboration outcomes will be valorized. For example, valorization through publications of fundamental issues by academics will be publicly release whereas the applied outcomes have to stay protected for ensuring its confidentiality. Thus, if external collaborations can provide valuable advantages for uncertainty mitigation, it implies to consider value capturing issues in parallel.

CORPORATE UNCERTAINTY MITIGATION THROUGH A CLEAR GUIDELINE PROVIDED BY STRATEGIC ROADMAP

As companies have to meet the financial expectations of the shareholder board on a long term, the corporate strategy is the cement of all activities leading at the operational, financial and marketing companies' departments. It ensures coherence and alignment of the different actions to serve a global common long-term objective including process or product novelty. But as stated, innovation processes induce the necessity to cope with a high level of diversity related with both theoretical or technological concerns and collaboration between specialists or organizational departments. This diversity will induce a complex reporting structure and suggest considering strategic issues especially dedicated for innovation concerns. Indeed, while corporate strategies focuses on the ability to create and capture value on a sustainable way, innovation strategy tries to optimize allocation and interaction between the resources involved in novelty, in order to take profit from external opportunities, internal resources and processes capabilities for improving outcomes of innovation projects.

Therefore, the implementation of an innovation strategy has to provide corporate-based tool to manage diversity induced by innovation and should tightly drive the decision and the communication involved between stakeholders. This strategy should provide a guideline about how theoretical, human, organizational and technical resources hold by the firm should be allocated in order to meet the long term objectives through a clear, univocal and long term planning of novelty concerns (18) (See Figure 2-A). In a dynamic industry, the ability to actively plan the future, taking into account both internal and external threats and opportunities represent a valuable competitive advantage (19). Furthermore, that gives a clear insight about theoretical or technical knowledge needed to be transferred or investigated (13). This dynamic context remains the main challenge for the formulation and the implementation of an efficient innovation strategy. Nevertheless, before considering strategic innovation issues and set up a long term strategic orientation for the future, the firm needs to deeply understand the present by evaluating its market positioning, know-how and operational or financial limitations. This implies a deep comprehension of the company's business model by all its managers for ensuring that they deeply understand their respective responsibilities.

This combination of a profound business model understanding and a sound innovation strategy provides a specific framework which rationally defined the risk in link with technological innovation that the company should or should not support. Innovation strategy determines the extent to which the firm is prepared to support risky investment which is related to what the company wants to be in the future. Its implementation has to translate the risk aversion across operational decisions linked with technological innovation projects given its specific innovation framework (See Figure 2-A) (20,21).

Such a strategic innovation planning provides a long term vision and has to be implemented through the whole organization to improve its global performances and its internal collaboration ability. Nevertheless, several researches show that most SMEs (small and medium enterprises) do not engage strategic planning (19). While a significant share of biotechnology industry's sales revenues are made by of SME (3), this lack of strategy could induce a misalignment and a decrease in collaborations efficiency in the whole biotechnology industry. Therefore, the three folded strategy, business model and corporate culture have to be considered in parallel. First because it encompasses the company's identity ensuring a favorable context for communication and mutual comprehension and secondly because it provide an accurate guide-line for uncertainty management.

FACILITATE BOTTOM-UP REPORTING AND ACCEPT FLEXIBILITY

The high integration and communication between different company's departments has been discussed as a key aspect for uncertainty management of novelty and innovation strategy implementation. This close

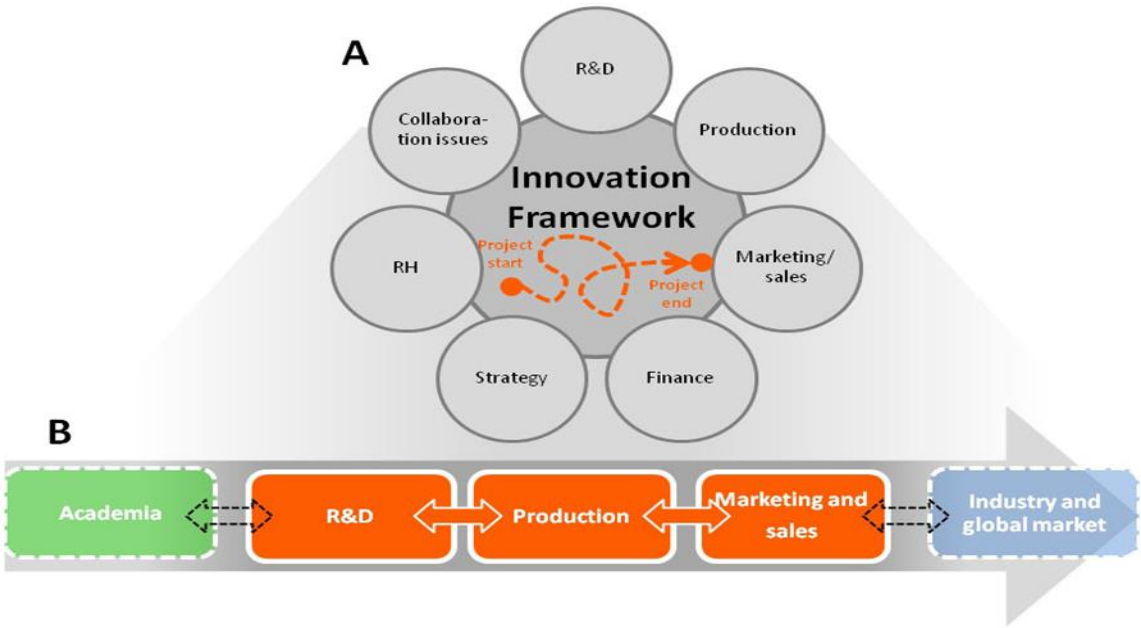

Figure 2: A. Description of the multidisciplinary collaboration requirement to define an accurate innovation framework useful for uncertainty management in live science technological innovation in. This innovation framework includes a set of tasks which can be decently undertaken. It's among these allowable tasks that the sinuous evolution of the project will take place (represented by the winding dotted orange line); B. Information and know-how sharing dynamic from the theoretical idea emerging in academia (green box) toward the release of the novel product on the market (blue box). During the development steps on the corporate level (orange boxes) a deep coordination of R&D, Production, and Sales departments is required to efficiently face uncertainty and sinuosity within the technological innovation framework previously defined by the company's departments.

interconnection between different corporate functions suggests an efficient reporting structure based on valuable quantitative and qualitative indicators. Furthermore, it suggests that managers involved in an innovation process are able to understand the internal operational constrains linked with a given project. But this requires to organize company's departments in order to be able to consider bottom-up reporting both about operational results and constrains faced by teams in charge of the operational development of an innovation project. Indeed, financial or strategic decisions about technical innovation cannot be taken without a profound understanding of the underlying operational constraints. This non-financial bottom-up reporting is very different with the traditional reporting mainly based on profitability or performance key indicators largely in place within non-technological companies (22). However, in a context of intensive innovation, it remains sensible to nuance operational results with its incorporated constrains or limitations. Following the same idea, the valorization of a research project only through the calculation of its net present value is not the better method according to the large uncertainty and technical limitation incorporated at the operational level and which cannot be considering through cash flows.

At the management level, this suggested that a reporting structure for technological innovation projects should enhance intensive information sharing between R&D, production and marketing/sales departments. These three departments should actively collaborate during the design, the production and sales phases for ensuring that the innovation product will meet the market expectation and the company's quality standards (See Figure 2-B). Project managers in charge with novelty should understand the constraints induced by the collaborative and operational dimensions of technological innovation in live science. Basically they need to integrate that processes leading to novelty are not fluid but deeply winding. Success and failures are essentially unpredictable, serendipity and luck are important and some failures are inevitable or cannot be prevented. There are simply too many unknowns for ensuring an accurate planning of the research, development and design steps (23). Therefore, managers have to accept flexibility in order to ensure that emerging operational constrains will be freely reported at every stage of the project. As a matter of fact, the later a

constraint will be taken into account, the bigger will be its financial consequences on the project achievement. Furthermore, this flexibility in the management mode ensures a larger open-minded attitude toward suggestions coming from employees (23). It is never too late for a good idea and creativity encouragement can provide valuable operational advantages for facing technical difficulties.

IMPROVE VALUE CAPTURING STRATEGY THROUGH A BALANCED SECRECY CULTURE

As stated previously, the ultimate goal of innovation is to deliver value for clients and support the company ability to compete efficiently on a long term. Given that the fast emergence of new technologies strongly enhance the reduction of the products life cycle, the ability to make profit in a value chain commonly evolve in time (13). For example, in this frame, Solvay S.A., one of the world wide chemical company recently announced its willingness to sell its polyamides activity while commodities polymers a polyolefins and PVC were at the basis of its commercial strategy a few decades ago. Thus, the ability for a firm to capture value is directly linked with its ability to master its position on the industry value chain and continuously reassess its positioning by detecting promptly the emergence of opportunities (24, 25). Furthermore, the return related with innovations could quickly decrease with time and both flexibility and a good appraisal of threats are keys of success.

Nevertheless, in order to maximize the value extraction from novelty, the innovation strategy needs to include a dimension for ensuring the protection of sensitive knowledge or information. In this way, legal protections, as patents, can be an effective but expensive way to protect some key aspects of an emerging technology. On the other hand, complexity and secrecy can also serve as a barrier to avoid copying by competitors. In the biotechnology industry, many innovations are protected by an optimal combination provided by both patent and secrecy in order to reduce the financial resource required for protecting know how (26) and to fit with the product life cycle dynamic. However, this parallel protection needs to be considered at the beginning of the innovation project mainly if complex external collaborative structures are involved. For example, in case of collaboration with academics, fundamental aspects highlighted during the project were generally investigated by academics and will be partially or fully published. As consequence, these aspects could not be patented anymore and should be protected by another way like their intrinsic complexity. In this way, even with an accurate public description of a few aspects in link with fundamental back-grounds of an innovating issue, competitors could not capture value from it without harsh investments and complex structural organization. Indeed, some capabilities cannot be bought and need times to be profoundly implemented, and thus, should be the basis of a robust value capturing approach.

On the other hand, secrecy can sometimes appear as a powerful tool for knowledge protection. Nonetheless, in a highly collaborative context in which effective communication is a key factor of success, it can appear as a paradox. Actually, secrecy can easily be implemented towards routine operations without badly impact the communication efficiency which have been highlighted as a major transversal requirement for innovation projects achievement. But, firms have to implement a balanced positioning between secrecy culture, communications facility and intellectual property management. Indeed, if all the operational aspects become opaque and abstract because of secrecy, it will deeply impact the employee's motivation and the company will be deprived of ideas coming from technicians or operators close to operations. On the other hand, a fully transparence of processes and operations will threaten the ability for capturing value by increasing the risk of being copied by competitors.

CONCLUSION

Strategic, organizational and collaborative issues are the three main dimensions to reconcile the mismatch between financial reporting with the operational constraint and uncertainty in link with live science novelty. The emergence of these three transversal concerns in an industry that is traditionally based on scientific excellence, suggests the necessity of a new generation of scientists able the cope with both the high theoretical complexity and the corporate profitability requirement. Communication skills of scientists with business understanding are deeply improved as they are able to integrate operational or financial risks, organizational and marketing considerations in their theoretic or technical approach. Furthermore, it allows building essential win-win collaboration with academia to take opportunities emerging from basis investigations. These modern scientists are able to valorized technological innovation projects on a long term horizon according to the intellectual, industrial and economical context dynamic.

Finally, theoretical and technical complexity in live science innovation has been discussed as the main limitation for biotechnology industry expansion. In this

frame, companies have to avoid falling into the trap to solve complexity with complexity itself. Indeed in high-technology live sciences industry, the quote "Keep It Simple and Smart" should be definitely a major dimension for innovation processes management and R&D project selections. Giving a simple solution to a complex problem enhance the ability to implement a performing innovation culture which will be at the origin of competitive advantages development focusing on operations' technological aspects.

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Article

The Chinese Medical Device Market: Market Drivers and Investment Prospects

Weifan Zhang
is a PhD student at the University of Sussex.

Rebecca Liu
is a Lecturer at Lancaster University.

Chris Chatwin
is a Professor in Engineering at the University of Sussex.

ABSTRACT

The economy in China has experienced rapid growth and been remarkably successful ever since the reforming and opening-up policy. Like China's economy, the Chinese medical device market is developing rapidly; this paper identifies important parameters controlling this market. Regression analysis shows that the number of hospital visits, aging population and the number of hospitals have a positive relationship with medical device revenues. Therefore, they are the main drivers of the Chinese medical device market. Disease profile is another important market driver. Analysis of the main market drivers, illustrates that the Chinese medical device market offers significant investment opportunities.

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Keywords: China, medical device market/industry, market drivers, investment, aging population

INTRODUCTION

The global medical device market is highly centralized.[1] The market share of the developed countries accounted for more than 80% of the global medical device market share (US: 42.4%, Europe: 33%, Japan: 11%) in 2011.[2] With superior know-how in technology and/or management, international companies are typically larger than domestic companies and have a competitive advantage due to the economies of scale.[3] According to Charles Hill and Vernon's product life cycle theory, the developed countries will export their production and technology from their relatively saturated market to the developing countries due to the market pressures and other competition in their established markets.[4–6] Despite China only accounting for 3% of the global medical device market share,[2] this study shows that the developing countries' medical device markets are experiencing rapid growth, especially in China. Increasing medical expenditure, rising healthcare consumption and health awareness improvements are all possible factors in promoting the development of the Chinese medical device market. The Chinese government's healthcare reform has injected additional "power" into the development of the medical device market. In fact, by the end of 2011, the Chinese medical device industry output value was 688.42 billion yuan, total percentage of GDP is 1.40%. Figure 1 shows the Chinese medical device industry output value and its total percentage of GDP, its value continues to climb from 2001 to 2011. In 2011, the percentage of medical device industry output value accounted for 1.40% of Chinese GDP. Although the output value of the medical device industry is currently a limited proportion of the national economy, Figure 1 shows a rising trend year by year except 2008.

China's high-end medical device market is dependent upon imports and dominated by foreign companies' products, especially for the diagnosis and treatment devices. Table 1 shows the Chinese medical market trade statistics according to the China Chamber of Commerce for Import & Export of Medicines & Health Products (CCCMHPIE) in 2010. The overall trend of the Chinese healthcare market shows that export value is

Correspondence:
Weifan Zhang, University of Sussex, UK. Email: zhangweifan@yahoo.co.uk

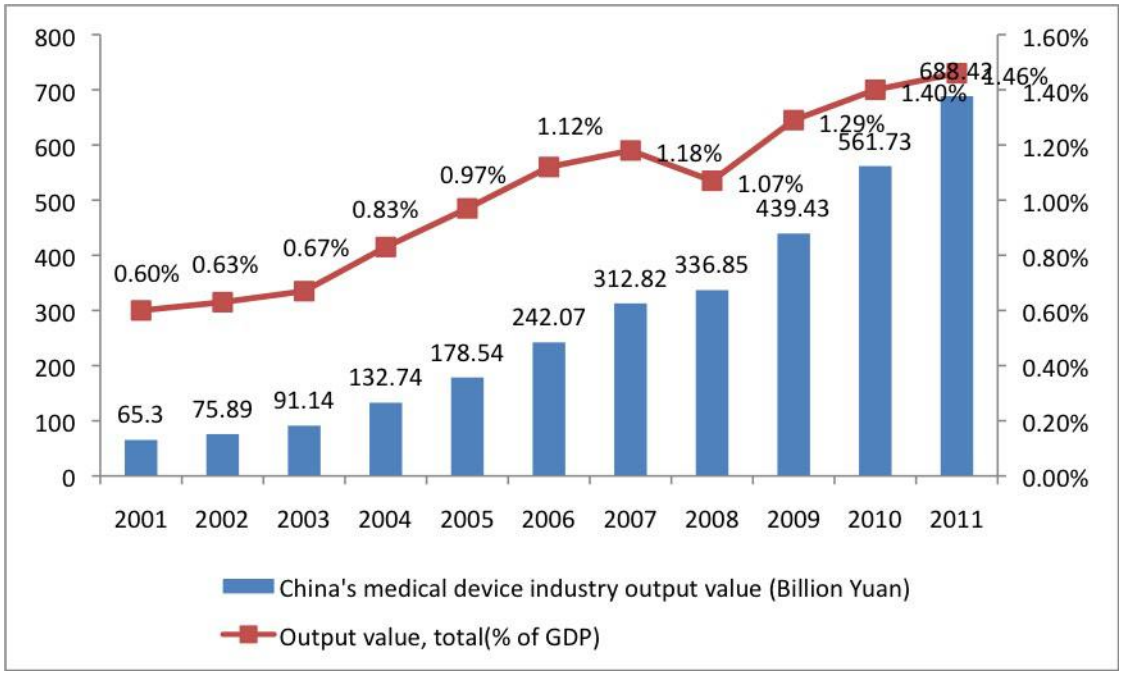

Figure 1: China's medical device industrial output value and its total (% of GDP).
Source: National Bureau of Statistics of China[7, 8]

higher than import value; hence the export value of the pharmaceutical and medical device industry is higher than the import value. However, only the import value of medical diagnosis and treatment devices is higher than the export value, which took a 29.05% share of total import volume in China. By comparison, medical dressings, disposable products, health protection and recovery products, dental equipment and materials, total only 6.8% of import volume, which is only one-quarter of the import volume of the medical diagnosis and treatment sector.

More specifically, Table 2 illustrates the trade statistics for medical devices in China in 2010. The total export value of medical devices reached USD 13.86 billion in 2010, while the total import value reached USD 7.3 billion. North America and Asia are the main export target areas for China, which accounted for 29.23% and 33.7% of the total export volume; the U.S. and Japan are the main export target countries, which absorbed 27.91% and 10.39% of the total export volume respectively. Europe and North America are the main exporters to China, which accounted for 39.01% and 31.41% of the total import volume. Germany and the U.S. are the main importing countries, which provide 17.34% and 30.71% of the total import volume.

For the Chinese medical device market, with growth from many sources of demand, medical diagnosis and treatment devices still have a great growth potential. China now has a fee-for-service healthcare system financed largely by payments from patients, employers and health insurance companies.[11] However, many patients especially high income people are willing to pay more money by themselves on their treatment, especially for cancers, heart disease, cerebrovascular disease, etc., which needs to use high-tech medical diagnosis and treatment devices or high-grade drugs, which is not affordable for low income people. For example, the average fees for CT whole body scan is nearly 2500 yuan (about USD 400) in China, this is not a small expenditure for low income people; they always choose the most economic ways to treat their diseases. However, China's health institutions especially the Tier-3 hospitals[i] have a strong demand for high-end diagnostic devices due to

i There are three levels of Chinese hospitals: Tier-3 Hospitals (6%) tend to be the best and highest level (first class) hospitals, which may offer the most comprehensive medical treatment; complex clinical diagnosis, advanced scientific research and R&D abilities, which are provincial and municipal hospitals in big cities; Tier-2 Hospitals (34%) are providing comprehensive medical services, basic teaching and research functions, which are municipal hospitals in smaller cities as well as district and county hospitals; Tier-1 Hospitals (25%) are grass-roots healthcare institutions, providing basic medical services, which are the primary healthcare facilities in small towns; Other healthcare institutions account for 35% of total medical institutions.

Table 1 China's import and export structure of medicines and health products, 2010. (Unit: million USD)

Trade name		Export Value	Export value growth rate annually (%)	Share in total export volume (%)	Import Value	Import value growth rate annually (%)	Share in total import volume (%)
Total		39,733.10	24.87	100	20,464.36	23.98	100
1. Traditional Chinese Medicine		1,944.47	22.78	4.89	687.95	22.61	3.36
2. Pharmaceuticals		23,930.02	28.17	60.23	12,440.84	20.53	60.79
3. Medical Devices		13,858.61	19.83	34.88	7,335.57	30.45	35.85
3.1	Medical dressings	4,687.51	11.95	11.8	207.77	25.63	1.02
3.2	Disposable products	1,922.27	15.42	4.84	880.76	27.73	4.3
3.3	Medical diagnosis and treatment	4,543.60	25.56	11.44	5,944.73	30.34	29.05
3.4	Health protection and recovery products	2,416.41	30.87	6.08	149.37	83.83	0.73
3.5	Dental equipment and materials	288.82	16.51	0.73	152.94	21.37	0.75

Source: CCCMHPIE, 2011[9]

the rising number of visits and inpatients, changed disease profiles, etc.

Data

The improvement of medical and health services has greatly increased the market capacity for the Chinese medical device industry. The important medical device industry drivers are (1) *demographics*, the percentage of the global and Chinese population above 65 years old is growing. (2) *unmet clinical needs*, the trend of using new medical devices or products to address diseases or medical needs that previously were simply not treated is increasing. (3) *procedure penetration*, there is a tendency among doctors to use more medical products and procedures. (4) *pricing*, positive pricing trends have generally been favourable in the medical device industry. Medical products are not selected on the basis of price. (5) *geographic reach*, the market potential for the highly-populous less-developed countries (including China) is very compelling.[12] Studying the market growth drivers of the Chinese medical device market provides information for effective investment in China.

Data for medical device industry revenues from 2000 to 2012 was collected from the China Statistics Yearbook on High Technology Industry.[13] Other data such as the number of hospital visits and number of hospitals were collected from the China Health Statistical Yearbook.[14] Data on 65+ population was collected from the China Statistical Yearbook.[15] In this study, datasets contain every mainland Chinese province and city except Hong Kong, Macao and Taiwan. Data on the number of hospitals does not include other health institutions such as Grass-roots Health Care institutions,[ii] Specialized Public Health Institutions[iii] and other healthcare institutions. The detailed data are shown in the Supplement Table A.

ii Grass-roots Health Care institution includes community health centre and station, sub-district health centre, village clinic, outpatient department, and, clinic (infirmary)

iii Specialized Public Health Institution includes Chinese Centre for Disease Control and Prevention (CDC), specialized disease prevention and treatment institution, health education centre, maternal and child health centre, emergency centre, centre for blood collection &

Table 2 China's import and export markets of medical devices in 2010. (Unit: million USD)

Country		Export Value	Export value growth rate annually (%)	Share in total export volume (%)	Import Value	Import value growth rate annually (%)	Share in total import volume (%)
Total (All countries)		13,858.61	19.83	100	7,335.57	30.45	100
Asia		4,669.96	12.87	33.7	1,938.77	29.28	26.43
Europe		3,631.06	18.53	26.2	2,861.38	34.38	39.01
North America		4,051.03	24.48	29.23	2,303.79	25.81	31.41
1.	U.S.	3,867.61	24.72	27.91	2,252.64	26.48	30.71
2.	Germany	778.06	14.72	5.61	1,271.74	35.43	17.34
3.	Japan	1,440.07	-13.5	10.39	1,113.90	26.99	15.18

Source: CCCMHPIE, 2011[10]

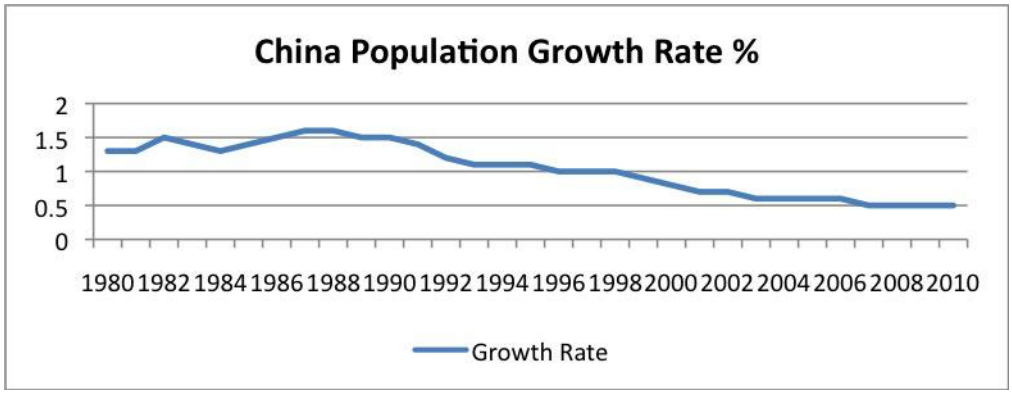

Figure 2: The growth rate of Chinese population from 1980 to 2010

Methods and Empirical Analysis

In the real economic environment, one variable is affected by several factors. Multiple regression analysis has been selected as the research method in this study. Assume the regression equation is:

$$Y_i = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_i x_i + \mu_i \qquad (1)$$

where Y is the dependent variable, x are the explanatory variables, μ the stochastic disturbance term, and i the ith observation.[16] Using the data in Supplement Table A, we set: Y = medical device revenues, x_1 = number of hospital visits, x_2 = 65+ population, x_3 = hospital quantity. From Microsoft Excel we obtained the following regression result:

$$\hat{Y}_i = -1026663.83 + 370.46x_1 + 6119.01x_2 + 3.70x_3$$
$$t = (-7.6946)\ (6.1616)\ (1.5722)\ (0.2008) \qquad (2)$$
$$R^2 = 0.9928\ \bar{R}^2 = 0.9904$$

where $\hat{Y}_2$ = estimator of Yi, $\bar{R}^2$ = adjusted R, $t = t$ value, used for t test.

Regression shows that the number of hospital visits, 65+ population and hospital number together explain 99% of the variation in medical device revenues. The estimated value of the coefficients of the: number of hospital visits, 65+ population and hospital number are 370.46, 6119.01 and 3.70, respectively. The detailed data are shown in the Supplement Table B.

Hypothesis testing (the t test) assumes H_0:$\beta_i = 0$, ($i = 1, 2, 3$). Regression illustrates that the t of $\hat{\beta}_1 = 6.1616$, t of $\hat{\beta}_2 = 1.5722$, t of $\hat{\beta}_3 = 0.2008$. The t test of significance decision rules is shown in the

supply, centre for health supervision and centre for family planning service.

Supplement Table C. If we assume α[iv]=0.05, degrees of freedom (df) = n−4 = 13−4 = 9[v]. According to percentage points of the t distribution (Supplement Table D), $t_{\alpha/2,df} = t_{0.05/2}(9) = 2.262$. Therefore, $t_1 = 6.1616 > t_{0.05/2}(9)$, which is significant, so reject $H0$, which means that the number of hospital visits has significant impact on medical device revenues. $t_2 = 1.5722 < 2.262$ and $t_3 = 0.2008 < 2.262$, so accept $H_0{:}\beta_2 = 0$ and $H_0{:}\beta_3 = 0$, which are insignificant.

The regression model is based on several assumptions, one of the assumptions is that "There is no exact collinearity between the x (explanatory) variables". Insignificant t values but a high overall R^2 is one of the signals for multicollinearity.[16] After correlation using Excel we obtained $r_{12} = 0.9644$, $r_{13} = 0.9423$, $r_{23} = 0.9831$, which means three explanatory variables are highly correlated. Thus, we regress Y on x individually. Detailed data are shown in the Supplement Table E.

$$\hat{Y}_i = -609743.60 + 553.34x_1$$
$$t = (-17.23)\ (26.49)\ R^2 = 0.98 \qquad (3)$$

The regression (equation 3) shows that the number of hospital visits variable is highly significant, and $t_{\alpha/2,df} = t_{0.05/2}\ (11) = 2.201$. $t_1 = 26.49 > t_{0.05/2}\ (11)$, therefore reject H_0. The same with equation (2)'s results, which means the number of hospital visits has significant impact on medical device revenues.

$$\hat{Y}_i = -1748028.05 + 19391.36x_2$$
$$t = (-14.20)\ (16.73)\ R^2 = 0.96 \qquad (4)$$

The regression (equation 4) and t test ($t_2 = 16.73 > t_{0.05/2}\ (11) = 2.201$) illustrates that the 65+ population variable was statistically insignificant, whereas now it is highly significant.

$$\hat{Y}_i = -1897611.31 + 114.02x_3$$
$$t = (-9.98)\ (11.61)\ R^2 = 0.92! \qquad (5)$$

$t_3 = 11.61 > t_{0.05/2}\ (11) = 2.201$, and regression equation (5) shows that hospital number now has a significant impact on medical device revenues, whereas in equation (2) it had no effect on medical device revenues.

According to equation (3), there is a positive linear correlation between the number of hospital visits and medical device industry revenues, which means every one million change in the number of hospital visits will cause a positive change of 553.34 million yuan (RMB) in medical devices revenues.

The huge population and aging population are one of the factors for the growth of China's pharmaceutical market,[17] as well as the medical device market. According to equation (4), the regression shows that every one million change in 65+ population will cause a positive change of 19391.36 million yuan in medical devices revenues. It is clear that the 65+ population is the most important driver of the medical device market. From the year of 1990 to 2010, the Chinese population increased from 1.14 billion to 1.341 billion. However, the population growth rate declined since 1990.[18] Figure 2 shows the trend of Chinese population growth rate from 1980 to 2010, the detailed data are shown in the Supplement Table F. The total population increased slowly, but the population growth rate decreased year by year since 1990 due to the decrease in fertility and mortality.[19] The reduction in population growth rate speeds up the growth in the aging population. An important need of the "aging society" is high quality healthcare, because the elderly are experiencing increasing rates of chronic diseases,[20] someone in their 80's is very likely to have four or five chronic diseases. Therefore, the medical device market in China is set to expand.

Equation (5) illustrates that the number of hospitals has a positive linear correlation with medical device revenues.

Other driving forces such as diseases cannot easily use quantitative method to assess their impact. China now belongs to the upper middle income countries;[21] of the top ten leading causes of death in the middle income countries, seven are chronic disease-related deaths, which accounted for 91% of total deaths.[22] The higher burden of chronic diseases in low – and middle income countries is manifest in China,[23] which means these diseases will cost a great deal. Although digestive diseases, respiratory diseases, infectious and parasitic diseases are the top ten leading causes of death in low – and middle income countries, we need to focus more attention on cancers, cardiovascular diseases and cerebrovascular diseases, which account for the top three percent of total deaths in China.[22] The top three leading causes of death in middle-income countries are cardiovascular diseases, cerebrovascular diseases and respiratory diseases,[23–25] there were 2.8 million deaths from cardiovascular diseases in China in 2003.[24] Cancer caused the highest mortality and has maintained the first position among the five leading causes of death (cancers, cardiovascular diseases, cerebrovascular diseases, diseases of the respiratory system and injury, poisoning & external causes) in China. The major risk factors causing cancers are tobacco consumption, chronic infections, diet and lack of physical activity, etc.[26] Cancer is a leading cause of death globally,

iv α ($0 < \alpha < 1$) is known as the level of significance.

v n means number of observations.

accounting for 7.6 million deaths in 2008.[27] Nearly 70% of cancer deaths occurred in low – and middle-income countries. It is predicted that deaths from cancer will increase, with an estimated 13.1 million deaths in 2030.[28] Cancer is a big problem for society worldwide as well as for China. With the gradual increase in the number of patients and mortality, the demand for diagnosis and treatment devices will inevitably increase. Good market prospects indicate that medical devices for these diseases have great investment potential.

DISCUSSION

This study suggests that the Chinese medical device market is not only driven by the three variables (number of hospital visits, 65+ population and number of hospitals) but is also impacted by the diseases and the government healthcare policy. The purpose of medical devices is to assist with: patient stratification, diagnosis, prognosis, treatment and treatment planning; the macroeconomic variables such as population structure; disease profiles and economic level can affect the demand for medical device services. Disease profiles affect the development of medicine as well as medical device capabilities and the total medical device market. Therefore, diseases should be one of the elements driving medical device investment.

If the incidence or mortality from the disease is low, the demand and frequency of use of the appropriate diagnosis and treatment equipment will be relatively low, the investment payback period for such medical devices will be long for hospitals; in such a scenario, it is difficult for hospitals to recover the cost of medical devices throughout their entire life cycle. So only the large general hospitals will consider purchasing such medical devices. Small and medium-sized hospitals do not have the capacity to buy such equipment. Thus, the market demand for medical devices with low disease incidence is relatively small; investment risk is large and does not have financial investment value. If the incidence or mortality of the disease is high, the demand and frequency of use of the appropriate diagnosis and treatment equipment will be relatively high, the large general hospitals will be very motivated to purchase such medical devices as well as small and medium-sized hospitals because the investment payback period for such devices will be short.

The medical device market has sustainable growth because of the general demographic trends, especially the growth of the aging population and the continued prevalence of diseases.[29] For the Chinese medical device market, the growth of hospital visits, aging population, number of hospital and diseases show that the market has great investment opportunities. The main medical devices companies' (such as GE, Philips and Siemens) investment activities and/or mergers and acquisitions in China give good indicators of how the market is developing.

The limitation of this study is that appropriate explanatory variables are hard to find, three explanatory variables made the sample size too small to perform regression analysis. Other market drivers like disease and policy are hard to assess through regression analysis. The multicollinearity often happens in multiple regression analysis, the adjusted results reported herein are more reliable.

CONCLUSION

According to the regression analysis, the number of hospital visits, 65+ population and number of hospitals are the main drivers of the Chinese medical device market. Diseases are another driving force. Analysis of the prevalence of diseases shows that cancers are the big challenge for the whole medical area, the health care system is experiencing huge pressures from both changing and increasing demands.[30] Therefore, significant opportunities exist in the Chinese medical device market due to the growth of the number of hospital visits, 65+ population, number of hospitals and diseases.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest

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Article

Investor Experience in Biotechnology

William Bains
is Founder of Rufus Scientific Ltd.

Daniel Rabbie
is Regulatory Affairs Manager at The Cell and Gene Therapy Catapult.

Weiyi Yao
is a Researcher PHD Student at University of Leeds.

David Ricardo Munoz Guzman
is CEO of Novellus Biopharma AG, Switzerland.

ABSTRACT

Biotechnology is viewed as an industry that combines scientific innovation, entrepreneurial management and experienced investment to drive innovation, primarily in biomedicine. This paper examines the third of these assumed preconditions. We find that the majority of investors in biotechnology companies over the last decade by number or by value have not been experienced, and that the majority of investors in biotechnology companies have invested in less than three such companies in the decade, suggesting that they have very limited experience of biotechnology. 13% of investment syndicates contain no investors who have made more than three biotechnology investments. Investor inexperience is disproportionately high in Seed and Series A rounds, but has little correlation with amount invested. Investor inexperience is found in all categories of investors and all territories, although US investors tend to have greater experience than those outside North America. The banking crisis of 2008-11 has not materially changed this. We suggest that the conventional image of biotechnology investment as the careful selection and nurturing of young companies by experienced investors is incomplete. This has implications for candidate investor selection by entrepreneurs, and for government support of biotechnology by supporting investors or investment mechanisms.

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Keywords: venture capital, finance, experience, seed, start-up, policy

INTRODUCTION

Biotechnology has been perceived historically as an industry enabled by institutional investors who back private companies with substantial risk capital, commonly termed venture capital (VC) [1, 2]. After a dip in VC investment in 2008-9 [3, 4], a number of reports suggest that VC investing in biotechnology is back to pre-credit crunch levels[5] [6–9], although others suggest that VC investment in biotech remains substantially [10, 11] or slightly [4, 12, 13] lower than before the credit crunch. VC continues to be presented as an attractive asset class for investors compared to public stocks [14, 15], despite fairly robust evidence to the contrary [16, 17].

Correspondence:
William Bains, Rufus Scientific, UK. Email: william@rufus-scientific.com

Venture capital is commonly understood to be "a professionally managed pool of capital that is invested in equity-linked securities of private ventures at various stages in their development" [18–20]. The standard model of the VC business is that it invests in companies with high risk and correspondingly high rate of return if successful [19], especially in early-stage companies with high capital requirements such as companies developing biotechnology products. VC mitigates the risk of such investment by substantial engagement with investee companies [21–23]. Unlike investment by individuals ("Business Angels"), VCs can deploy substantial funds into a young company, improving their chance of success; it is a common observation that young, capital-rich technology companies have a better chance of success than young, capital-poor ones [16, 24–27]. As well as cash, venture investors' personal entrepreneurial experience is central to their proposition that they add value as well as cash to an investee company (although the real value of this has been questioned [28]). Both execution experience [22] and industry experience and contacts

[29] are important, and correlate with ability to access a wider deal flow [30] and with exit outcomes [31].

While the relevance of the conventional model of VC economics (reviewed in [20]) to biotechnology has been questioned [16], VC remains the investment class most mentioned as a major goal of start-up companies in the sector [5, 16, 32–35]. Other investment sources, such as business angels and 'seed funds' are often seen as bridges to VC investment, and VC-backed companies are reported to be more successful than ones finding other sources of finance [20, 36] (but see [35, 37–39]).

This paper addresses the question of whether this picture of institutional investors in biotechnology companies is accurate. In particular, discussion at many investment events reveals an audience of very diverse potential investors listening to pitches from biotechnology (and other) companies. Do these different investors actually invest in biotechnology? A related question is whether the credit crunch has affected the type of investors backing biotechnology, and the amount they are investing.

To identify who actually invests in young biotechnology companies, we have explored investment data over the period 2005 thru 2014. We specifically studied institutional investment in private companies, and not either investment in public companies (including IPO investment) nor investment by private individuals ("Angels"). Angel investment, and related crowdfunding investment, is a critical source of start-up capital for all technology-based companies. However the motivations, investment methods, investment capabilities, and subsequent behaviour of angels is very different from institutional investors, and so aggregating the two is not worthwhile.

METHOD

Biotechnology

In this paper we define 'biotechnology' pragmatically as being companies exploiting new life science discoveries or technology. Thus we do not confine ourselves to healthcare biotechnology (which is the usual investment focus of VC funds identifying themselves as 'biotechnology' investors [1]). We confine our analysis to investment that could be relevant to the creation or growth of a biotech company, i.e. equity investment (or related loan agreements) by an institutional investment vehicle into private companies. Biotech companies in the UK had been diversifying their financial strategy to acquire funds from a range of investment and revenue sources [4, 10, 11]: we do not consider these other sources of early capital, such as profit or grants, in this study.

Investment Data

Data on venture investment deals in biotechnology and associated industries were extracted from the MedTrack database (http://www.medtrack.com/). All of the deals coded in the database as relating to companies in the industry sectors biotechnology, pharmaceuticals, healthcare, medical devices were used. Deals coded as Venture Financing, Venture Capital or Growth Expansion Capital with deal dates 2005 thru 2014 were extracted. Manual inspection of these showed that some were actually sales of VC-funded companies rather than VC funding deals, and these were excluded.

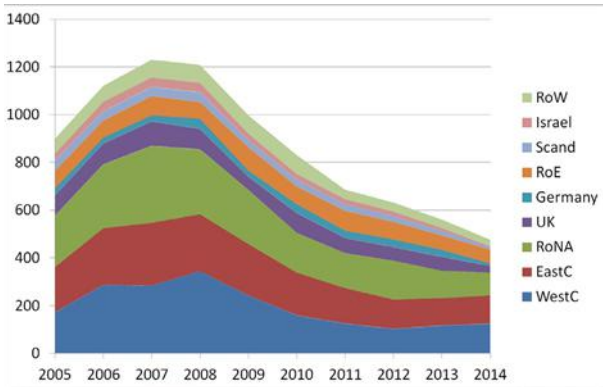
Company names, the country of incorporation and websites addresses were validated manually using internet resources, primarily the Internet Wayback Archive (http://archive.org/), Bloomberg Businessweek (http://investing.businessweek.com), New Statesman (http://www.newstatesman.com/company-profiles/healthcare), and VC Experts (https://vcexperts.com/). Company ages were compiled manually from the same sources, primarily Bloomberg Businessweek or companies' own website histories. When neither of these resources nor further internet searches yielded a clear date of foundation of the company, the date for first registration of the company domain name was used as a proxy for foundation date. The year of domain-name registration was found to correlate well with the self-reported year of company formation date with a correlation coefficient of 0.643 for companies founded after 1997 (when the Internet Archive started indexing company web sites). Company location was taken from the company web site where it was announced (or inferred from company telephone contact numbers). For companies with more than one location, the location of the major activity or corporate headquarters was used. Note that this is often not the same as the location of company registration, which may be a 'legal fiction' and not an operating reality. Information on the nature of a company's business and its stage of development of that business was also compiled manually from the company web sites.

Deal sizes were extracted automatically from MedTrack text data, and converted to US dollars.

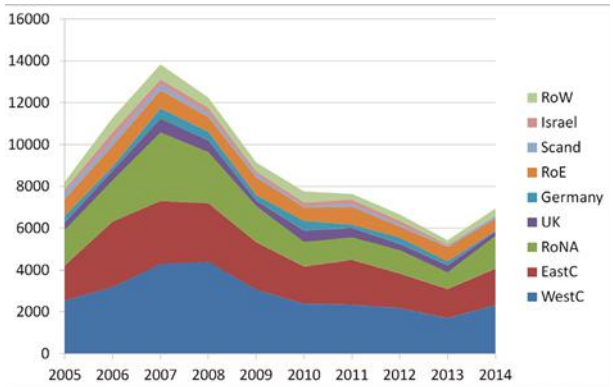
Details on investors were taken from investor web sites or from the web resources mentioned above. Investors were classified into one of seven classes, as described below. Investor countries of operation were coded. A total of 8654 investment deals involving 4939 companies and 5364 investors were analysed.

All data analysis was performed in Excel.

A: by number



B: by aggregate value



C: Amount, by investment round.

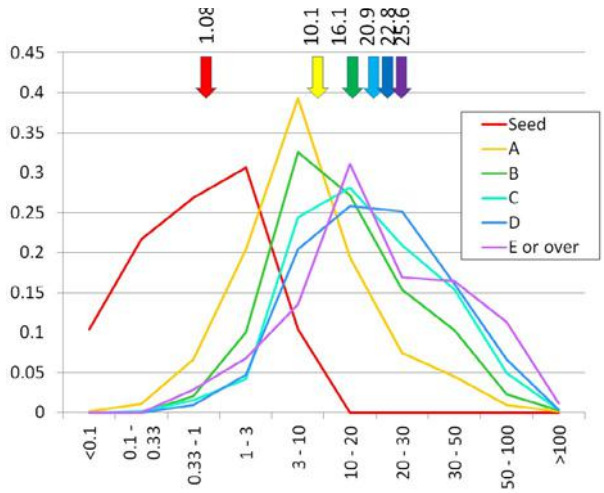


Figure 1: Distribution of investment, by year.
Investment in biotechnology companies 2004 thru 2014. Panels A and B: investment by year. **A:** Y axis – number of deals, X axis year in which the investment was completed. **B:** Y-axis aggregate value of deals, X axis year in which the investment was completed. **C:** Fraction of deals by value. Y axis – fraction of all investment deals made in the 2004 – 2014 time period in each value class. X axis – announced value of the investment. Shown separately are deals identified as 'Seed', 'Series A' etc. Deals with no identified series or no announced value were not included in this data set. Arrows show the average value of deals in each series in this data set.

RESULTS

Investment in biotechnology companies remains primarily a US phenomenon; $^{2}/_{3}$ of the number of investment deals and $^{3}/_{4}$ of the dollar value invested since 2005 has been in the USA, and this has not changed significantly over the last decade. Investment has declined substantially in biotechnology since 2007 in all regions in terms of the number of deals and the value invested (Figure 1).

We would expect the global financial crisis in 2008 – 2011 to have affected investment patterns, and a wide range of studies suggest that it did, although they are inconsistent as to what that effect was. We believe this inconsistency is largely because different studies observed different classes of investor, investee company, and investment type. Thus while some researchers [10, 11, 40] found a substantial decline in investment when studying private, relatively early stage investment in life sciences, others [4, 5, 12, 13] found a much more limited decline and others found that investment had recovered pre-credit-crunch levels [5] [6–9] in a set that included IPOs and post-IPO

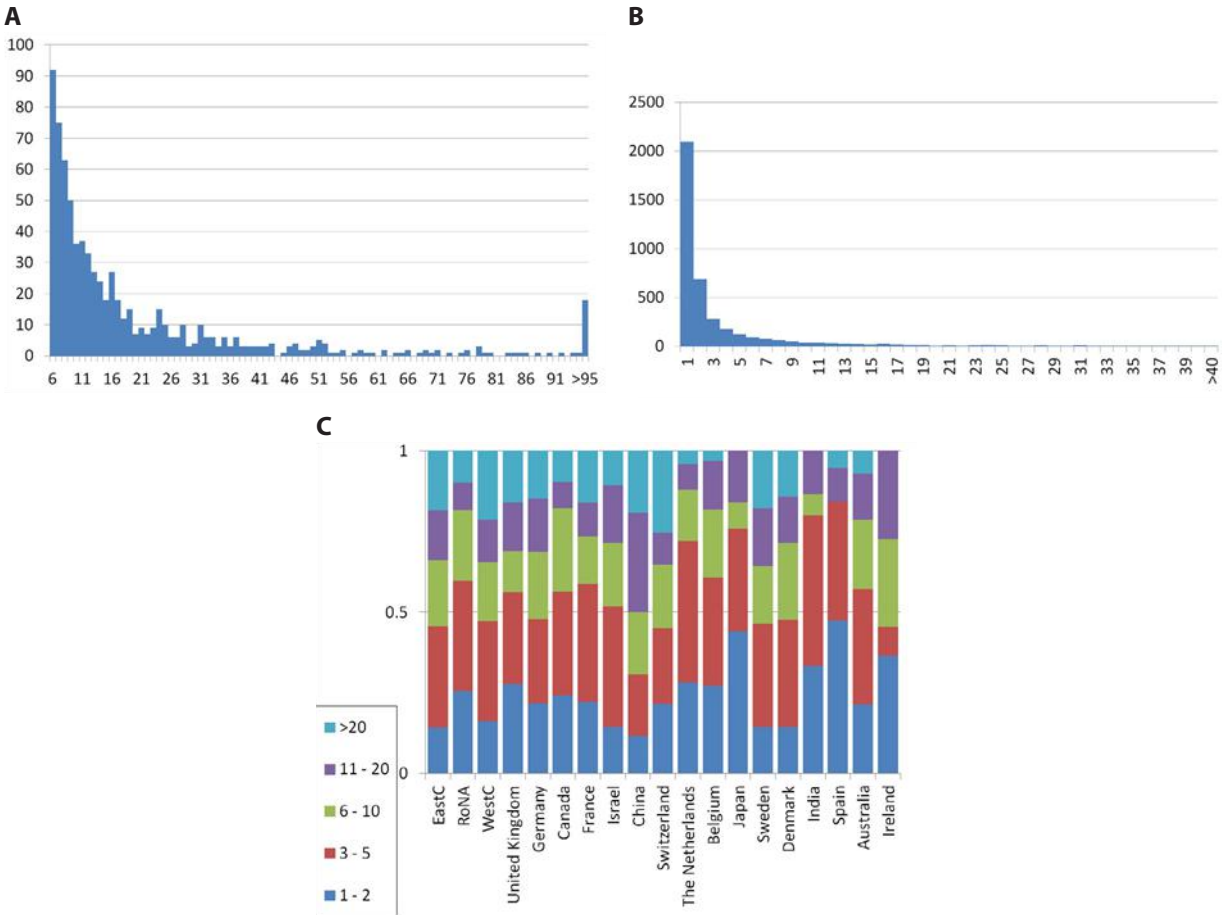


Figure 2 : Investor experience in investing in biotechnology.
Investor experience, as defined by investor activity. A: and B: X axis: number of investments in biotechnology companies made by investors in this data set between 1995 and 2014 inclusive. Y: number of investment groups making this number of investments. A: Investors making any investments. B: Investors making at least 6 investments. C: number of investments made by investors, by country in which the investor has their head office. EastC – East Coast of USA (CT, DC, DE, MA, MD, NH, NJ, NY, PA, RI). WestC – West Coast of USA (CA,OR, WA). RoNA – rest of the USA. Investors headquartered in these 18 countries were involved in 8398 out of 8641 investments in the database.

financing. It is plausible, therefore to suggest that the pattern of investment has changed more than the aggregate amount over the period of the 'credit crunch'.

Investor Experience

An underlying assumption in the conventional story of how VC operates is that VC deploys substantial cash and substantial experience in investing. VCs are experts in investing, who themselves invest in experts in particular technologies. In this model, the value that investors bring is through their close involvement with companies [41], and the more innovative the company, the closer the involvement [22]. In particular, investors with extensive experience in the industry provide great added value and significant validation (and hence support for future fundraising)[42].

We were surprised to find that the evidence does not support this model. The large majority of investors in the data set have little experience in investing in biotechnology companies. Over 2000 investors have made only one investment in biotech in the period 2005 thru 2014, and of the 5364 investors mentioned in the database, only 1737 had invested three or more times (Figure 2). While the fraction of relatively inexperienced investors varies with territory (Figure 2C), inexperienced investors make up a significant fraction of all investors in all territories.

(We note that the word "inexperienced" in this context means having little experience of investing in

medtech or biotech companies. Investors may have very extensive experience in investing in other industries.)

Investors that were not disclosed could not be analyzed and were ignored: this may distort the statistics, but we observed that the highly active investors generally were willing to have their involvement in investee companies known, and so were less likely to be listed as 'Undisclosed Investors'. Thus, if anything, Figure 2 under-estimates the number of investors with a small number of investments in this data set.

Leaders and Followers

The apparent lack of experience in the investors in biotechnology companies is surprising. However the effects seen here might be an artifact of how investors judge investments. Typically an investment round will consist of one or more experienced investors who take on the majority of the work in evaluating deals, performing due diligence, setting round price and terms etc., and one or more investors who take a more passive role who may or may not be experienced. The former investor(s) are called the Lead Investor(s), the latter Followers [22, 43]. The Lead Investor should have industry experience, but the Follower Investors need not, they just have to trust the competence of the Lead Investor. So a round might include one or two experienced investors and several highly inexperienced ones. (This is not very likely: it is well known that venture investors prefer to invest in syndicates of similarly experienced investors [44]. However such an arrangement is plausible if, for example, a seed-stage investor wished to participate in a Series A round that was beyond their financial capacity, and which was outside the remit of other, similar Seed-stage funds.) There is good evidence that acquiring a good Lead Investor is indeed a signal of company quality [42, 45].

If this were true, we would expect there to be many inexperienced investors in biotechnology, but very few inexperienced syndicates. However Figure 3 shows that this is not the case. 21% of the investments are made by syndicates in which the most experienced investor has done less than 8 biotech deals in the last decade, 13% are made by syndicates in which no member had invested in more than 3 deals (Figure 3A). During the credit crunch there was a small move to more experienced syndicates (Figure 3B), but this has reversed since. There is also no obvious correlation between the experience of the least and the most experienced investors (Figure 3C).

A caveat to the conclusion above is that the roles of Lead and Following investors could be separated in time. A company can signal its quality by acquiring a well-regarded investor in one investment Round, and thereby acquire investment from other investors in a subsequent round even if those investors are basing their investment decision on the investor syndicate rather than deep knowledge of the industry. This would match Hsu's observation [46] that entrepreneurs value association with investors that they perceive to be of high quality. If this were the case, then we would expect the patterns of investment seen in Figure 3. We would also expect that the number of syndicates containing no experienced investors would be greater in later rounds, and that companies with inexperienced investors would be greater in later rounds, and that companies with experienced investors as their initial investors may complete more rounds of investment than ones with inexperienced initial investors. Figure 4 tests tests whether inexperience is concentrated in later rounds, and finds the reverse. Inexperienced syndicates are disproportionately present in Seed and Series A rounds. Figure 5 tests whether having an inexperienced initial syndicate reduces the chance of raising further funds in a later round, and shows no significant evidence of this; there is a slight increase in the total number of rounds with initial syndicate experience, but not the substantial difference we would expect if having an experienced investor invested in a company helped to attract future investment.

Deep Pockets and Investor Experience

The arguments above explore whether inexperienced investors invest in biotechnology because they see validation of investment propositions from present or past involvement of more experienced groups. An alternative explanation is that inexperienced investors are investing under different financial criteria from experienced ones. There are two versions of this explanation.

Investment round amounts range from $100k to $100M, and it is unlikely that the motivation of investors making investments at the extremes of this scale will be the same. Regardless of whether the round is called 'Seed', 'Series A' etc., smaller amounts of investment are usually signals of a young, immature company being funded to validate a key technical or market concept, larger amounts of investment usually signal a more mature proposition being funded to grow. This second category is the specialism of Growth Capital funds which tend to be more generalist, focusing on the financial performance of a company rather than its industry-specific technical potential. Inexperienced investors might therefore be primarily Growth investors, putting substantial sums to work in growing companies that had already shown their commercial viability and overcome industry-specific technical hurdles. If this were true, we would expect experience to correlate, at least weakly, with amount invested. (Note that this is

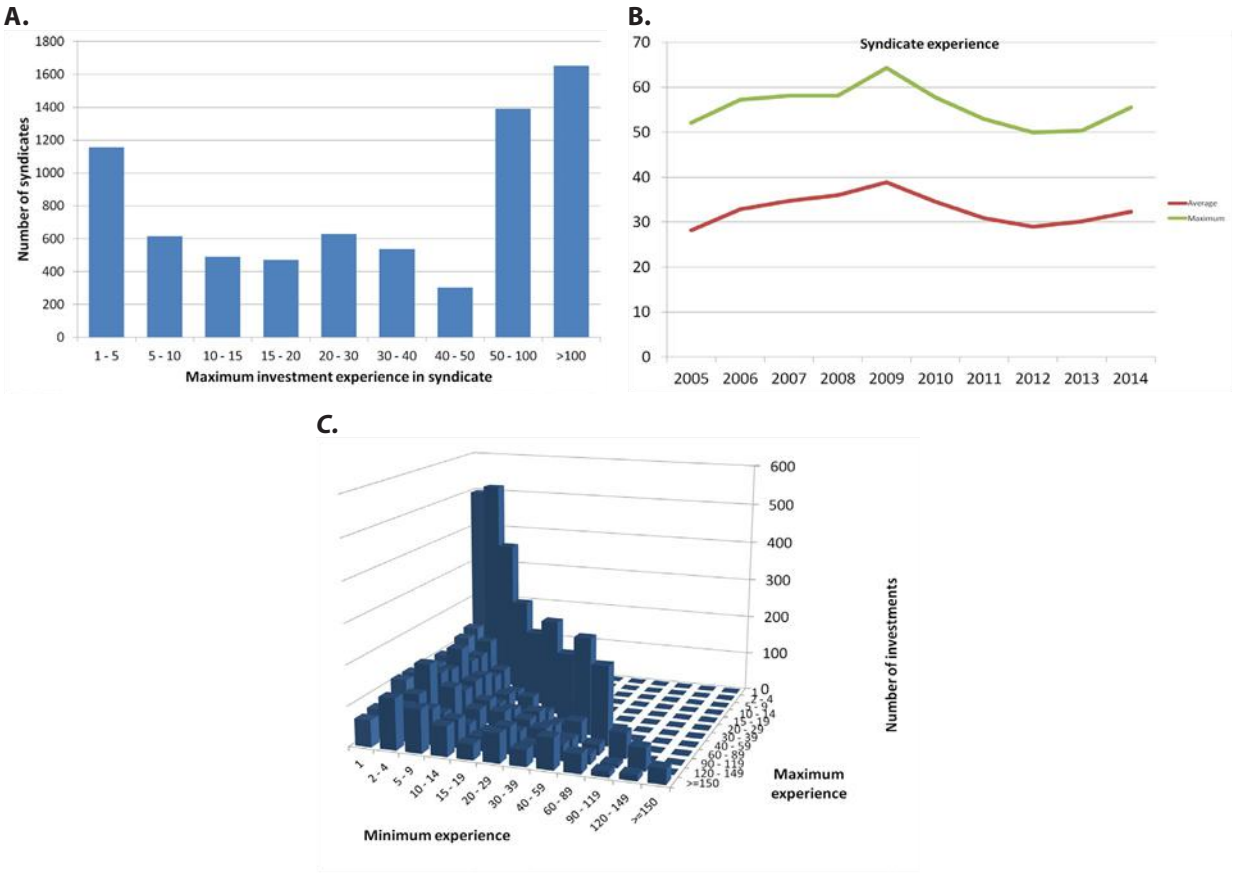


Figure 3: syndicate experience distribution.
Distribution of investor experience (number of deals the investor participated in, in this data set) within each deal. **A:** Measure of the most experienced investor in a deal. X axis: number of investments made by the most experienced investor in the syndicate reported as investing in a deal. Y axis: number of deals in the data set in which this maximal experience was found. **B:** changes in experience with time. X axis: year. Y axis: average experience (number of investments in the data set) and maximum individual investor experience in the dataset for each syndicate. **C:** Correlation between the experience of the most and least experienced members of an investment syndicate. X axis: experience of the least experienced member of a syndicate. Z axis: experience of the most experienced member of a syndicate. Y axis: number of deals. Note that the experience of the least experienced member of a syndicate cannot be greater than the experience of the most experienced member, so half of the values are zero. The high values on the maximum=minimum line are related to deals in which only one investor is named.

not the same as the correlation of experience seen with Series in Figure 4 While the average amount per investment round increases with each round, there is substantial overlap between the amounts raised in the post-Seed round (Figure 1C).

Alternatively, large, generalist investors with very substantial funds at their disposal may wish to 'explore' potential new areas of investment by putting what for them is a very small fraction of their fund into those new areas in order to gain inside knowledge, visibility, and a track record in the field. In this hypothesis, the large number of investments are small investments, whether they are called "Seed", "Series A" or "Series D" – they are investors putting a small amount of money to work in a field with which they are not familiar, in order to gain access to deal flow, experience of the field, or understanding of the industry. This hypothesis predicts that inexperienced investors would preferentially be found to invest in smaller rounds. (It is not practical to identify the fraction of each round that investors are contributing, as this information is rarely made public.)

These hypotheses both suggest a correlation of experience and round size (as opposed to round Series), a correlation probed in Figure 6, and found to be largely untrue. While very large investment rounds are backed by syndicates with at least one highly experienced

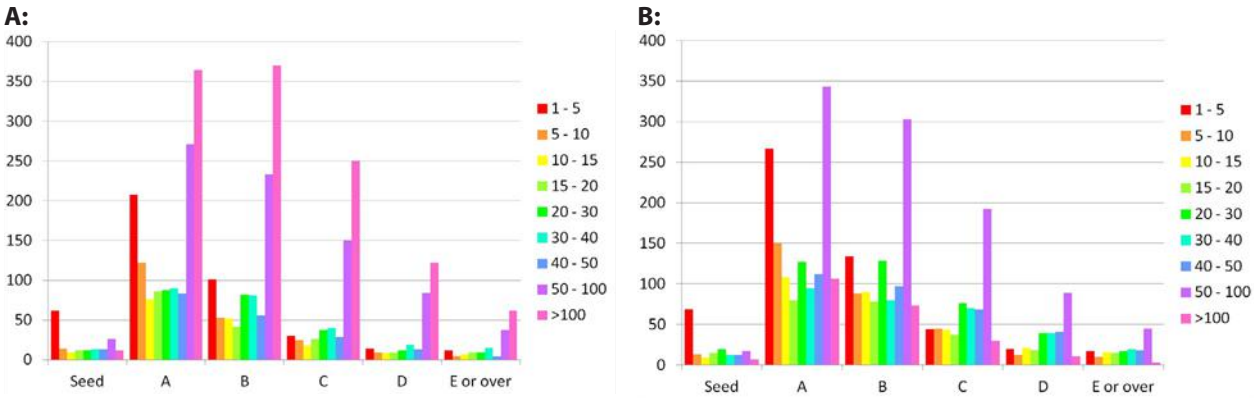


Figure 4: Experience vs. investment series.
Experience of investor syndicates in biotechnology companies, 2004 – 2014, by round. Y axis: number of investments. X axis – investment round. Each bar shows the number of investments made by a syndicate with a different level of experience, i.e. different number of prior investments in biotech in the time span analyzed here. A: maximum experience in a syndicate. B: average experience in a syndicate.

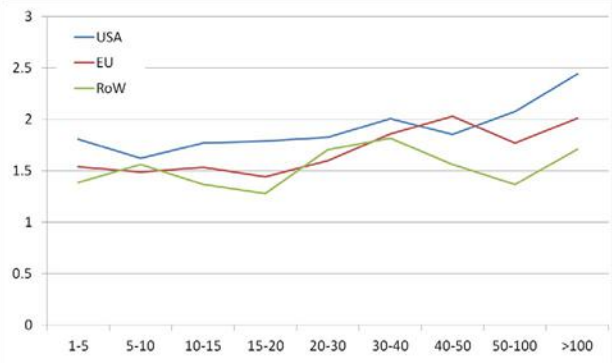


Figure 5: Number of rounds vs. initial investor experience.
Average number of investment rounds completed by companies in the database, as a function of the maximum experience in the investor syndicate (i.e. the total number of investments made by the investor in the syndicate that had made the most investments). Y axis – average number of investment rounds. X axis – maximum syndicate experience.

investor, and very small investments (investment rounds that are in effect Seed rounds, even if they are not called that) have a disproportionately small number of highly experienced investors, the bulk of investment rounds between $1M and $100M show a uniform distribution of experience. For rounds between $1M and $100M, the correlation coefficient between amount raised and *maximum* syndicate experience is 0.38, between amount raised and average experience 0.25.

We are therefore left with the rather surprising conclusion that a substantial fraction of investments in biotechnology and medical technology companies over the last decade have been made by investors with very limited experience of investing in biotechnology or healthcare, and a number of explanations based on the conventional model of VC behavior are not supported by the data. Given that investor experience is often cited as a major benefit for investee companies, [22, 29–31], the number of syndicates taking the risk of investing without substantial knowledge of the sector is unexpected.

Effect of Boom and Bust 2005 Thru 2014

The explanations tested above all assume that investors are acting like rational, experienced, knowledgeable agents. Another explanation is that they are not rational or knowledgeable, but are just following the trend. There have been periodic booms in investment in biotechnology, usually following a strong IPO market and driven at least in part by these areas as being seen as 'hot' investment fields in which it was easy to make money (reviewed

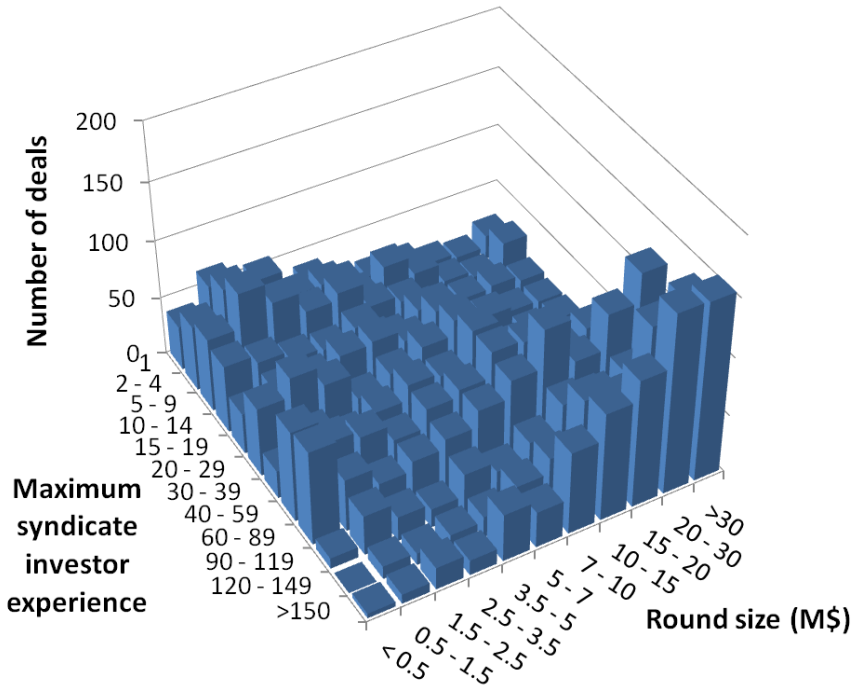


Figure 6: Experience vs. round size.
Investment deals classified by maximum syndicate experience (Y axis) and size of investment round (X axis). Height of bars (Z axis) is the number of investment deals falling into each category.

in [47]). The booms in 1982-4 [48, 49], 1998-2002 [50, 51], 2005-7 [52–55] all showed a growth in investor groups and a subsequent shake-out three or four years after the end of the boom, with the latest decline being particularly severe, and affecting all forms of tech investing [51, 56–58]. In essence, many investors piled into the area without the experience to make a sustained success of their business. If this cohort of inexperienced investors is showing up in the figures, then we would expect the frequency to inexperienced investment to change over the Credit Crunch as VC numbers declined. Equally plausible, it has been observed that more experienced investors invest in riskier and more innovative startups in hot markets, and so might leave these to inexperienced investors when the markets turned down [59]. In either case we might expect that Credit Crunch would change the fraction of inexperienced investors, either the fraction investing overall or the fraction investing in young companies. We therefore examined whether the number of inexperienced investors had changed significantly over the last decade. The results are summarised in Figure 7. We divided the data set into investments 2006 thru 2008 (before the financial crisis took effect), 2008 thru 2011 (the height of the crisis) and 2012 thru the first half of 2014 (post-crisis). While the second half of 2008 was actually the start of the crisis, the average time to close a VC investment in a UK biotechnology company is 9 months from formal business plan [16], so most deals closed in the first half of 2008 had been in negotiation since 2007. We have also grouped investment into geographic area, whether the investor is experienced (has at least 15 deals in the dataset) or not, and whether the company is young (less than four years old).

Results are shown in Figure 7. It is clear that across all territories investment numbers have fallen, as noted previously in Figure 1, but the average amount reported to be invested shows less clear cut patterns. There is no consistent reduction in the fraction of deals done by inexperienced investors. Most changes are seen in investment in older companies – inexperienced investment in young companies remains unexpectedly stable. There is a trend for experienced investors outside Europe to put more money into both early and late stage deals, but in Europe the model for the few investments made seems to be similar before, during and after the credit crunch. So no matter what the reason for inexperienced investment in biotechnology, it does not seem to be driven primarily by the exuberance of the investment environment in 2005-7 nor the gloomy environment of 2008-12.

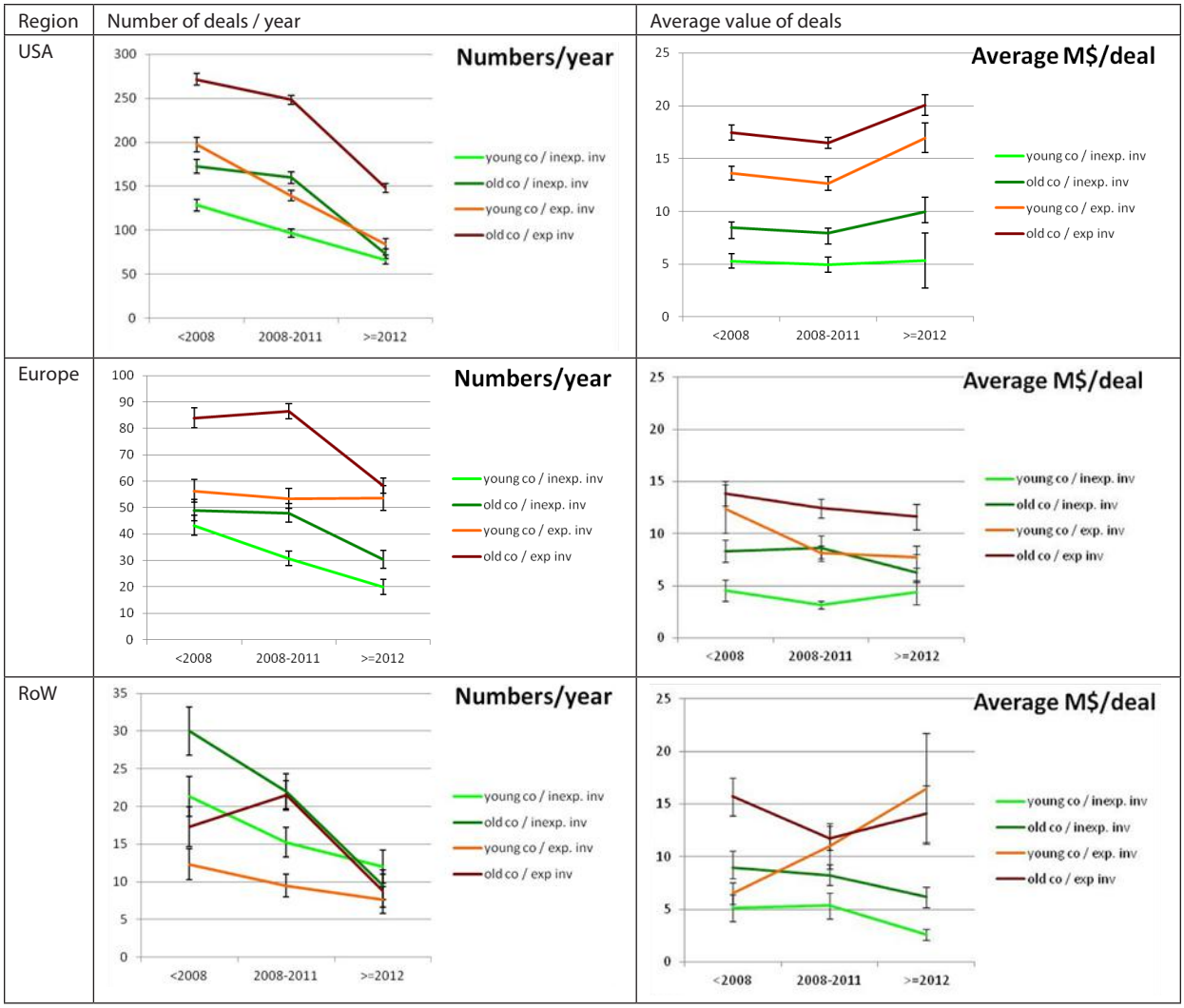


Figure 7: Geographic analysis of investments.
Changes in investment patterns over the Credit Crunch. Investments were categorized into USA (including Canada), Europe (including Scandinavia) and the Rest of the World. Investee companies were classified as young ('Young Co') (<4 years from foundation at the time of the investment) or old ('Old Co') (>=4 years from foundation to investment). Investors were classified as experienced ('Exp. Inv.") if they have at least 15 investments in the database, or inexperienced ('inexp. Inv") if they have less than 15 investments in the database. Shown are the deals for the periods Jan 2004 – Dec 2007, Jan 2008 – Dec 2001, and Jan 2012 – June 2014. Left panel – average number of deals per year. Right panel – average size of the deals.

Investor Classes and Experience

Throughout the analysis above we have analysed investors as a uniform class. While this is reasonable in that their input (cash) and output (equity, realised as cash on exit) is the same, they are in fact differentiated by their business model. Fund strategy is defined by the fund management groups. We therefore classified 1737 management groups in this data set into 14 types, listed in Table 1, which we further classified broadly according to their business model: Corporate (groups investing on behalf of a large corporation), Soft (groups investing for political and social goals as well as financial ones), and conventional investment groups classified on whether they typically provided pre-VC capital (Pre-VC), VC stage investment, Growth capital or General investment products. Some investors can fall into several categories. For example, a number of state-funded seed funds call themselves venture funds, although in reality they invest before VC would invest, and are driven primarily by regional employment growth concerns rather than

Table 1: Investor types

Investor type	Group	Number	Comments	Example
Corporate venture group	Corporate	237	Investment by companies whose primary business is not investment, such as Hitachi or GSK, or named investment subsidiaries of them	SR One, Novartis Ventures
Family office	General	7	Self-identified private investment groups for families	Aeris Ventures, Braganza AS
General investment group	General	191	Investors with a wide remit in general investment, and sometimes banking	Carnegie Investment Bank, Credit Suisse, Rothschild & Cie Banque
Growth Capital	Growth	86	Any group identifying itself as 'growth capital'. Usually intermediate between 'venture capital' and 'private equity'	Fidelity Biosciences, Taiwan Global BioFund
Private Equity / Hedge	Growth	150	Any group self-identifying as 'Private Equity' or 'Hedge Fund' or equivalent terms	Ampersand Ventures, Casdin Capital LLC, InvestBio Ventures
Accelerator / Incubator	Pre-VC	45	Investors who provide seed funds, start-up support and mentoring, and some element of physical facility support	Misgav Technology Center, P.U.L.S. AB, Rocket Ventures
Angel / Angel group	Pre-VC	141	Angel groups: individual angels are rarely named in this data set	Mass. Medical Angels, Robin Hood Ventures
IP exploitation company	Pre-VC	18	Investors who provide seed fund, company creation support, but not physical facilities	IP Group, Business Development Bank of Canada, Carrot Capital Healthcare Ventures
Charitable / non-profit	Soft	8	Any entity which invests in companies but whose principle goal is non-profit, other than academic or research institutions	Peierls Foundation, Inc, Richard King Mellon Foundation
Institutional Venture	Soft	97	Academic, research or other institutions whose principal goal is non-profit	Netherlands Cancer Institute, Rose-Hulman Institute of Technology, The Royal Society
Regional government backed	Soft	100	Regional or local government-backed fund. These may have commercial input, but their governance is primarily political	Oklahoma Seed Capital Fund (USA), Mercia Fund (UK)
State-backed	Soft	25	National or super-national government-backed fund. These may have commercial input, but their governance is primarily political.	Suomen Teollisuussijoitus Oy (Finland), NESTA (UK)
Other private specialist group	VC	130	Investment groups that clearly operate a VC-like business model, but do not identify themselves explicitly as VC	Aberdere, Split Rock Partners
Venture Capital	VC	502	Any group that self-identifies as Venture Capital.	Index Ventures, Atlas Ventures, Sofinnova Venture Partners

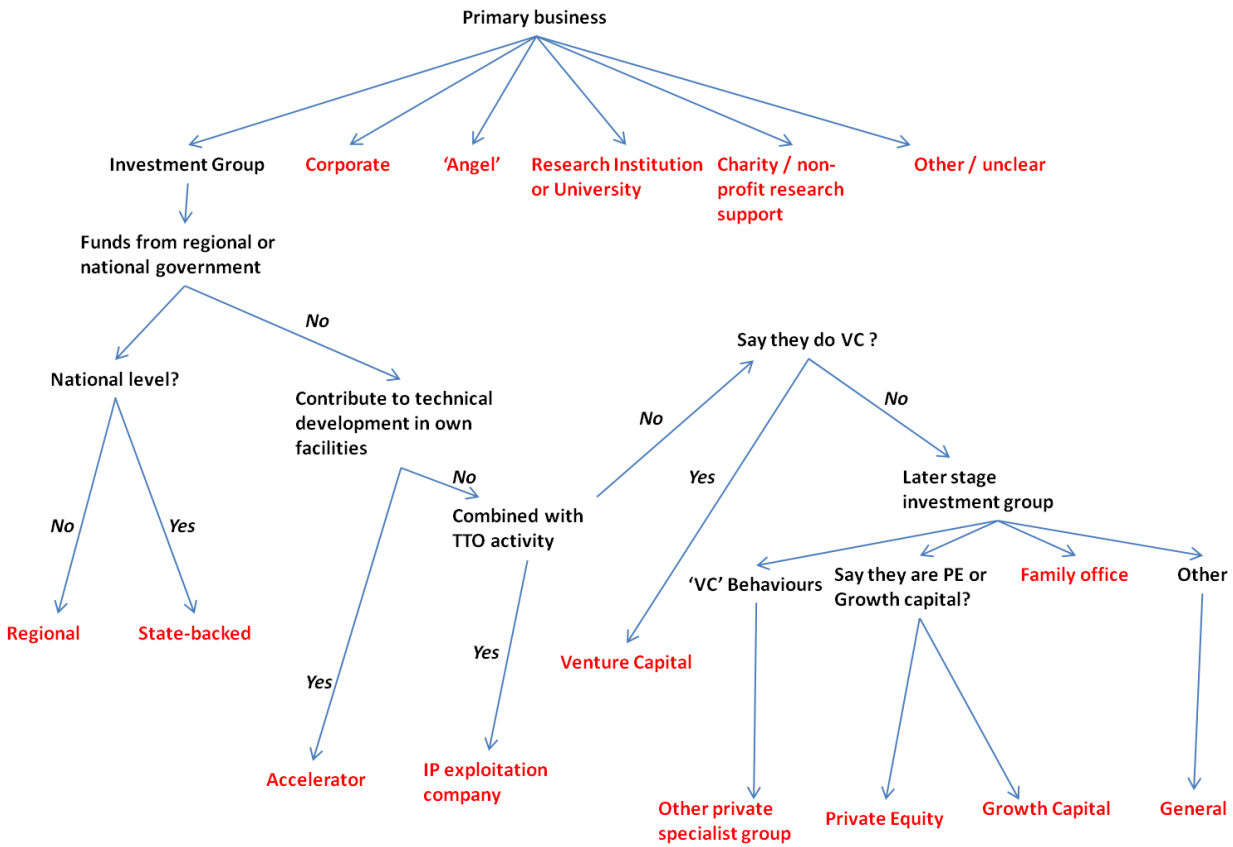


Figure 8: investor classification triage.
Investors were classified on their stated business model into the following categories. Accelerator / Incubator, Angel / Angel group, Charitable / non-profit organization, Corporate venture group, Family office, Growth Capital, Institutional Venture (i.e. a fund tied to a specific, non-profit or non-investment institution such as a hospital), Other private specialist group (i.e. a group that says they execute a VC-like model of hands-on, intensive investing in early stage high risk enterprises, but which do not explicitly say they are a VC group), Private Equity / Hedge, Regional government backed (i.e. any fund that primarily gets its funds from regional government as opposed to commercial entities), State-backed, Venture Capital. Any investment group that was clearly a dedicated investment organization but did not fall into any of the categories above was classified as *General investment group*. The logic for selecting a category for any specific investor is shown in the figure.

by return on investment. We therefore defined a 'triage' to attempt to classify funds systematically based on their likely motivations, which is summarised in Figure 8.

Management groups were classified manually. To make this a manageable task, investment fund/groups that had only invested once were not analysed. No attempt was made to classify investors based on their financial or other performance – if they said they were a Venture Capital investor, then they were classified as such. Investors' headquarters were identified for all investors, and subsidiary offices identified for investors which were not multinational or global corporations with offices in more than six countries.

We had a number of expectations of the results of this analysis, as no doubt will the reader, but as few of them were fulfilled it would be futile to list them here. In summary, as expected from Figure 2C, US investors tended to show a greater average experience than ones from the rest of the world. This is not surprising given that most biotech investment happens in the USA (Figure 1). US VCs and VC-like investment groups show more experience than those in other territories, again reflecting the dominance of the USA in VC investment in biotech. Interestingly, IP Commercialization groups (such as IP Group and Imperial Innovations) show much greater average experience in Europe, again reflecting that this business model is better established in Europe. Other investors groups showed no substantial deviation in *average* experience from the USA>EU>RoW trend.

However the distributions of experience are revealing (Figure 9B). For this, investors are grouped into the six business models summarized in Table 1, as the numbers

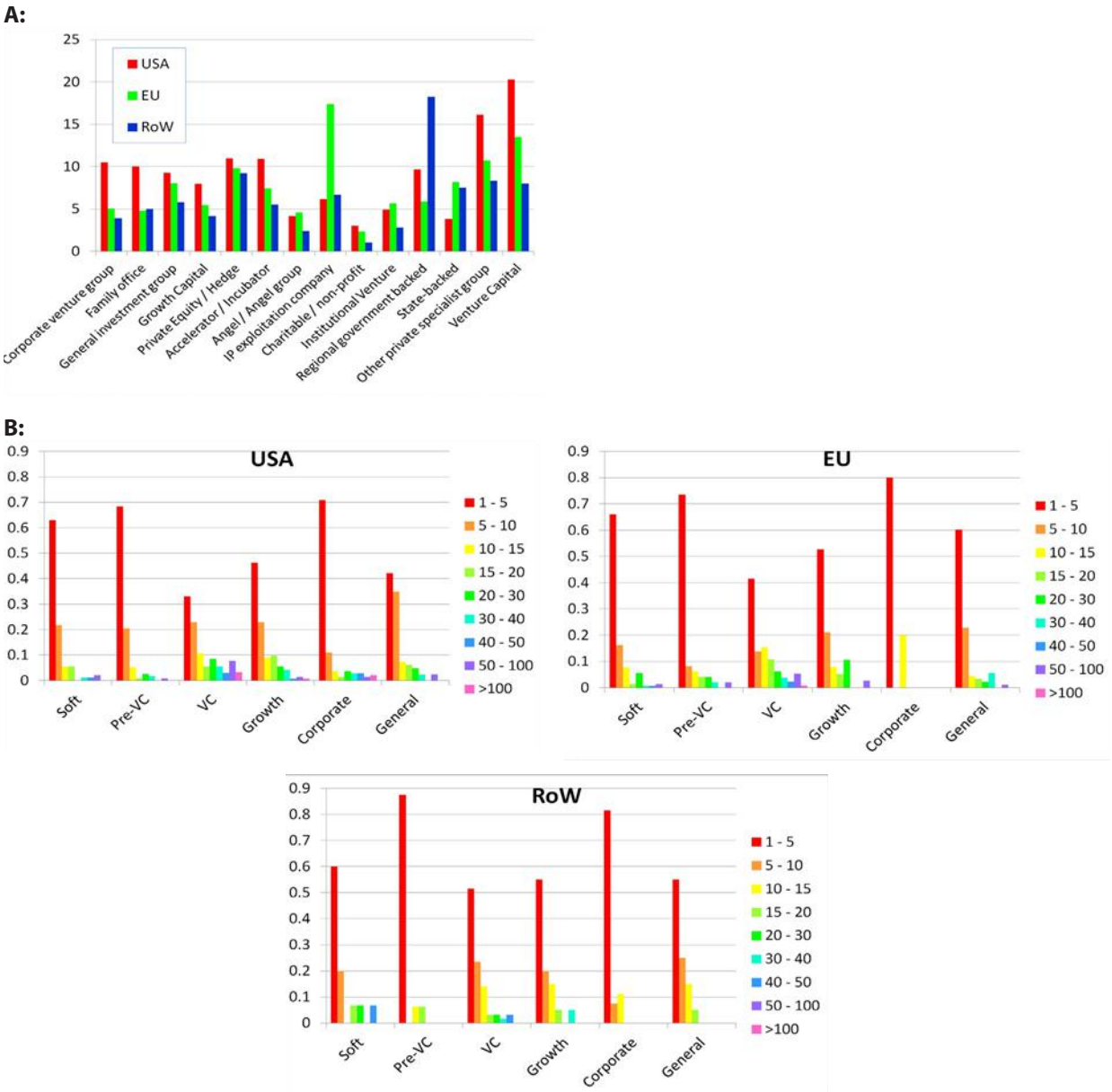


Figure 9: Investor experience by investor type.
Experience by investor type. A: Average experience for each of the 14 investor types in three territories – USA (including Canada), Europe (including Scandinavia) and the rest of the world. Y axis – average experience (average number of investments made by that investor type in the dataset). X axis – investor type, as described in Table 1: Investor types1. B: Distribution of experience in each of the six business model categories summarized in Table 1: Investor types1. Each panel represents a different geography, as per panel A. Y axis – number of investors making this number of investments in the whole data set. X axis – Categories of investor business model. Each bar represents a category of experience.

in some individual groups of investor type are too small to analyze. Even after grouping, the numbers in the Rest of World category remain small. But in all territories, all business model groups show a large number of inexperienced investors, and a steep decline in the number of investors with investor experience. Figure 9B is apparently in conflict with Figure 9A. For example, Figure 9B shows a large fraction of the VC group have limited experience, whereas Figure 9A show VC average experience to be high. This is because the VC average values in Figure 9A are pulled up by a small number of VCs with very large numbers of investments – however they are outnumbered

(if not out-invested) by a large number of inexperienced investors. Similarly the relatively high average number of deals done by European corporate investors hides a large number of groups that did 5 or less deals, by including a small number of investors that did a large number of deals; specifically, Roche Ventures, Takeda Ventures (Europe) and DSM account for 25% of all deals involving a European corporate investment group.

We conclude that lack of experience is not confined to any one type of investor.

DISCUSSION

We have analyzed the way that investors invest in biotechnology companies from a large database of investments made over the last decade. To our surprise, we find that many investments are made by investors with little prior experience in investing. As it is widely understood that experience is a key success factor for investing (and indeed experience in execution is a team factor that investors themselves insist on in their investee companies), we explored why this might be so. Several potential explanations were explored and found not to be supported by the data, among them that this represented investment by syndicates of which at least one member had substantial experience, and that the large numbers of inexperienced investors represented 'soft' funding sources such as regional development funds with no remit to make a competitive financial return.

The study is limited to data in the public domain. Some funds may have invested in companies but not put any press announcement out about it. However we consider it unlikely that this is a general explanation for the trends seen here. While there may be specific cases where an experienced investor has publicized only a few of their investments, it is more plausible that an investor's PR policy would either be to publicize or not to publicize. We also did not explore whether investors invested in other industries, which would give them experience of general investment, financial management and equity-related negotiation even if not of the biotech industry and its many perils.

A major limitation is that we did not examine whether an inexperienced *group* was nevertheless made of experienced *individuals*. It is a common pitching tactic for investee companies as well as investment groups seeking funds to cite the experience of the individuals if they have not worked together before as a group. There is good evidence that an individual's past performance as a member of a team translates poorly to future performance in another team in the investment context [60], so it is unclear whether this argument is valid. However we can suggest that some of the inexperience of the teams seen in this study is offset by the presence of highly experienced members in those teams. Probing this would be the subject of future study.

With these caveats, we suggest that the conventional image of biotechnology investment as the careful selection and nurturing of young companies by experienced investors is clearly incomplete. The majority of investors, and a substantial fraction of investment syndicates, have little experience in biotech. The argument that getting 'good investors' is worth a significant discount on valuation [46] is made even stronger by this observation – if most investors cannot provide genuine support based on experience of biotech companies, then finding the few that do could be of substantial value to a start-up. Entrepreneurs might wish to adjust their pitches accordingly. (We would not wish to suggest that entrepreneurs with less-than-outstanding propositions actively seek out those inexperienced investors …)

Secondly, there is a widespread belief in government in most developed countries that new biotechnology start-ups are a good thing, and the way to encourage their growth is by encouraging investment [16, 20, 61–64]. The second half of this argument is based in part on the belief that investors bring experience that start-ups lack (as well as cash). It would at least be worthwhile for governments wishing to support start-up biotechnology to understand that the balance of experience is actually often in favour of the start-up, and channel investment funds accordingly.

Lastly, we should ask whether this apparent lack of investor experience makes any difference. After all, many entrepreneurs feel that investor 'help' is just interference, and all that investors really bring is money. Exploring this topic thoroughly would require an analysis of the fate of investee companies that is beyond the scope of this study. However we note that Figure 5 and Figure 6 suggests that whether an investment syndicate has an experienced investor or not makes little difference to whether the investee company raises $1M or $100M, and whether they can go on to raise further investment rounds. This suggestion that, contrary to received wisdom, investor experience is irrelevant to future financing success deserves further study.

CONCLUSIONS

Investment in early stage, private biotechnology companies has declined systematically since the start of the credit crunch. Despite reports of rising investment in the industry as a whole, support for early stage companies remains low. Throughout the period 2005 thru 2014 a significant fraction of investment in biotechnology companies worldwide has been from investors with limited

prior experience in investing in biotechnology companies. None of the explanations for this that are based on the conventional view of VC investor behavior are supported by the evidence. This suggests that our model of how investors decide to invest in biotechnology companies in the real world (as opposed to in economic models) is flawed. This has implications both for governments seeking to support new, innovative companies, and for entrepreneurs seeking finance for their start-ups.

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Article

The BIEM Verification Study: Experienced Venture Capitalists Assess a Biopharmaceuticals Innovation Expertise Model

Moira Gunn
founded and directs the Business of Biotechnology Program in the School of Management at the University of San Francisco, where she is an assistant professor. The former President of SIBER, the Society for International Bioentrepreneurship Education and Research, she also hosts Tech Nation, and its regular segment BioTech Nation, which air on the NPR channel of SiriusXM, among other venues.

Nola Masterson
is Founder and Managing Director of Science Futures Management Company, LLC, and an Adjunct Professor in the Business of Biotechnology Program in School of Management of University of San Francisco.

Paul Lorton, Jr.
is a Professor of Management Information Systems in the School of Management at the University of San Francisco.

Jacques Baronet
is a Professor of Entrepreneurship and Innovation Management at the University of Sherbrooke, Quebec, Canada.

ABSTRACT

Developing biopharmaceutical therapies is a scientifically complex endeavor, requiring from ten to fifteen years of effort with successive rounds of increasingly greater investment capital in a risk-intensive landscape. With failure rates at 88%, and an all-attempts-averaged investment of over $2B per approved drug, discussions of what leads to success and/or failure are pervasive. In this milieu, the BIEM (Bioenterprise Innovation Expertise Model) model was developed so that the status of a bioenterprise could quickly be assessed. Assessing the BIEM model, 20 biopharmaceuticals venture capitalists with 30 years average biotechnology industry experience, all having board experience, most having served as board chairs, and 80% having been CEO's and/or presidents, rated the innovation expertise disciplines of BIEM 2.0 as to their importance in the scientific discovery through market-ready product innovation phase of biopharmaceutical development. Despite a small sample size, statistically significant insights were produced, verifying the BIEM model. The most important innovation expertise disciplines were intellectual property, science, regulatory expertise, and venture capital, in that order. Further, the strongest correlations linked regulatory expertise and science, and equally so, intellectual property and venture capital. Additional insights with respect to the profiles of the biopharmaceutical venture capitalists themselves is also presented.

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Keywords: BIEM model; Bioenterprise Innovation Expertise Model; entrepreneurial model testing; business model testing; biopharmaceutical failure; biopharmaceutical success, venture capitalist surveys, venture capitalist studies

Correspondence:
Moira A. Gunn, University of San Francisco, US. Email: gunn@usfca.ed

INTRODUCTION

Global biopharmaceuticals revenues in 2014 were reported to be $160B, some 20 percent of the traditional pharmaceuticals industry, with industry expectations that the biopharmaceuticals market share would grow.[1] However, viewing

the biopharmaceuticals sector in terms of revenues can be misleading, as it does not recognize the substantive entrepreneurial efforts underway to create new products.

AN ENTREPRENEURIAL VIEW OF THE BIOPHARMACEUTICALS SECTOR

Developing biopharmaceutical therapies is a scientifically complex endeavor, requiring from ten to fifteen years of effort with successive rounds of increasingly greater investment capital in a risk-intensive landscape. Considering all drug candidates entering Phase I clinical trials, the failure rate is 88%, and so for any drug candidate which actually does becomes an approved product, the all-attempts-averaged investment is estimated to be over $2B before any revenue can be realized.[2] Measured by investment monies raised, BioCentury's Walter Yang has reported that $110B was raised in 2015 from venture capital, IPOs, and debt sources, with another $70B invested in partnership funding.[3] These were the reportable investments; however, as Yang indicated, the amounts raised in known deals were not always disclosed, and thus an accurate figure would be greater.[3] A simple calculation reveals the insight that current investment in new products exceeds total industry revenues, a bellwether for its current entrepreneurial stance.

Some of this expenditure is due to the maturing of biopharmaceuticals development, since the profile of capital needs throughout the breakthrough-science-to-market-ready-product life cycle (science-to-product innovation phase) is not flat. While there are any number of variants, in biopharmaceuticals, each successive clinical trial phase (I, II & III) requires longer periods of time and a greater investment of capital. While the venture capital community is often associated with early stage investment, it is present throughout. Venture capital contributed a record $12B in 2015, up from $9B in 2014.[3] Yet, the $70B in partnership funding in 2015 plays a somewhat different role. Partnerships between biotechnology companies and large pharmaceutical firms, also present throughout, goes beyond the availability of substantial capital to bringing clinical and regulatory expertise and relationships, management experience, manufacturing sensibilities and ready access to manufacturing, and the pedigree of the pharmaceutical firm itself. This carries weight for the entire bioenterprise, especially in attracting other investment monies. When partnerships are successful, they can lead directly to licensing, or preferably, acquisition, which can occur at any stage in the development process, and trigger the beginning of the venture capital investor exit.[4,5]

The venture-capital-pharmaceutical-partner transition serves both parties: one for exit and ROI; the other to acquire product. The value of these partnerships has been understood for some time. Czerepak and Ryser noted in 2008 that "Of the 103 FDA approvals from January 2006 to December 2007, 47 (45%) are from biotech companies, 16 (16%) are covered under biotech-pharma partnerships; and 40 (39%) are from pharmaceutical companies, four of which are from programmes acquired or license from biotech companies".[6] In short, of the 103 new drug applications which were approved, 67 (65%) came from the biotechnology industry.[6] By 2010, $40B was invested in partnerships, and by 2015, partnership funding had increased to $70B.

SUCCESS AND FAILURE IN THE BIOPHARMACEUTICAL INNOVATION PHASE

Risk aside, need for capital aside, the science-to-product innovation phase is daunting.

> *"The endeavor carries innate risk. Simply stated, the bioenterprise must drive nascent science to stable, commercially-available and ultimately profitable products and services, an exercise for which success can neither be predicted from the outset, nor at numerous points along the way. Achieving commercial success requires a multi-disciplinary and creative entrepreneurial organization, which can operate within a continually-challenging and unprecedented business context."*[7]

Numerous views of what is necessary to be successful, or what causes failure, have been written about widely. One major focus is on problems in the regulatory sphere, such as the 2014 report, "Science and Regulatory Reasons for Delay and Denial of FDA Approval of Initial Applications for New Drugs, 2000-2012", published in the *Journal of the American Medical Association*.[8] Sacks, et al., on staff at the FDA, examined some 300 NME (New Molecular Entity) applications made between 2000 and 2012. ("The FDA's Center for Drug Evaluation and Research (CDER) … classifies biological products in an application … as NMEs for purposes of FDA review."[9]) Half of the NME applications were approved on first submission, while ultimately, another 25% were approved after one or more resubmissions. Of note, on average, rejection on first submission caused a median delay of 435 days. From a business standpoint, a delay of over a year can have serious consequences, including an uptick

in funding needs, a decrease in investor confidence, staff re-alignment, and worse. The report noted that the "applications that were eventually approved were often able to address initial safety, manufacturing, and labeling concerns, but efficacy concerns were less likely to be successfully managed."[8] While this extremely detailed report cannot be summarized easily, the remaining NMEs either had structural problems in the design of their trials that could have been avoided with "early and frequent dialogue between the FDA and drug sponsors addressing critical aspects of study design", or the truly unfortunate outcome, when everything has been done right, but the result was "inadequate efficacy compared with standard of care".[8] This was the case for 20 of the 151 rejections, or 13%. Clearly, safety, manufacturing and labeling are the named standouts, while prescience on ultimate efficacy is a larger question.

Another view of the regulatory issues failure/success quandary came from scientific researchers at Brigham and Women's Hospital/Harvard Medical School. Wang, et al. determined similar findings with its 2013 review of FDA advisory committee denials for new drugs applications (NDAs) and biologics license applications (BLAs) applied for between 2007 and 2009.[10] In this study, 52 drug applications were examined, 18 (35%) from large companies, and 34 (65%) from small companies. Half of the denials on first submission denials on the basis of safety were eventually approved, but only 1 out of 12 based on efficacy eventually gained approval. By the end, 78% of large company applications were accepted, while 56% of the small company applications were accepted, potentially pointing to the advantage of partnerships.[10]

Looking at problems in the regulatory space in terms of investment decisions, Schueler and Ostler queried venture capitalists.[11] Supported by the Swiss Biotech Association, 18 European venture capitalists responded to their questions, and while almost 75% of the venture capitalists considered the regulatory issues important, more than half *linked regulatory with intellectual property*, meaning that a negative investment decision might result if there were regulatory challenges, even if the intellectual property was strong. A breakdown of various aspects in a drug candidate at various stages of funding (seed funding, early stage, late stage) was created. The need to link regulatory issues with science was also expressed, with one respondent providing this input: "'Regulatory strategy is mainly influenced by science. Consequently, science and regulatory affairs should be closely linked … engage a regulatory scientist in your R&D team!'"

The Boston Consulting Group took a broader view of success and failure.[12] They analyzed the performance of some 842 molecules from 2004 to 2011, where the "full development outcome was known."[12] 205 obtained regulatory approval, and 637 failed in Phase II, or later. Eighteen attributes were analyzed, from geographic location of company, to R&D spend, to market size, and even molecular properties. None of these attributes correlated with success *or* failure. What did correlate with success was excellent scientific acumen, precisely in the form of publications per $R&D, patents per $R&D, and citations per publication, with the highest positive rating of success led by "early termination of projects", along with other "indicators of good judgement", such as R&D tenure, frequent mention of ROI, and frequent mention of decision-making.[12]

The Boston Consulting Group's focus on "good judgement" might keep an effort from pursuing massively expensive clinical trials that could be perceived as ticklish from the start with respect to efficacy. More significantly, with respect to the focus of this paper, many of the characteristics that the Boston Consulting Group identified were related to the bioenterprise and its management, as opposed to solely observing problems in the regulatory space.

ANOTHER VIEW OF THE BIOENTERPRISE – THE BIEM MODEL

The BIEM model was originally developed so that the status of a bioenterprise could quickly be evaluated. In 2004, Dr. Moira Gunn, host of *Tech Nation,* a weekly radio program which airs on such venues as the NPR channel of SiriusXM, created a new weekly segment, *BioTech Nation.* In just over two years, Gunn had conducted one-on-one interviews with over 150 national and global biotechnology industry professionals, including CEOs, Chief Scientific Officers, bioscience researchers, industry leaders, policymakers, elected officials, educators, and more.[13] During this period, she posed a standard set of questions to bioentrepreneurs:

- What is the product you are trying to create, or problem you are trying to solve?
- What is the science driving your product?
- What is your science-business value proposition?
- What/who is your competition?
- Where are the biggest risks? Largest challenges?
- Where are you in the science-to-product life cycle?
- What is its status today? How far from an actual product?

At the same time, Gunn became interested in biobusiness failures, and eventually developed a

twelve-point model for essential capabilities necessary in the science-to-product innovation phase of bioenterprise.

> *"When viewed from this perspective, successful bioenterprises were observed to assemble the right expertise at the right time at every turn in the biotechnology innovation life cycle. Agile organizations had an appreciation for a larger spectrum of expertise than did less flexible ones."* [7]

The result is the BIEM model, the Bioenterprise Innovation Expertise Model, which focused primarily on the biopharmaceuticals space. From this perspective, regulatory failure, while catastrophic, was a fairly infrequent event. It was more often startup failure, failure to secure venture capital financing, failure to secure intellectual property, failure to simply get organized or hire the right people or manage them effectively. She saw ineffective entrepreneurs who were good at raising money and would continue to get funding year after year without results, and otherwise successful managers who could accomplish great efforts, but did not understand they needed to constantly attract new investment dollars. She also saw startups which could not react to changes in the biotechnology economy. As described in its first appearance in the peer-review literature:

> *"The essence of this model reveals itself when considering the bioenterprise as a whole. While breakthroughs in science are expected, there are also scientific setbacks. The creativity and resilience required to ensure that investment capital is in place goes hand-in-hand with a readiness to construct previously unexplored investment vehicles … How last year's marketplace behaves may be completely different from this year's marketplace – there are competitor's products, a changing regulatory scene, negative and/or positive media, and much, much more. … The sudden perception by the public that there may be a bioethical or social problem can be made worse and/or better by the media, as well as by engaging, mishandling and/or avoiding the right and wrong players. Throughout this process, team dynamics in the science business arena takes on even greater meaning, with the need for high-functioning teams being absolutely essential.*
>
> *The Bioenterprise Innovation Expertise Model reflects a dynamic of the expertise needed to address the challenges of bioenterprise, which itself must be both robust and creative, and is frequently called upon to address situations which are arguably unprecedented. Such is the nature of science-business."* [7]

It is important to notice that clinical and regulatory requirements have been collapsed into a single point, as is all science. While they may carry a heavier weight in the end, they are nothing without intellectual property. Venture capital, in all its forms, is a constant throughout the effort. In a sense, what was assembled were key disciplines that were also "stopping" disciplines. If they were not available to the bioenterprise at the correct time, then the bioenterprise would fail. The original BIEM model appeared in the peer-review literature in 2013 and 2014.[7,14]

Following this effort, considerations began on developing a model for biomedical devices. It became clear that the original BIEM model also applied, but with two differences. First, in the biomedical device sector, the product could be a standalone device, or an embeddable technology, be it hardware, software or both, which required a greater emphasis on technology. As a result, Science/Technology, or Sci/Tech, was added to as an expertise area, and co-located with "Science". The other feature, not observable in the graphic, is that the timeline to market-ready product for biomedical devices is usually much shorter, and the investment capital requirements are significantly less, bearing in mind the experience of Theranos, Inc.[15]

The current version of the BIEM model is BIEM 2.0, and is depicted in Figure 1.

VALIDATING THE BIEM MODEL

The BIEM model was also used as a conceptual framework in the Business of Biotechnology program in the School of Management at the University of San Francisco, with the intention that all students would become facile at qualifying any bioenterprise proposition by virtue of its status vis-à-vis the BIEM model.[7] While the model has been formally published for some time, and discussed on numerous occasions with industry professionals, it had not been formally tested; thus, a formal validation study of BIEM was considered, and "how" to test the model was as important as "who" should test it.

Research Design and Methodology

For the pilot phase, it was proposed that potential respondents would not only need substantive biotechnology

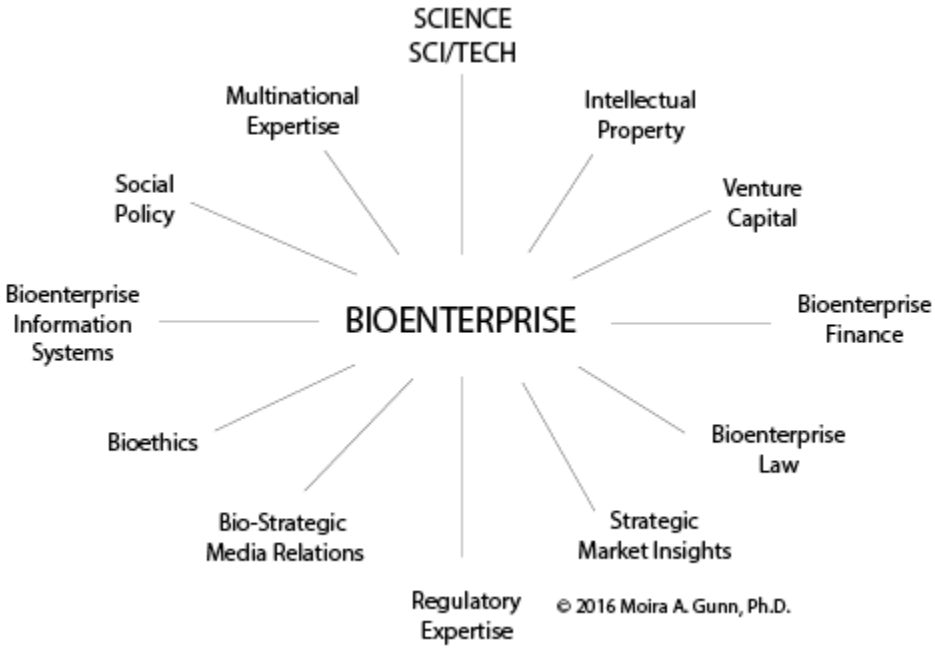


Figure 1. BIEM 2.0 (Bioenterprise Innovation Expertise Model) – Essential Capabilities

industry experience, but also would need expertise at the overall enterprise level throughout the science-to-product innovation phase. The target initial candidates could be venture capitalists, whose involvement with bioenterprise starts early and can continue through to enterprise maturity. Even so, if it were possible to collect data from venture capitalists at all, this would likely produce a small sample size.

Large samples have frequently been used to test models in the field of entrepreneurship and business climate perceptions,[16–18] but the need for a large sample size can change if experts are consulted. For example, Kaufman et al. showed that experts' ratings were more consistent than non-experts' ratings in consensual assessment technique in creativity, and Holthausen et al. showed the predictive reliability of expert opinion.[19–20] A smaller sample has other advantages, such as reachability of respondents even among very busy people, such as biotechnology venture capitalists. Still, a smaller sample size makes it difficult to use certain statistical analyses providing clues to convergent validity and discriminant validity. For instance, MacCallum and Widaman and Hair et al. recommend minimum sample sizes such as 250 respondents to perform factor analysis which can be used to observe convergent validity.[21–22] Even de Winter et al. propose certain restrictions on sample sizes smaller than 50 for performing a factor analysis such as levels of loadings, number of factors and number of variables.[23] Consequently, it was decided to simply observe the data and calculate whatever statistics were possible.

The BIEM model at that time was intended to be descriptive of both biopharmaceuticals and biomedical devices. These are two different entrepreneurial endeavors, requiring different skill sets and perspectives. Thus, it was decided that two different pilot surveys would be developed, one for biopharmaceuticals and one for biomedical devices. Respondents could participate in each should they have both experiences.

The Survey Instrument

With respect to the twelve (12) expertise areas: science or sci/tech, intellectual property, venture capital, bioenterprise finance, bioenterprise law, strategic market insights, regulatory expertise, bio-strategic media relations, bioethics, bioenterprise information systems, social policy and multinational expertise, thirteen(13) questions were created, with "Sci/Tech" divided into two questions for science and technology separately. Since the respondents were not given detailed explanations for these expertise areas, some were simply explained in place. For example, "Intellectual Property" became "Intellectual Property (securing initial patents)", and "Regulatory Expertise" became "Regulatory Expertise (Clinical Trials, FDA Applications, et al.)".

The questions were posed on a 9-point Likert scale, with three descriptors placed along the continuum: two at each extreme, and one at the mid-point. The descriptors enabled rating of an innovation expertise from

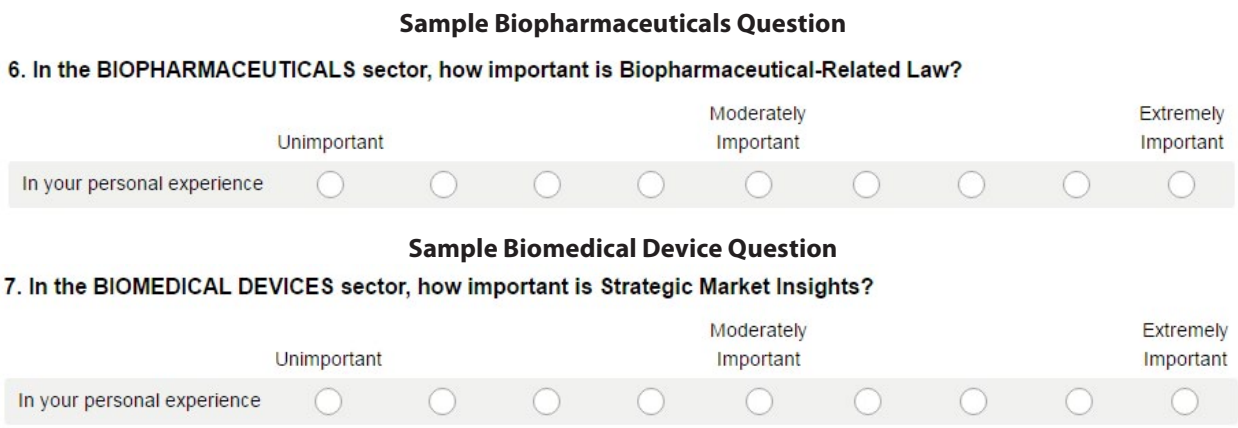


Figure 2. Sample BIEM Model Verification Study Questions

"unimportant" to "moderately important" to "extremely important". While a 5-point Likert scale is statistically sufficient to measure differences in a subject population,[24] this requires pre-knowledge of the likely range of answers. Since this was an initial test of the BIEM model, a 9-point Likert scale was chosen to give an expanded response range to the survey takers.

Sample questions are displayed in Figure 2.

At the end of all BIEM innovation expertise questions, the survey taker is encouraged to suggest missing innovation expertise of their own, via the question: "If any, list other essential expertise areas that you would include in the Science-to-Registered-Product Life Cycle?"

As the education and experience of the respondents could affect their answers, other questions were also included in the survey. For example, educational background, number of years in the biotechnology industry, and history of bioenterprise positions was asked. Since longtime industry experience can lead to the development of professional expertise not apparent in educational degrees or positions held, the respondents were asked for their assessment of their own expertise in the BIEM model, and to qualify whether they considered it a primary or secondary expertise. The primary/secondary expertise question in the biopharmaceuticals survey is depicted in Figure 3.

Subject Population

For the pilot phase, as mentioned earlier, potential respondents were sought that not only possessed biotechnology industry experience, but also had expertise at the overall bioenterprise throughout the science-to-product innovation phase. The target initial candidates were venture capitalists.

RESULTS AND OBSERVATIONS

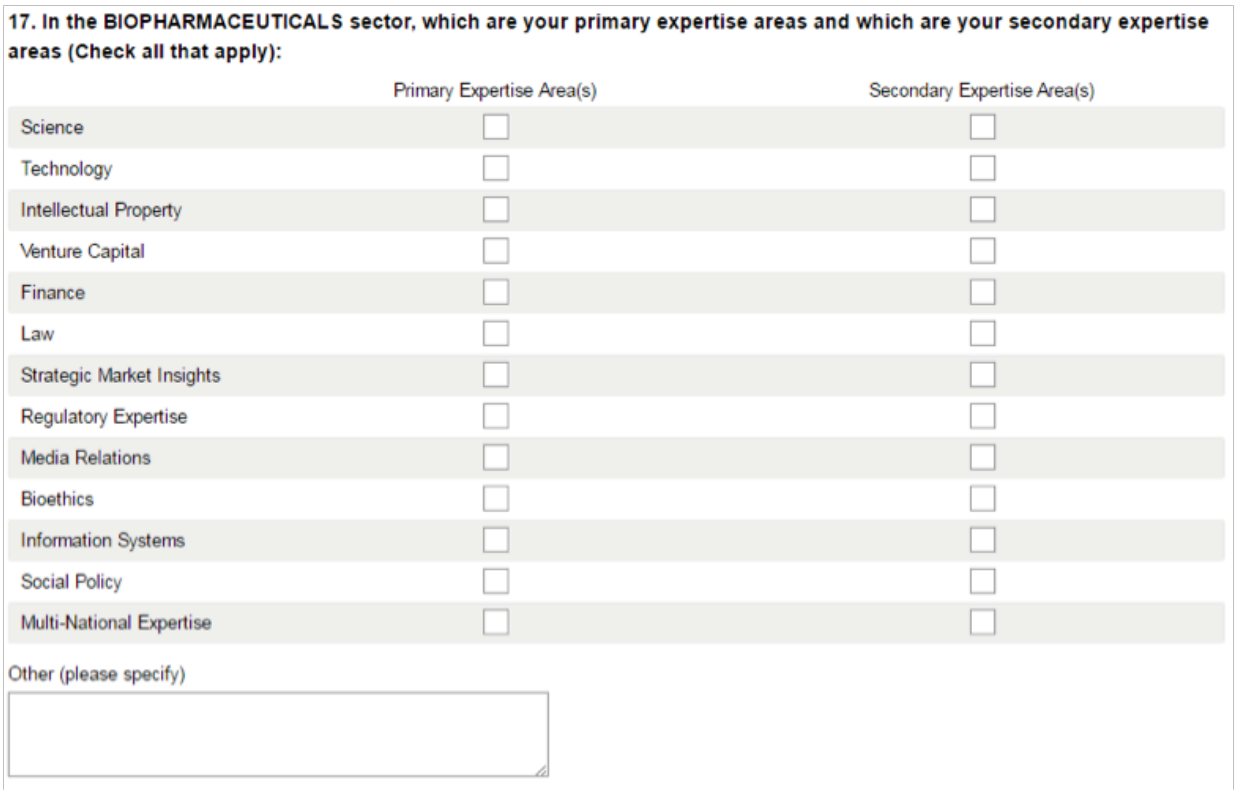
As with any pilot study, there is much to determine from first responders, including the appropriateness of questions, the time involved to take the survey (5 minutes had been the target), the desire to collect other aspects of data, the decision to stop collecting certain data, etc. In this initial pilot phase, some 34 venture capitalists, primarily from the San Francisco Bay Area, were successfully recruited. Of these, 22 responded to the biopharmaceuticals survey, and 12 venture capitalists responded to the biomedical device survey. Given these initial response levels, it was decided that a more in-depth study of exclusively biomedical device aspects of the BIEM model would be performed at a later date, and an assessment of the biopharmaceuticals aspects of the BIEM model would be the focus.

As the BIEM model is based on expertise necessary to the bioenterprise, survey takers should have sufficient industry experience to recognize each expertise in practice, and the lack thereof. Given the ten-to-fifteen year span from scientific discovery to actual product, we reduced responses to those whose biotechnology careers spanned at least one full cycle through the entire science-to-product innovation phase.

The final sample of respondents reported on in this paper reflects 20 biopharmaceuticals venture capitalists with 20 years minimum biotechnology industry experience.

Biopharmaceuticals Respondent Profile – Pilot Phase

Having qualified with 20 years minimum experience in the biotechnology industry, the 20 venture capitalists in fact had a biotechnology career average of 30 years,


17. In the BIOPHARMACEUTICALS sector, which are your primary expertise areas and which are your secondary expertise areas (Check all that apply):

	Primary Expertise Area(s)	Secondary Expertise Area(s)
Science	☐	☐
Technology	☐	☐
Intellectual Property	☐	☐
Venture Capital	☐	☐
Finance	☐	☐
Law	☐	☐
Strategic Market Insights	☐	☐
Regulatory Expertise	☐	☐
Media Relations	☐	☐
Bioethics	☐	☐
Information Systems	☐	☐
Social Policy	☐	☐
Multi-National Expertise	☐	☐

Other (please specify)

Figure 3. Biopharmaceutical Expertise BIEM Model Self-Assessment Question

all had served on numerous corporate boards, 90% had been board chairs, and 80% had also been CEO's and/or presidents in the biopharmaceutical sector. All were still active venture capitalists. This is proposed to be a small expert sample, as described by Kaufman, et al. and Holthausen, et al.[19–20]

Assessment of the BIEM Model Innovation Expertise Capabilities

The experienced biopharmaceuticals venture capitalists had a very cohesive response to the importance of the innovation expertise capabilities identified by the BIEM model. The data shows an inter-rater reliability of .950 for average measures (F = 19.9; p< .001) pointing to a high level of agreement among VCs when evaluating the 13 items listed. This demonstrates that the venture capitalists are 95% in agreement.

In terms of the importance of each innovation expertise, the disciplines considered "extremely important" were intellectual property, science, regulatory expertise, and venture capital, in that order. The least important, although still regarded as "moderately important", were multinational expertise, social policy and media relations, this last being the lowest ranked. No expertise was eliminated, and while some minor rewording is anticipated, no new innovation expertise emerged.

The assessment of innovation expertise elements as "moderately important" to "extremely important", without the addition of new innovation expertise disciplines, is proposed as validating the model. The average responses of the experienced biopharmaceuticals venture capitalists can be found in Figure 4.

The Interrelation of the BIEM Model Innovation Expertise Capabilities

Table 1 contains the correlations among the various innovation expertise disciplines, while Table 2 identifies the highest and lowest correlation for each innovation expertise.

Three pairs of innovation expertise disciplines most strongly correlate with each:

- Regulatory expertise and science were most strongly correlated with each other
- Intellectual property and venture capital were most strongly correlated with each other.
- Technology and Information Systems were most strongly correlated with each other.

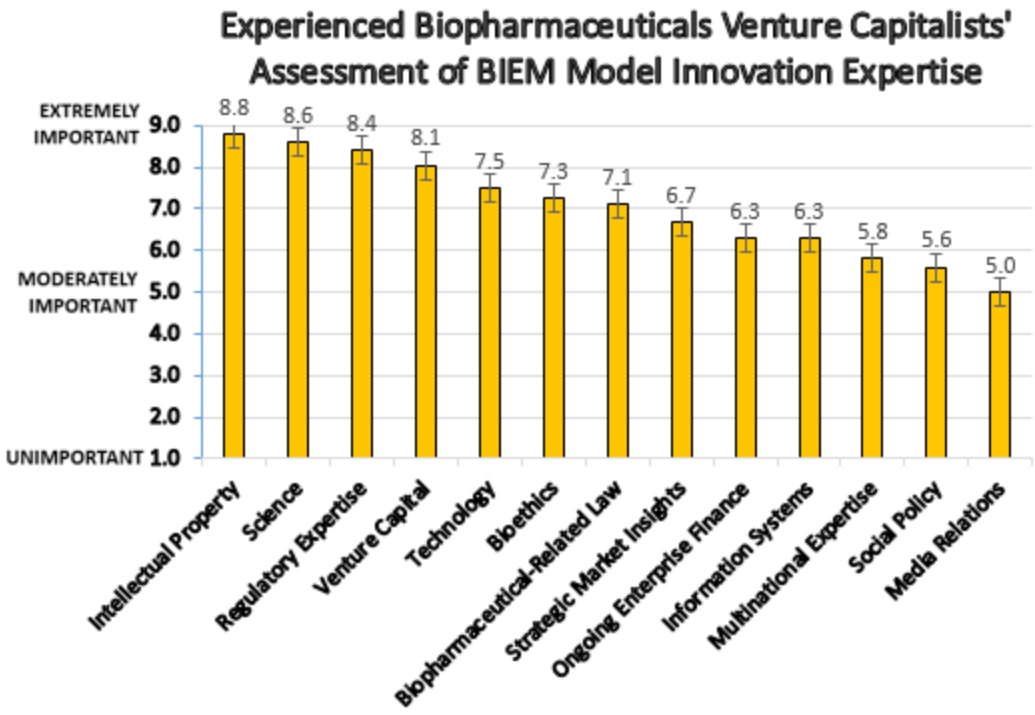


Figure 4. Experienced Biopharmaceutical Venture Capitalists' Assessment of BIEM Model Innovation Expertise

Since the expertise identified in the first two pairs, intellectual property, science, regulatory expertise, and venture capital, are the highest ranked disciplines, this is an important finding, especially given that in their interrelation, there is little to no crossover. Regulatory expertise and science have modest to no correlation with either intellectual property or venture capital.

While technology and information systems were also most strongly correlated with each other, they are in the high-moderate to low-extreme range, and are perhaps interrelated due to their shared technical nature.

Other insights are that biopharmaceutical-related law and strategic market insights had their highest correlation with information systems. In addition, there is virtually no correlation between intellectual property and bioethics, while the lowest correlation for technology is also bioethics, and the highest correlation for bioethics is regulatory expertise, suggesting that ethics is believed to be crucial to the regulatory process.

Comparison to Outcomes from Earlier Studies

Comparing the BIEM Verification Study outcomes with the Schueler and Ostler findings, there appears to be both agreement and some elements of discordance.[11] In the survey of 18 European venture capitalists whom they surveyed, 75% of the European venture capitalists considered regulatory intelligence important, while the BIEM model venture capitalists rated "regulatory expertise" at 8.4 out of 9 points, being "extremely important", although they ranked regulatory expertise in third place below intellectual property and science.

Over half of the Schueler and Ostler respondents *linked regulatory with intellectual property*; however, this was not the case for the BIEM study respondents.[11] In the BIEM results, the *least correlation* for regulatory expertise *was intellectual property.* (See Tables 1 and 2.)

The Schueler and Ostler survey results did present some evidence that the relationship between science and regulatory was present in their survey data, publishing one respondent's input that "Regulatory strategy is mainly influenced by science" and the accompanying recommendation to "hire a regulatory scientist".[11] In the BIEM study, however, this link was found to be of the highest significance, in that regulatory expertise and science were *most strongly correlated with each other.*

It is not possible to compare survey designs or results with the information available, but the elements of agreement and discordance are at least superficially evident, and potentially deserve further consideration.

Table 1. Correlations among BIEM Innovation Expertise Disciplines As Assessed by Biopharmaceutical Venture Capitalists**

INNOVATION EXPERTISE	IP	Science	Regulatory	Venture Capital	Tech	Bioethics	Law	Market Insights	Ongoing Finance	Info Systems	Multi national	Social Policy	Media Relations	
Intellectual Property	1	0.207	0.064	0.524	0.109	0.000	0.193	0.240	-0.118	0.170	0.171	-0.105	0.122	Intellectual Property
Science	0.207	1	0.674	0.341	0.209	0.355	0.111	0.126	0.175	0.384	0.387	0.292	0.047	Science
Regulatory Expertise	0.064	0.674	1	0.146	0.254	0.578	0.322	0.365	0.460	0.609	0.315	0.335	0.237	Regulatory Expertise
Venture Capital	0.524	0.341	0.146	1	0.451	0.234	0.375	0.308	0.280	0.437	0.314	0.426	0.350	Venture Capital
Technology	-0.109	0.209	0.254	0.451	1	0.025	0.352	0.348	0.718	0.773	0.222	0.498	0.203	Technology
Bioethics	0.000	0.355	0.578	0.234	0.025	1	0.422	0.408	0.209	0.359	0.161	0.452	0.365	Bioethics
Bio-Related Law	0.193	0.111	0.322	0.375	0.352	0.422	1	0.623	0.236	0.674	0.277	0.460	0.432	Bio-Related Law
Strategic Market Insights	0.240	0.126	0.365	0.308	0.348	0.408	0.623	1	0.177	0.694	0.084	0.099	0.399	Strategic Market Insights
Ongoing Enterprise Finance	0.118	0.175	0.460	0.280	0.718	0.209	0.236	0.177	1	0.596	0.483	0.537	0.360	Ongoing Enterprise Finance
Information Systems	0.170	0.384	0.609	0.437	0.773	0.359	0.674	0.694	0.596	1	0.387	0.568	0.420	Information Systems
Multinational Expertise	0.171	0.387	0.315	0.314	0.222	0.161	0.277	0.084	0.483	0.387	1	0.682	0.457	Multinational Expertise
Social Policy	0.105	0.292	0.335	0.426	0.498	0.452	0.460	0.099	0.537	0.568	0.682	1	0.559	Social Policy
Media Relations	0.122	0.047	0.237	0.350	0.203	0.365	0.432	0.399	0.360	0.420	0.457	0.559	1	Media Relations

*** For a correlation coefficient (Pearson r) to be of a magnitude to allow rejection of H0 r=0 and a sample size of 20, the value of r needs to be .444 or greater. For a table of these probabilities for Table 1, contact the authors.*

Table 2. Highest and Lowest Correlations among BIEM Innovation Expertise Disciplines As Assessed by Biopharmaceutical Venture Capitalists

INNOVATION EXPERTISE	IP	Science	Regulatory	Venture Capital	Tech	Bioethics	Law	Market Insights	Ongoing Finance	Info Systems	Multi national	Social Policy	Media Relations	
Intellectual Property	1	0.207	0.064	0.524	0.109	0.000	0.193	0.240	0.118	0.170	0.171	0.105	0.122	Intellectual Property
Science	0.207	1	0.674	0.341	0.209	0.355	0.111	0.126	0.175	0.384	0.387	0.292	0.047	Science
Regulatory Expertise	0.064	0.674	1	0.146	0.254	0.578	0.322	0.365	0.460	0.609	0.315	0.335	0.237	Regulatory Expertise
Venture Capital	0.524	0.341	0.146	1	0.451	0.234	0.375	0.308	0.280	0.437	0.314	0.426	0.350	Venture Capital
Technology	0.109	0.209	0.254	0.451	1	0.025	0.352	0.348	0.718	0.773	0.222	0.498	0.203	Technology
Bioethics	0.000	0.355	0.578	0.234	0.025	1	0.422	0.408	0.209	0.359	0.161	0.452	0.365	Bioethics
Bio-Related Law	0.193	0.111	0.322	0.375	0.352	0.422	1	0.623	0.236	0.674	0.277	0.460	0.432	Bio-Related Law
Strategic Market Insights	0.240	0.126	0.365	0.308	0.348	0.408	0.623	1	0.177	0.694	0.084	0.099	0.399	Strategic Market Insights
Ongoing Enterprise Finance	0.118	0.175	0.460	0.280	0.718	0.209	0.236	0.177	1	0.596	0.483	0.537	0.360	Ongoing Enterprise Finance
Information Systems	0.170	0.384	0.609	0.437	0.773	0.359	0.674	0.694	0.596	1	0.387	0.568	0.420	Information Systems
Multinational Expertise	0.171	0.387	0.315	0.314	0.222	0.161	0.277	0.084	0.483	0.387	1	0.682	0.457	Multinational Expertise
Social Policy	0.105	0.292	0.335	0.426	0.498	0.452	0.460	0.099	0.537	0.568	0.682	1	0.559	Social Policy
Media Relations	0.122	0.047	0.237	0.350	0.203	0.365	0.432	0.399	0.360	0.420	0.457	0.559	1	Media Relations
					Highest Correlation			Lowest Correlation						

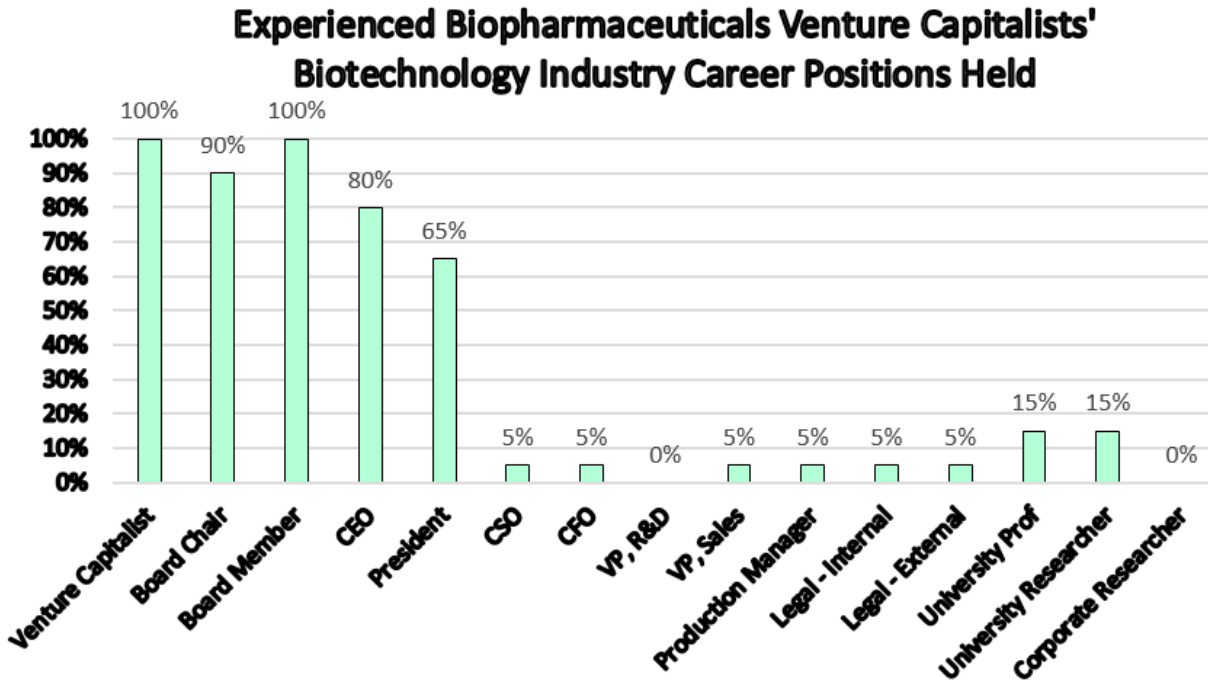


Figure 5. Experienced Biopharmaceuticals Venture Capitalists' Biotechnology Industry Career Positions Held

Secondary Findings from Venture Capitalists' Career Profiles

Some insight may be possible from the positions held by the biopharmaceuticals venture capitalists over their careers. While 100% had obviously been venture capitalists, all had served on boards, and 90% had served as board chairs. In terms of actually running biotechnology companies, 80% had been CEOs while 65% had been presidents, and the data revealed that while not all CEOs had been presidents, all presidents had been CEOs. University professors and researchers were also represented (15% each), with several solely being just one or the other. Other career positions were minimal or nonexistent, while there was a single Chief Scientific Officer and a single Vice President for Research and Development.

The career position profiles of the biopharmaceuticals venture capitalists can be found in Figure 5.

Secondary Findings from Venture Capitalists' Education Profile

The formal educations of the BIEM venture capitalists presumably occurred many years ago, yet it remains informative. Despite having made investments in biopharmaceuticals for many years, only 30% had an undergraduate degree in the life sciences, with 25% having performed graduate work in the life sciences. 40% had an undergraduate in engineering, mathematics or non-life science, while 20% had undergraduate degrees in economics. The remainder had liberal arts degrees.

With respect to advanced degrees, 20% had PhD's in the life sciences, 15% had other PhD's, 15% did graduate work in engineering, one venture capitalist held a JD, and one venture capitalist was an MD. The most common graduate degree was an MBA; 60% of the venture capitalists held an MBA.

Secondary Findings from Venture Capitalists' Self Assessed Innovation Expertise

Over a long and engaged career in an ever-changing and challenging landscape, significant professional expertise is developed over time, and it is not necessarily represented completely by degrees earned. Recognizing that expertise grows over 30-year careers, the venture capitalists were asked which innovation expertise disciplines in the BIEM model reflected a primary expertise they felt they personally possessed, and which reflected a secondary expertise for them, if at all. Venture capital was

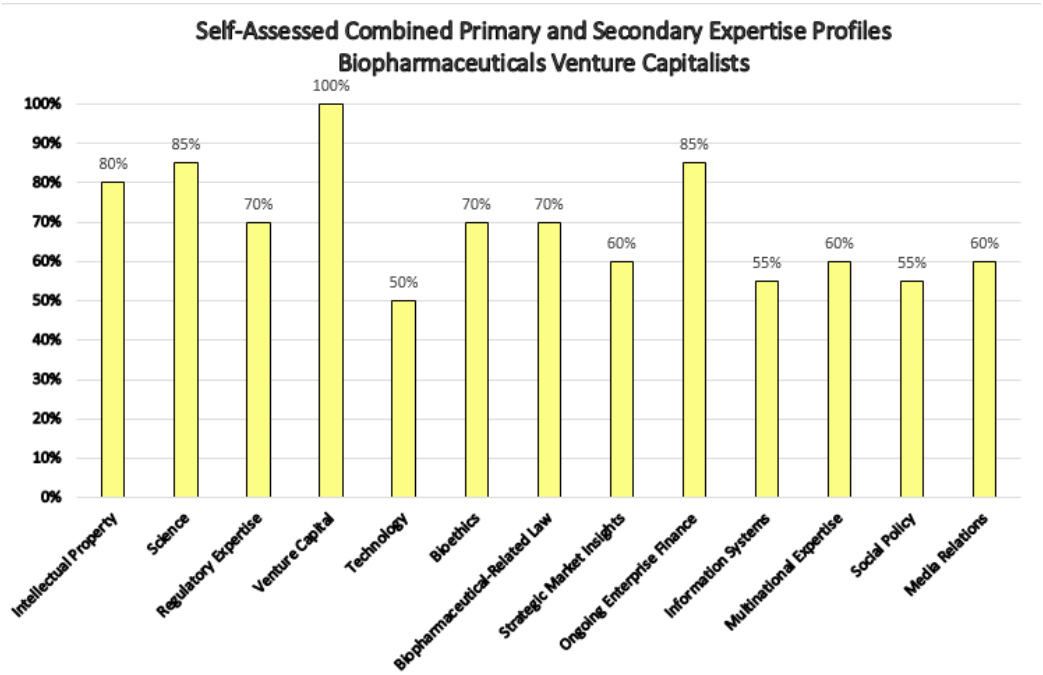


Figure 6. Combined Self-Assessed Primary and Secondary Expertise Profiles of Biopharmaceuticals Venture Capitalists

identified as a primary expertise for every respondent. While intellectual property was the listed as the most important expertise needed, only one venture capitalist (the sole attorney) listed intellectual property as a primary expertise, 75% listed intellectual property on their secondary expertise list, and 20% did not list it as a personal expertise whatsoever.

Figure 6 depicts the self-assessed combined innovation expertise disciplines reported. In this graphic, as there was no directions as to how to distinguish between a primary and secondary expertise, if either box was checked, the respondent was assigned the expertise. The combined expertise assessments are ordered by the importance assigned in their rank assessment of the BIEM innovation expertise disciplines. While ongoing enterprise finance was only considered moderately important in the BIEM assessment, and ranked in 9th place, the board control these venture capitalists exert would be enough to ensure that financial operations are in order. Financial operations are undeniably a vital organ in any business enterprise.

CONCLUSION

The efforts to verify the BIEM 2.0 model resulted, not only in verifying the bioenterprise innovation expertise model, but its subject population, with its small, but expert, sample size, produced statistically significant insights into the importance of various expertise in the science-to-product innovation phase, as well as their interrelationships.

In order, the most innovation expertise disciplines are intellectual property, science, regulatory expertise, and venture capital. The link between regulatory expertise and science is of the highest significance, equally so between intellectual property and venture capital. These are important findings for bioenterprise and its bioentrepreneurs.

The additional insights with respect to the experienced biopharmaceutical venture capitalists are of interest to any number of participants in the biotechnology industry, including those that seek venture capital, and those desiring to become venture capitalists.

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For their willingness to participate in the study, the authors would like to thank all the venture capitalists that participated.

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Legal & Regulatory Update

Recent Developments in Compulsory Licensing of Pharmaceutical Patents in India

Viren Konde
is Biotechnology Analyst and Healthcare Consultant, iHealthcareAnalyst, Inc.

ABSTRACT

On March 9, 2012, under Section 84(1) of the Indian Patents Act, the Controller General of Patents granted the country's first and only compulsory licence to Natco Pharma to sell Bayer AG's patented oncology drug Nexavar (Sorafenib Tosylate). Since then, India has not issued any other compulsory licence even though two more such applications have been received. India has also implemented a special compulsory licence regime under Section 92A(1), for the manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity to address public health needs. In view of the recent developments, and given the economic consequences of compulsory licensing, it has become important for multinational pharmaceutical companies procuring patents and doing business in India to understand the country's compulsory licensing laws and reevaluate their business strategies, while domestic companies pursue alternate options to access patented lifesaving medicines within the legal system.

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Keywords: TRIPS, compulsory licence, pharmaceuticals, Indian Patents Act

INTRODUCTION

In January 1995, when the WTO came into existence, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement introduced minimum standards for protecting and enforcing intellectual property rights based on the existing multilateral treaties administered by the WIPO, including new monitoring and dispute settlement provisions. At the same time, TRIPS (Article 30 and 31) also provided a reasonable fetter on the rights of the patentee, thereby allowing member countries to enact provisions, *inter alia*, for granting compulsory licence (CL) to prevent the abuse of patent right.[1,2] Provision for granting compulsory licence exists in the patent laws of developed (Canada, France, UK, USA, Italy, Germany and Australia) as well as developing (Zimbabwe, Ghana, Brazil, Ecuador, Malaysia, Thailand, Mozambique, Zambia, and India) countries.[3]

A compulsory licence is a statutorily created licence that allows certain parties to use or manufacture a product encompassed by the claims of a patent without the permission of the patent owner (patentee) in exchange for a specified royalty. Compulsory licensing is enabled under four sections of the Indian Patents Act. These are Section 84 (general CLs to be issued by the Controller on application), Section 91(issue of CL by the Controller for a related patent on application), Section 92 (issue of CL by the Controller based upon a notification by the Central Government of circumstances of national emergency or in circumstances of extreme urgency or in case of public non-commercial use) and Section 92A (issue of CL by the Controller on application for manufacture and export of patented pharmaceutical product to any country having insufficient or no manufacturing capacity in the pharmaceutical sector for the product to address public health problems).[4,5]

The Indian Patents Act, 1970 and its Amendment, 2005 contains two very broad compulsory licensing provisions under Sections 84[6] and 92[7].

SECTION 84(1)

Under Section 84(1), the Controller of Patents can issue a compulsory licence three years after the issuance of a patent on any of the following grounds:

Correspondence:
Viren Konde, Biotechnology Analyst and Healthcare Consultant, India.. Email: virenkonde@gmail.com

a. The reasonable requirements of the public with respect to the patented invention have not been satisfied, or
b. The patented invention is not available to the public at a reasonably affordable price, or
c. The patented invention is not worked in the territory of India.

Bayer AG v Natco Pharma Ltd.

The Controller General of Patents Designs and Trademarks of India granted country's first and only compulsory licence to Natco Pharma Ltd., an Indian generic drug manufacturer to sell Bayer's patented chemotherapy drug Nexavar (Sorafenib Tosylate, i.e. Carboxy Diphenyl Substituted Ureas) that extends the patient's life by half a year but does not cure the underlying condition. The compulsory licence was issued under Section 84 of the Indian Patents Act on the grounds that the drug was not meeting the reasonable requirements of the public; the drug was not available to the public at a reasonable price and the drug was not being sufficiently "worked" in India as required by the law.

On March 3, 2008, Bayer's patent IN215758 was granted in India and Bayer received regulatory approval for importing and marketing the drug in India. The Indian Patent Office (IPO) found that despite the huge demand, Bayer did not import the drug in 2008 and only a small quantity was imported in 2009 and 2010 and the drug was available to a small percentage of eligible patients (about 2 percent), which did not meet the requirements of the public. Secondly, Bayer cited the cost of drug at a huge price of Rs 280,000 per month (approximately US$ 5,600), which was not "reasonably affordable" to the general cancer patient in India. On the other hand, Natco proposed to sell the drug within India at a price of not more than Rs 8,800 (approximately US$ 176) for a pack of 120 tablets required for one month's treatment and also committed to donate free supplies of the medicines to 600 needy patients every year. Finally, Bayer's patent was not being "worked" in India as Nexavar was not being manufactured in India. Importation from manufacturing facilities outside India did not satisfy the mandatory requirement of working the patent in India. Bayer also refused the request from Natco for a voluntary licence to marketing the drug only in the territory of India. The compulsory licence was issued with 7% royalty to be paid to Bayer.[8]

Bristol Myers Squibs Company v BDR Pharmaceuticals International Pvt. Ltd.

On October 30, 2013, the Controller of Patents of India rejected BDR Pharmaceutical's (BDR) compulsory licence application to sell a generic version of Bristol Myers Squibs's (BMS) blood cancer drug, Sprycel (Dasatinib) for Chronic Myeloid Leukemia (CML) on procedural grounds that sufficient efforts had not been made by BDR to seek a voluntary licence from BMS. The order states that BDR proposed to make the drug available at Rs 8,100 per month per patient (approximately US$ 162), whereas BMS sold the drug at Rs 1,65,680 per month per patient (approximately US$ 3314).[9]

Under Section 84(6)(iv) of Indian Patents Act, any applicant before applying for a compulsory licence must first attempt to procure a voluntary licence from the patentee on reasonable terms and conditions and if such efforts have not been successful within a "reasonable period" not ordinarily exceeding six months, the applicant is free to file a compulsory licence application. In this case, BDR initially requested for a voluntary licence to BMS for manufacturing Dasatinib. In response, BMS raised a series of questions challenging BDR's basic regulatory standards and Good Manufacturing Practices requirements, quality assurance due diligence, commercial supply teams, safety and environmental profile, and risk of local corruption. BDR considered this reply as 'clearly indication of rejection of the application for voluntary licence' and did not make any efforts to retaliate in its defense and exercised the option of filing of compulsory licence. Therefore, the IPO rejected BDR's application on the grounds of lack of *prima facie* case considering insufficient efforts to obtain a voluntary licence for the drug.

AstraZeneca AB v Lee Pharma Ltd.

On August 18, 2015, the Controller of Patents Office in India rejected the Lee Pharma's compulsory licence application for AstraZeneca's Saxagliptin, sold under the brand name Onglyza and Kombiglyze, and prescribed for Type-II Diabetes Mellitus on all the three grounds of Section 84(1): (a) that the substitutes to the drug are readily available in the market; (b) the claim that requirements of public with respect to the patented invention are not being satisfied has not been proven; and (c) the applicant has failed to *prima facie* demonstrate that the patented invention is not worked in the territory of India.[10]

Lee Pharma has stated in its application that (a) there are around 60 million diabetes type II patients in India,

and that 'even if' only 1 million were to be prescribed Saxagliptin, there is more than 99% shortage of the drug in Indian market; (b) the cost for importing one tablet in India is only Rs 0.80 per tablet and the same is being sold by AstraZeneca at market price of Rs 41-45 per tablet (approximately US$ 24-27 per month per patient), whereas the applicant's proposed selling price at Rs 30 per tablet (approximately US$ 18 per month per patient); and (c) the drug is not manufactured in India even after 8 years of grant of the Indian patent by BMS, rather is being imported to India by BMS or AstraZeneca and marketed by AstraZeneca.

However, there were several possible points of contention to Lee Pharma's claims as it seemed to be predicated on a number of factors: First, Saxagliptin is one of at least four (Sitagliptin, Vildagliptin and Linagliptin being the others) available Dipeptidyl Peptidase-4 (DPP-4) inhibitors used to treat Type II Diabetes which are also available in India. Second, the applicant's cost and availability claims were obscured given that patients can already obtain an Indian-manufactured generic version of a similar drug for slightly less than the applicant's proposed selling price, and third, the Controller of Patents stated that to manufacture in India is not a necessary precondition in all cases to establish working in India.

SECTION 92

Under Section 92 of the Indian Patents Act, compulsory licences can be granted on notification by Central Government:

1. In a case of a national emergency (including a public health crisis), extreme urgency or in the event of public non-commercial use; (Section 92(1)); or
2. For export (Section 92A(1)).

In January 2013, Department of Industrial Policy and Promotion (DIPP) under Ministry of Health & Family Welfare set up a Committee for invoking CL provisions on three commonly used anti-cancer drugs in India: Trastuzumab (or Herceptin, used for breast cancer), Lxempra (or Lxabepilone, used for chemotherapy) and Sprycel (or Dasatinib, used for leukemia) under Compulsory Licensing provisions of Section 92(1) of the Patents Act, 1970.

Herceptin, owned by Genentech, (a subsidiary of Roche) was originally priced at Rs 1,10,000 per dose and a breast cancer patient ordinarily requires between 18-20 doses per year that ranges between Rs 22,00,000 to Rs 25,00,000 (approximately US$ 44,000 to US$ 50,000). The price was subsequently reduced marginally to Rs 75,000 per dose i.e. Rs 15,00,000 per year (approximately US$ 30,000), when civil society groups had petitioned the government to adopt policies to reduce the price of drug. Similarly, the patents for the remaining two drugs, Lxempra and Sprycel, both owned by Bristol Myers Squibbs (BMS) has cited the costs at Rs 80,000 and Rs 15,000 per dose (approximately US$ 1,600 and US$ 300), respectively.

SECTION 92A(1)

Section 92A(1)[11] of the Indian law states that a compulsory licence shall be available for manufacture and export of patented pharmaceutical products to any country having insufficient or no manufacturing capacity in the pharmaceutical sector that need them to address public health problems on the condition that the importing country should have issued a compulsory licence or, by notification or otherwise, allowed the importation of these products from India. Whereas, Section 92A(2) states that the compulsory licence is to be granted solely for manufacture and export of the concerned pharmaceutical product, as per the terms and conditions specified by the Controller of Patents, and which must be published. However, no special rules have been put into place to implement Section 92A and this may be viewed as ensuring transparency and appropriate safeguards against implementing the flexibilities under TRIPS.

PRE-EMPTING STRATEGIES TO COMPULSORY LICENSING

Exclusive Voluntary Product Licensing Deals

Multinational companies (MNCs) may sign exclusive voluntary product licence deals with domestic firms. Unlike under compulsory licensing, the MNCs may have the freedom to set the terms at which domestic firms may sell generic versions of their drugs, and this would not only help drug makers to expand the market but also avoid compulsory licensing action. Some of the examples of such deals include: (a) between India's Strides Arcolab Ltd. and the United States-based Gilead Sciences Inc. for a group of HIV/AIDS drugs; (b) Pune-based Emcure Pharmaceuticals Ltd. and Swiss drug manufacturer F. Hoffman La Roche Ltd. for patented cancer drugs; (c) United States-based Merck and India's MSD Pharmaceuticals Pvt. Ltd. and Sun Pharmaceuticals Industries Ltd for patented diabetes drugs; and(d) Swiss drug manufacturer Novartis and Mumbai-based Lupin for a chronic obstructive pulmonary disease drug.[12]

Tiered Drug Pricing Structure in Separate Markets

Pre-empting the move to issue compulsory licences, MNCs may follow a differential pricing system for a drug in developed and developing countries. With assured market separation, the MNCs may offer prices comparable to the prices that a local generic firms would charge, which eliminates the need for compulsory licensing. Therefore, the multinationals will have to explore ways and means of engaging with the government, public bodies and civil society at large to ensure that reasonable profit is not perceived as profiteering.[13] The foreign drug makers may offer these medicines at different tiers of prices for government supply, patient access programmes, hospitals in rural areas and non-profit organizations.

For example, the European Commission Council Regulation (EU, 2002, 2003) intended to create a voluntary global tiered pricing system for key pharmaceuticals for the prevention, diagnosis and treatment of HIV/AIDS, TB and malaria and related diseases for developed countries, developing countries and least developed countries and to prevent product diversion to other markets by ensuring effective safeguards.[14]

CONCLUSION

For many years, pharmaceutical patents and their impact on prices have been a major international debate over insufficient access to lifesaving patented medicines in developing countries. The source of conflict has largely revolved around the implementation of an intellectual property system in the developing world, and the TRIPS mandated international patent laws.

In India, the grant of compulsory licences has been riddled with technical and legal roadblocks. The Natco-Bayer ruling led to extensive debate within the international and domestic pharmaceutical industry and met with a great deal of disapproval from the multinational enterprises regarding the compatibility of the decision with TRIPS. However, India maintained that it had not violated any multilateral trade agreement by granting the compulsory licence and was well within the requirements of international and national legislation, as the Doha Declaration clearly states that member countries are free to determine the grounds on which such licences can be granted. Affordability and availability of life saving patented medicines is a key issue in India considering high disease burden, poor coverage of public insurance and poor per capita income. Therefore, it is believed that, the resultant competition from compulsory licences in the pharmaceutical industry in India would help discipline the market and regulate the prices.

Although, no more compulsory licences have been granted so far, the Indian government has decided to grant innovator drug companies a hearing, whenever an Indian company petitions for the government to grant a compulsory licence on a patented drug. Now, probably, it is time for the multinational companies to change their policies, and adopt to differential pricing and business environment in India, while the Indian companies need to evaluate alternate options for improving and facilitating affordable access to life saving patented medicines within the Indian legal system.

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Post-Grant Review of U.S. Patents: A Primer

Stefan Michael Miller
is a partner at the New York office of Kirkland & Ellis LLP, and a member of the firm's Intellectual Property group. Dr. Miller formerly prosecuted patent applications before the United States Patent & Trademark Office and is now a litigator handling chemical, pharmaceutical, and biochemical patent cases. Dr. Miller earned his B.S. in Chemistry from the University of Texas at Austin, his Ph.D. in Organic Chemistry from Yale University, and his J.D. from New York University School of Law.

Gregory R. Springsted
is an associate at the New York law firm of Kirkland & Ellis LLP and a litigator in the firm's Intellectual Property group, primarily handling chemical, pharmaceutical, and biochemical patent cases. Mr. Springsted obtained his B.S. in Chemistry from the University of Richmond and his J.D. from New York University School of Law.

ABSTRACT

The validity of an issued U.S. patent may be challenged in a number of forums including the courts and before the United States Patent & Trademark Office. With the enactment of the Leahy-Smith America Invents Act in 2011, a number of important changes to post-grant review of patents have occurred. This article provides an overview of available options.

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The Leahy-Smith America Invents Act (AIA), enacted in 2011, altered post-grant review proceedings at the United States Patent and Trademark Office (PTO), changing the landscape of patent litigation. Under the AIA, potential litigants have an array of new choices when seeking to challenge the validity of patents—all without resorting to litigation in the district courts. The PTO now hosts four types of post-grant proceedings:

1. *inter partes* review (IPR), which replaces *inter partes* reexamination, the long-standing administrative option to challenge patents,
2. post-grant review (PGR),
3. a temporary post-grant review of patents claiming certain covered business methods (CBM), and
4. *ex parte* reexamination, which remains essentially unchanged from before the AIA was enacted.

Correspondence:
Stefan Michael Miller, Partner, Kirkland & Ellis LLP, US.
Email: dichromik@gmail.com

The three new post-grant review proceedings provide distinct fora for challenging patents with different standards of review than in district court and the International Trade Commission (ITC), making a careful decision as to where to file all the more important to potential litigants. The following details key aspects of each forum that can provide decision points for the choice of one forum over another.

POST-GRANT PROCEEDINGS GENERALLY

Post-grant proceedings are proceedings before specialized PTO administrative law judges, known as administrative patent judges (APJ), in the Patent Trials and Appeals Board (PTAB) wherein an adverse party challenges the validity of a patent. As a general rule, post-grant proceedings are less expensive and faster than traditional litigation in the courts, due to a statutorily prescribed timeline for PTAB review. In fact, post-grant proceedings generally conclude within 18 months of filing the petition for review and cost significantly less than district court litigation. But there are some downsides to administrative proceedings. For instance, the whole toolbox of patent invalidity is not always available before

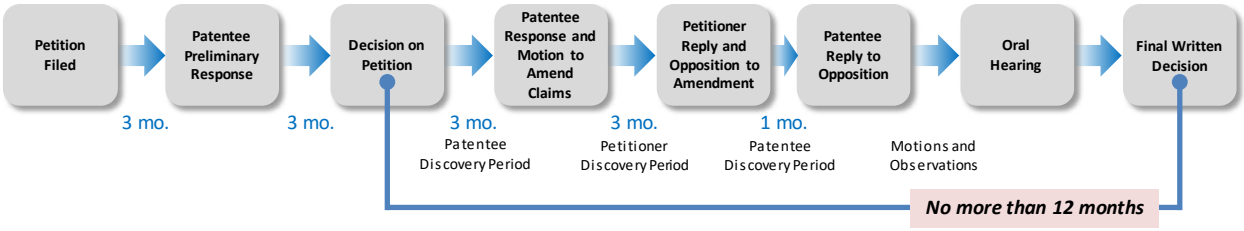

Figure 1: IPR, PGR and CBM Timeline

the PTO; challengers alleging invalidity before the PTO are limited to certain attacks while others are unavailable or available only under certain circumstances.

Each type of post-grant review has slightly different features, and deciding where and how to file means appreciating these differences.

Inter Partes Review

Inter Partes Review (IPR) permits a third party to petition for review of a patent to determine whether it is invalid. The word "inter partes" is Latin for "between the parties," and an IPR is so-called because the challenger remains a party to the proceeding (unlike, for example, *ex parte* proceedings discussed below). An IPR occurs before a panel of three APJ who issue final written decisions appealable to the Federal Circuit.[1]

What type of arguments can a challenger raise? A challenger may argue that a patent is invalid as anticipated (lacks novelty) or rendered obvious (lacks an inventive feature) in light of patents and printed publications as described in the patent statute.[2] Importantly, however, a challenger may not raise arguments directed to written description or enablement—in other words, one cannot argue that the patent disclosure is insufficient to support the claimed invention. A challenger is also prohibited from arguing that a patent is invalid for claiming non-patentable subject matter. This can be a key issue in biotechnology cases because, recently, certain diagnostic assays have been found invalid in the district courts for claiming non-patentable subject matter.[3] In evaluating a petition, an IPR will only be instituted if the challenger can show "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."[4]

There are circumstances in which a party may not petition the PTO for *inter partes* review of a patent. For instance, IPRs may only be filed starting nine months after a patent issues or when any post-grant review proceeding involving the patent is resolved, whichever is later.[5] Moreover, a party is barred from filing an IPR if it has filed a declaratory judgment action asserting invalidity in district court with respect to the patent at issue or if more than a year has passed since the party was served with a complaint asserting infringement of the patent at issue.[6] Notably, a party's counterclaim of invalidity in an infringement suit does not preclude the filing of an IPR—only filing for declaratory judgment of invalidity triggers the bar.[7]

Although challenges are limited in scope and in time, IPRs have significant benefits over traditional litigation. First, an IPR (like PGR and CBM review discussed below) has a statutorily prescribed timeline—from filing to decision, an IPR generally lasts no longer than 18 months, as shown in Figure 1.[8] Once a petition for IPR is filed, the PTAB will decide whether to institute an IPR within six months. Upon institution, the patentee has the opportunity to amend claims amidst a period of limited discovery.[9] At close of discovery, approximately seven months after institution, the patentee and challenger are afforded an oral hearing and receive a final written decision soon after that—by statute, the time period from institution to decision must be no longer than twelve months, with a possible six month extension upon a showing of good cause.[10]

Significantly, IPRs afford the patentee and the challenger the possibility of settlement, unlike previous post-grant proceedings.[11] A potential settlement is an additional tool in the arsenal of the challenger, and an opportunity for the patentee to avoid a determination as to the validity of a weaker patent if it so chooses.

Most importantly, however, post-AIA proceedings before the PTO have a different evidentiary standard for proving invalidity of the patent. In district court, a challenger must prove a patent invalid with clear and convincing evidence. In an IPR, the evidentiary standard is merely a preponderance of the evidence, a more relaxed standard.[12] This lower standard makes it easier to prove a patent invalid, essentially negating a patent's presumption of validity. In fact, this lower standard has resulted in a high percentage of claims being cancelled when challenged before the PTO. According to the most recent data available, a total of 14,332 claims have been challenged in IPRs that have proceeded to a written decision. Of these claims, 6774 were found unpatentable by PTAB, 1608 were cancelled by the patentee, 1330 were found patentable by PTAB, and 4620 remain patentable

because they were not addressed by the written decision.[13] Thus, 58 percent of the claims in patents that proceeded to a written decision were cancelled. Moreover, in approximately 87 percent of final written decisions, at least one claim of the challenged patent was cancelled.[14]

Inter Partes Reexamination

Pre-AIA, the familiar *inter partes* reexamination was the only form of adversarial post-grant review at the PTO, but it has been eliminated by the AIA and replaced by IPR. Like IPR, reexamination was a challenge to the novelty and/or obviousness of a patent brought by a third party. But beyond the substantive basis for challenging the patents, reexaminations differ greatly from IPRs—the procedure is quite different. Reexaminations could be filed at any point during the life of a patent with a showing of a "substantial new question of patentability" as to the challenged claims of the patent, rather than waiting nine months from issuance to challenge under the "reasonable likelihood" standard.[15] Additionally, reexaminations were heard by a panel of three patent examiners, rather than the specialized APJs available for IPRs, and were appealable to the Board of Patent Appeals and Interferences—an administrative body that no longer exists—rather than to the Federal Circuit directly.[16]

Post-Grant Review (PGR)

Post-Grant Review is another new proceeding before the PTO that has a wider range of bases on which to challenge a patent—essentially any invalidity grounds under the patent statute.[17] A tradeoff for this wide range of invalidity arguments is the severely limited timeframe during which a petition for PGR can be asserted. A third party may file for a PGR only during the first nine months after a patent issues.[18] Thus, only quick actors get the benefit of a full range of invalidity arguments before the PTO; after nine months challenges to the written description, enablement, and validity of the subject matter of a patent must take place in another forum.

Quick actors might not necessarily prevail in securing institution of PGR. Unlike the "reasonable likelihood" standard of IPR, a petitioner must show that at least one of the challenged claims is invalid by a preponderance of evidence.[19] Thus, in order to attack a patent with the full range of invalidity arguments, a petitioner must be prepared to show that a claim is more likely invalid than not, a higher standard of review than that of an IPR. This has proven difficult; recent data shows that no PGR trials have been instituted and only two challenges have been made.[20] However, because this process is so new, it is unclear whether it will remain difficult to institute PGR. If instituted, the PGR proceeds on the same timeline as an IPR and is subject to the same rules of discovery and procedure.

Covered Business Method Review

Although companies operating in the life sciences space are unlikely to encounter a significant number of patents that qualify as "covered business method" patents, it is worth noting that the AIA has provided a specialized review process for claims dealing with certain business methods.[21] A party may only file for review of a covered business method patent if it has been accused of infringement by the patent holder; other than that limitation, the procedure of covered business method patent review is similar to that of PGR and IPR.[22]

THE ROLE OF ESTOPPEL

Estoppel is a legal principle that bars a party from raising certain facts or claims in a proceeding or litigation. The AIA affords meaningful estoppel effects to the PTAB's post-grant decisions. When a final written decision is issued in a PGR or IPR, the petitioner may not bring any additional challenges to a patent in any forum if the challenge is based on "any ground that the petitioner raised or reasonably could have raised" before the PTAB.[23] This bar applies to challenges before the PTO, district court, and the ITC.[24] At first glance, this appears to be reasonable—a petitioner should not get two bites at the apple. However, particularly for PGRs, where the full range of invalidity arguments is available, this standard is actually quite burdensome. Because almost any invalidity argument "could be raised" in Post Grant Review, failing to succeed in a challenge to a patent severely limits a party's later options, especially because a party may not appeal any decision until after a final decision has been rendered, as discussed below. Moreover, the PTAB generally does not institute review based on all of the grounds raised in the petition,[25] and recent cases suggest that grounds on which the PTAB does not institute review will not be subject to estoppel; estoppel may arise only on claims and grounds that are addressed in the final written decision.[26]

APPEALS & POST-GRANT PROCEEDINGS

The PTAB's final written decision in a post-grant proceeding is appealable to the Federal Circuit directly, bypassing the district courts. This provides a major advantage over pre-AIA post-grant proceedings, which had to be appealed first to the Board of Patent Appeals and Interferences, a former administrative body at the PTO, before reaching the Federal Circuit. A direct appeal to the Federal Circuit greatly shortens the time to final resolution.

However, unlike in district court litigation, it appears that *only* a final decision is appealable; the AIA does not provide for interlocutory review of PTAB rulings and the Federal Circuit has affirmed this understanding of the AIA in rejecting appeals arising from non-final decisions, such as decisions not to institute proceedings.[27] This is a double-edged sword: waiting for a final decision makes it more difficult to appeal an adverse discovery decision or claim construction, but it guarantees speed as there will be no interruptions to the PTAB's timeline.

In practice, the inability to appeal adverse decisions, such as claim construction, as they are rendered could have enormous impact on the outcome of the case—and the validity of a patent. Where there are no factual disputes, the Federal Circuit reviews claim constructions by the PTAB *de novo* under the broadest reasonable interpretation standard, and where there are factual disputes as to the extrinsic evidence, the Federal Circuit reviews the factual decision for clear error—showing deference to the PTAB.[28] And because the PTAB construes claims according to their broadest reasonable interpretation, the scope of claims may differ from a district court's claim construction; depending on the scope, this may result in a potential advantage to either the challenger or the patentee.[29] In contrast, district courts construe claims according to their "ordinary and customary meaning" from the perspective of one of ordinary skill in the art at the time of the invention.[30] The PTAB's treatment of claim construction may change as the Supreme Court recently granted review of this issue.

Similarly, discovery disputes are not reviewable until the written decision is rendered.[31] Although few cases have yet addressed this, as the new post-grant proceedings at the PTO have not been in effect long enough to develop a significant body of law on the issue, the Federal Circuit's treatment of discovery disputes arising from other agencies suggests that the court will be rather deferential. For instance, the Federal Circuit reviews the discovery disputes of other administrative courts for abuse of discretion.[32] Nothing in the AIA suggests that the PTAB should be treated differently than other agencies. Thus, successful appeal of an adverse discovery decision will likely be difficult to obtain.

EX PARTE REEXAMINATION

One final proceeding before the PTO is *ex parte* reexamination, which remains available post-AIA. Although any party can request *ex parte* reexamination of a patent (including the patentee), upon institution, the process is not adversarial; in fact, a petition for *ex parte* reexamination can even be filed without revealing the filing party. Unlike the other forms of post-grant proceedings, the patentee is the only party that interacts with the examiners. Thus, a party seeking to challenge a patent does not have the benefit of discovery, claim construction, and motions practice as it would in the new post-AIA review proceedings. However, *ex parte* reexamination does not result in a true estoppel if the patent is found not invalid; one could conceivably attempt to invalidate a patent more than once. As a practical matter, though, it is difficult to invalidate a patent on prior art that was vetted during reexamination.

OTHER FORA FOR PATENT LITIGATION

District Courts

The obvious, traditional forum for patent litigation is district court. As discussed above, the PTO proceedings have various differences from litigation. First, district court litigation has no statutory limit on length—and cases can and often do last for years. Further, in district court, a patent has a presumption of validity; invalidity must by proven by the higher "clear and convincing" standard. This affords patentees an advantage at the outset, unlike at the PTAB. Additionally, claim construction takes place under the so-called *Phillips* standard, and claims are construed according to the "ordinary and customary meaning" from the perspective of one of ordinary skill in the art at the time of the invention.[33] This permits a patentee to have claims construed narrowly and with the benefit of expert testimony to explain the proper scope of the claims. Narrow claims, counterintuitively, generally benefit the patentee. If a claim is construed after expert testimony, the expert has an opportunity to opine as to the support for the claims in both the prior art and the patent specification. Thus, the construed claim is tailored to the patent itself, demonstrating to the judge precisely where support for the claim is found.

Another difference between district court and the PTAB is the discovery process. Although the PTAB's post-grant proceedings provide for discovery, the scope of discovery is quite limited, unlike in district court. In an IPR, for instance, discovery is generally limited to production of "any exhibit cited in a paper or testimony" and "relevant information that is inconsistent with a position advanced during the proceeding" and this information must be provided concurrently with any filing, such as the petition itself.[34] Parties can request additional discovery, but the PTAB rarely grants such motions.[35] In contrast, discovery in district court is a lengthy, intrusive affair.

Finally, a patent challenger will typically have the opportunity to conduct his or her trial before a jury. This can be a significant advantage for a sympathetic client whose counsel can create a narrative that appeals to the jury. Often, adept story-telling can tip the balance in close or difficult cases. As such, a patent challenger should identify counsel with a proven record of successfully trying cases before a jury to maximize his or her chances for a favorable verdict. Likewise, where other fora are utilized, in addition to litigation experience, specific expertise (such as before the PTAB) should be sought by a patent challenger (or a defendant).

International Trade Commission (ITC)

The ITC is another common forum for patent litigation. It permits patentees to exclude infringing products from the US market, but does not allow for monetary damages or for cancellation of a patent. Moreover, a party can only challenge *imported goods* that allegedly infringe a patent; a potential infringer cannot seek declaratory judgment of invalidity of a patent before the ITC, as it can in district courts, or seek cancellation of claims as before the PTAB. In addition to these substantive differences, ITC actions differ procedurally from traditional litigation in that they are heard before an administrative law judge (ALJ) rather than a jury, are reviewed by the full Commission before potential appeal to the Federal Circuit, and proceed according to a statutorily mandated time frame.

Of these, one of the more valuable differences is the speed with which an ITC action proceeds from filing to decision. At the ITC, a case is typically resolved via an initial determination by an ALJ within 12 to 15 months of filing in accordance with a statutorily mandated timeframe.[36] Following the initial determination, the parties are permitted to petition the Commission for review of any aspect of the decision, including findings of fact. Only after the Commission either reaches its final

Table 1: Summary of Post-Grant Forums

Forum	Allowable Grounds & Institution Standard	Average Time to Resolution	Estoppel?
Inter Partes Review	• Novelty and obviousness based on printed publications and patents • Must show reasonable likelihood of prevailing with respect to at least one claim	12 to 18 months after institution[41]	Yes
Post Grant Review	• Novelty, obviousness, written description and enablement • Must show that (i) more likely than not that at least one claim is unpatentable, or (ii) a novel legal question is raised	12 to 18 months after institution[42]	Yes
Covered Business Method	• Any ground of invalidity for patents granted under first-to-file provisions • If the patent was granted pre-AIA, limited prior art • Must show that at least one claim drawn to a covered business method is more likely than not unpatentable	12 to 18 months after institution[43]	Yes
Ex Parte Reexam	• Novelty and obviousness only, based on printed publications, patents, and admissions of the patentee • Must show substantial new question of patentability	~22 months[44]	No
ITC Proceeding	• Any ground of invalidity for patents, but only as a defense	12 to 15 months for initial determination[45]	No
District Court	• Any ground of invalidity for patents • Presumption of patent validity applied • Can be expensive compared to proceedings before the PTO	~26 months for contested judgment[46]	Yes

determination following review or declines to review the initial determination may a party appeal to the Federal Circuit.[37]

Perhaps the most drastic difference between the ITC and district court litigation is the limited remedy—exclusion orders. If a product is found to infringe a patent, the ITC has the power to forbid the importation of that product via either a global or limited exclusion order.[38] While this prohibits a party from importing the infringing product into the United States, it does not entitle the patentee to monetary damages; an ITC determination is forward-looking and most valuable for patents far from expiration.

In conjunction with the limited remedy, the ITC also provides unique benefits in terms of jurisdiction over defendants. Because the ITC is charged with investigating alleged infringement of imported goods, the commission has "*in rem* jurisdiction" over the imported good themselves—and can order their exclusion even without personal jurisdiction over the manufacturer. Essentially, filing at the ITC allows a patentee remedies against potential defendants over which a given district court may not be able to assert jurisdiction.[39]

WHAT DOES THIS ALL COST?

Of course, a major factor in pursuing litigation or a challenge to a patent is cost, and each of these proceedings has a different scale of cost. In part, this reflects the available options at each forum—in the district court, where all infringement and invalidity arguments (and full discovery) are available, litigation is generally more expensive than proceedings before the PTAB.[40] But even within a forum, cost varies due to the complexity of a given case; complex cases involving numerous experts and extensive discovery will naturally be more expensive. Moreover, ITC and district court proceedings are more likely to settle, often after discovery, which can mitigate a portion of the overall costs. Experienced counsel minimize costs by strategic scheduling of cases. For example, where possible, the parties can agree to early claim construction of a patent, which determines the meaning of claim terms in a case. Such claim construction can often be case dispositive. Counsel with expertise in document discovery can also save costs by working with opposing counsel to limit discovery, by crafting tailored requests for production, and by utilizing sophisticated data review and organization software. Ultimately, a careful weighing of the pros and cons of each forum, the importance of the case to a company's business objectives, and the need for expediency will drive a final choice of forum.

CLOSING REMARKS

Post-grant proceedings provide several avenues for attacking the validity of a U.S. patent, each with its own advantages and disadvantages. Some of the most salient features are summarized below in Table 1. A challenger seeking to invalidate a patent should carefully weigh these factors in pursuing relief through a particular forum. Finally, a challenger should carefully discuss with counsel the pros and cons of each forum with a particular focus on counsel's track record and expertise at each forum.

ENDNOTES

1. 35 U.S.C. § 319.
2. 35 U.S.C. § 311(a)–(b) (2012).
3. *See Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377 (Fed. Cir. 2015) (invalidating claims to amplifying and detecting naturally-occurring DNA because amplification steps are conventional).
4. 35 U.S.C. § 314(a).
5. 35 U.S.C. § 311(c).
6. 35 U.S.C. § 315(a)(1), (b).
7. 35 U.S.C. § 315(a)(3).
8. 35 U.S.C. §§ 316(a)(11), 326(a)(11).
9. Although the statute provides that a patentee may amend claims, the PTAB has held that a patentee must show that such an amendment would make the claim patentable. *Prolitec, Inc. v. Scentair Techs., Inc.*, 807 F.3d 1353, 1363 (Fed. Cir. 2015) (upholding PTAB ruling that "the patentee's burden on a motion to amend includes the burden to show patentability over prior art from the patent's original prosecution history").
10. 35 U.S.C. § 314(a)(11) (2012).
11. 35 U.S.C. § 317(a)–(b) (2012).
12. 35 U.S.C. § 316(e).
13. http://www.uspto.gov/sites/default/files/documents/2015-10-31%20PTAB.pdf at 12.
14. LegalMetric Inter Partes Review Report (March 07, 2016).
15. 35 U.S.C. § 312(a) (2000); 35 U.S.C. 314(a).
16. 37 CFR 41.61(a).
17. 35 U.S.C. § 321(b).
18. 35 U.S.C. § 321(c).
19. 35 U.S.C. § 324(a).
20. http://www.uspto.gov/sites/default/files/documents/2015-10-31%20PTAB.pdf at 12.

21. 37 CFR 42.302(a).
22. *See* 37 C.F.R. § 42.300 (2014).
23. 35 U.S.C. § 325(e).
24. 35 U.S.C. § 325(e).
25. *See, e.g., Harmonic Inc. v. Avid Tech., Inc.*, No. 2015-1072, 2016 WL 798192, at *7 (Fed. Cir. Mar. 1, 2016) (finding that the Federal Circuit does not have authority to review the PTAB's decision to institute review on only a subset of grounds raised in the petition).
26. See Dell Inc. v. Electronics & Telecommunications Research Institute, IPR2015-00549 (PTAB March 26, 2015) (permitting a second IPR on grounds raised in the petition for the first IPR but on which the first IPR was not instituted).
27. *See, e.g.*, *St. Jude Med., Cardology Div., Inc. v. Volcano Corp.*, 749 F.3d 1373, 1375-76 (Fed. Cir. 2014) (denying appeal of decision not to institute for lack of jurisdiction).
28. *See In re Cuozzo Speed Technologies, LLC*, 793 F.3d 1268, 1279–80 (Fed.Cir.2015); cert. granted *sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016).
29. *In re Cuozzo Speed Techs.*, LLC, 793 F.3d 1268, 1278 (Fed. Cir. 2015) cert. granted *sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (2016).
30. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005).
31. 35 U.S.C. §§ 141(c).
32. *Kirkendall v. Dep't of the Army*, 573 F.3d 1318, 1321 (Fed. Cir. 2009).
33. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005).
34. 37 C.F.R. § 42.51(b)(1).
35. *See, e.g., Garmin Int'l, Inc. v. Cuozzo Speed Techs. LLC,* No. IPR2012-00001, 2013 WL 2023626, at *4 (P.T.A.B. Mar. 5, 2013).
36. 19 U.S.C. § 1337(b)(1).
37. 28 U.S.C. § 1295(a)(6).
38. 19 U.S.C. § 1337(d).
39. *See Sealed Air Corp. v. Int'l Trade Comm'n*, 645 F.2d 976, 985 (C.C.P.A. 1981) ("An exclusion order operates against goods, not parties. Accordingly, that [limited exclusion] order was not contingent upon a determination of personal or in personam jurisdiction over a foreign manufacturer. The Tariff Act of 1930 (Act) and its predecessor, the Tariff Act of 1922, were intended to provide an adequate remedy for domestic industries against unfair methods of competition and unfair acts instigated by foreign concerns operating beyond the in personam jurisdiction of domestic courts").
40. *See* Am. Intellectual Prop. Law Ass'n, Report of the Economic Survey 37–38 (2015).
41. 35 U.S.C. §§ 316(a)(11), 326(a)(11).
42. 35 U.S.C. §§ 316(a)(11), 326(a)(11).
43. 35 U.S.C. §§ 316(a)(11), 326(a)(11).
44. *Ex Parte* Reexamination Filing Data, U.S. Patent and Trademark Office (Sept. 30, 2014) available at http://www.uspto.gov/sites/default/files/documents/ ex_parte_historical_stats_roll_up_EOY2014.pdf
45. 19 U.S.C. § 1337(b)(1).
46. LegalMetric Nationwide Patent Litigation Report (April 2015) at 32.

Meeting Review

Technology Commercialization & Partnerships for Global Health - Drugs, Vaccines and Medical Devices

Vasu Pestonjamasp

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The Association of University Technology Managers (AUTM) held its 2016 Annual Meeting in San Diego, CA (February 14-17, 2016). This event was attended by professionals that represented biotech and pharmaceutical companies, startup ventures, academic technology transfer offices, service providers and law firms. The goal of academic technology transfer is to assist the commercialization of research for public benefit. In accordance with this mission, and in addition to various other sessions, the AUTM Meeting focused on the aspect of partnerships with respect to commercialization of scientific discoveries. Some select highlights are described below.

A panel discussion entitled, "Partnering Without Borders: Accelerating Global Treatments to Patients," featured panelists Catherine Hennings, MS, MBA [PATH]; Ana Santos Rutschman, J.D. [Global Healthcare Innovation Alliances (GHIA); Duke University]; Ashley Stevens, Ph.D. (Focus IP Group, LLC) and Peter Soukas, J.D. [National Institutes of Health (NIH)]. The discussion was moderated by Julia Barnes-Weise; J.D., CLP [GHIA at Duke University].

Salient points from Julia Barnes-Weise's presentation are as follows. The identification of relevant disclosures; licensees/partners; negotiations of access to medicines provisions in the license agreement and eventual development of alliances are key with respect to the treatment of infectious disease outbreaks and neglected tropic diseases. Thus technology transfer plays an important role in this activity. GHIA team supports the Innovation & Technology Policy Lab (ITPLab). As discussed on its web page, The ITPLab serves as a source for knowledge creation and sharing; works across various technologies and employs an interdisciplinary and contextual approach in examining the roles of innovators, regulators, financiers, competitors, and the various communities that may be impacted by the innovations. GHIA's Ebola Alliance Project involves determination of major players; analysis of initial issues; development of questions; interviews of players; analysis of common and distinct issues and the development of potential partnering tools and incentives. While acknowledging Mark Feinberg (formerly of Merck), Julia Barnes-Weise mentioned that the industry's decision to engage in the project may be enabled by the appreciation of public health necessity and the opportunity to contribute to the acceleration of a promising vaccine candidate's development; understanding and acceptance that the engagement in Ebola vaccine development is for public health (and not commercial reasons); anticipation that the development of vaccine will be advanced via public sector partnerships to combine expertise, to share costs and risks, and to take care of uncertainties. The commitment of funding/donor organizations such as GAVI and UNICEF to obtain and deliver an efficacious and safe Ebola vaccine would also be important. Several things may be done in the context of Ebola Alliances; such as understanding what went right and replicating this for outbreaks in the future and also identifying and developing effective tools to address the hurdles that slowed the process. These can involve agreeing upon a common definition of an emergency global outbreak and also principles for alliance formation; drafting acceptable alternatives in terms of clauses for the main issues and Model Letters of Intent. In addition, future partners may be educated in the formation of partnerships for vaccines and therapeutics for infectious diseases. The needs, roles, intentions, apprehensions, hesitations and drivers for these partners can be different and thus need to be taken into consideration for alliance formation. Legal tools should be developed to address key issues and new provisions should be

Correspondence:
Vasu Pestonjamasp, vpestonjamasp@gmail.com

generated. Agreements that are necessary for the alliance's goals; are hardest to negotiate; model agreements that shorten the time to reach the agreement and those that can be standardized are important aspects to consider. Alliance formation can involve a large number of agreements per alliance and thus the IP ownership; data privacy and roles and standards issues become even more complex as compared to those associated with two party-agreements. The methodology for agreement provision alternatives for alliance formation has involved review of existing model and related agreements; identification of applicable key terms and of major approaches to specific issues; development of master chart of specific terms from designated agreements and the adaptation of existing terms to the needs of a multi party alliance for development of vaccines and therapies to treat and protect against an EIDO. Next steps include continual updating of provisions chart; alliance agreement outlines and the generation of incentive packages for various providers, and coordination and education across sectors.

Ana Santos Rutschman spoke on the " EU Initiatives to Encourage Accelerated Biopharma Innovation Alliances: The Innovative Medicines Initiative (IMI)." The information available regarding IMI mentions it to be Europe's largest public-private initiative. It involves collaborations among industry-based and academic experts and multi-party alliance model for the acceleration of biopharma innovation. IMI also provides funding structures for global infectious disease therapies. Several ongoing projects are listed under IMI, and these pertain to Ebola vaccine development, influenza vaccines, and combating bacterial resistance, among others. IMI's intellectual property (IP) provisions direct the IP regime of all projects supported by IMI and relate equally to all partners in the projects. The provisions pertain to those regarding ownership; transfer of ownership; joint ownership and protection of results. The provisions aim to provide a very practical contribution to enhancing drug development efficiency. The 2015 Ebola program has been designed to speed up all aspects of drug development and may potentially be applicable also to other diseases.

The presentation by Catherine Hennings, entitled, "Vaccine Development Partnerships for Global Health - Accelerating development of vaccines for low-resource countries," noted that the greatest challenges along the path of R&D to scale-up lie in the middle of the value chain. This is where PATH adds value. With 40 years of experience and 98 products in the pipeline, PATH has served several million people in 70 countries and has expertise in 5 platforms. PATH's goal includes acceleration of the development of new, lifesaving vaccines against selected major disease threats in the developing world. Not all vaccines are available, accessible in sufficient qualities or are affordable. Thus PATH's vaccine development activity includes generation of a target product profile, identification of candidates in line with the target product profile and creation of partnerships (academic groups, government labs, nonprofits, big pharma, biotechs, and development country vaccine manufacturers) to hasten vaccine development. Overall, PATH contributes technical expertise, facilitation of partnerships and financial resources. These collaborations positively influence the availability, accessibility, and affordability of vaccines in developing countries. PATH's partnership strategy for each vaccine development project ascertains that the global access goals can be met. In regards to the availability of the vaccines, a manufacturer is to provide agreed-upon volume or proportion of capacity for public sector purchase within defined territory, or a supply that is enough to meet the demand for agreed-upon public sector markets and territory. Together with the manufacturer, PATH puts in place an upper limit for the prices for specific territories and markets. The pricing can be tiered or may be sold at cost or with margin for some regions/markets. There can be various approaches to access to IP and global access. In exchange for global access commitments, PATH's partner can be allowed to own and control Background and Project IP. However, should the partner cease to continue develop/make affordable/make available the vaccine for low resource countries, a non-exclusive license to Background and Project IP can be triggered. For research collaborations with universities, PATH typically negotiates non-exclusive license to Background & Project IP; develops the technology, finds out commercial partners and sublicenses IP, and retains certain third party beneficiary rights. PATH and the partner may consider a staged agreement approach in which at an early stage, they agree on a target product profile (TPP) [with target price as a negotiated component of the TPP]. In the next stage, price ceiling within defined territory and markets may be negotiated. Each of the partnerships is unique and depends on the stage of technology development and business strategy of PATH's partner.

In his presentation, "The Role of Universities," Ashley Stevens provided the example of d4T, which was first discovered by Dr. Tai-Shun Lin and Dr. William Prusoff of Yale University with respect to its capability to treat HIV/AIDS. This research utilized significant government funding, and d4T was exclusively optioned then licensed to Bristol-Myers Squibb. Medicines San Frontieres asked Yale University to allow South Africa to import generic d4T into South Africa. After an initial rejection of this by BMS, the company subsequently agreed to not assert S. African patent. In 2011, Dr. Stevens and colleagues published their findings

that public sector has had a more immediate effect on enhancing public health than was previously thought in that during the past 30 years 153 new FDA-approved drugs were discovered through research conducted in public sector research institutions (PSRI). Since that study in 2011, the number of new drugs within USA and in non-USA regions have greatly increased. The process of taking a public sector-discovered drug to the global market may be modified to accomplish affordability. This can be via the change in licensing behavior with respect to developing country milestone and pricing; not allowing patenting in developing countries; having separate licensees for separate regions; mandatory sublicensing among companies and non-assert approach. Several examples of university technology partnerships were noted.

One other panel, "The Role of Academic Medicine in Creating New Medical Devices" included speakers Ashley Stevens, Ph.D. (Focus IP Group, LLC); Alan Bentley, M.S. (Vanderbilt University); Elias Caro, M.S.; AIMBE fellow (Wallace H. Coulter Foundation) and Stephen Harsy, Ph.D. (Director, Contract & Research Support Program, University of Arizona).

In his presentation, "Medical Devices, Physician Innovators, and the "Back Door," Alan Bentley quoted that the role of academic medicine in creating new devices is greater than previously thought. Many of the medical devices were patented by some M.D. in his/her name referred to as the "back door." In relation to IP, the back door can include an employee's failure to assign or disclose IP rights to one's employer; breaching the employment obligations, or engaging in legal protection/commercialization on one's own behalf. The back door (IP activity) can be more difficult to do with industry, foundation or other contractually funded research, but easier to achieve for concepts created with no research support; including some physician-generated innovations. There may be more than one scenario for this, including a physician's not being an employee. The Physician Payments Sunshine Act has been in place to improve the transparency of relationships among health care providers and pharmaceutical manufacturers, and is a part of the Affordable Care Act (2010). This Act requires companies to collect and track all financial relationships with physicians and teaching hospitals and to report them to the Centers for Medicaid and Medicare Services (CMS). The presentation noted the importance of company-physician relationship; naming rights and payment, and some case studies.

Stephen Harsy presented "The Source of Innovation in the Medical Device Industry: Insights from the Sunshine Act Open Payments Database." The Open Payments (federally run) program collects information about the financial relationships (Payments and other transfers of value, e.g., royalties and licenses fees, consulting, education, entertainment) among applicable manufacturers and group purchasing organizations (GPOs) with physicians and hospitals. The question posed in the presentation was if the Open Payments Database put together and managed by the CMS under the Sunshine Act could be used to understand and quantify the contributions academic medicine and universities make to innovation in the medical device industry. Dr. Harsy discussed that each reporting company is coded as pharma/device/financial services or other categories. The device companies are further coded as instrumental/surgical/dental or other categories. Dr. Harsy presented data regarding 2014 Sunshine Act royalty recipients and the amounts paid. In conclusion, he mentioned that in contrast to pharmaceutical innovation, most device innovation comes from physicians that are acting independently as compared to those that are working through their institutions. Capture of data pertaining to payments to universities and quantification of the innovations' impact to the device industry could be the next steps to follow.

Elias Caro spoke on "Translating University Innovation to Benefit Humanity." Patient care is Coulter Foundation's goal. This includes focusing on a roadmap to commercialize university inventions and involves key components such as Co-Principal investigators (Co-PIs); stakeholders; program management; a Boot Camp; an Oversight Committee and Project Business Advisors. The program management involves de-risking of the commercialization process along the way; from idea generation to follow-on funding. The intermediate steps include risk assessment and screening, and selection and risk reduction; with clinicians, industry and VCs on the review process. Coulter process involves various stages. These include mentoring by program management and matching the need and the technology; stakeholder's feedback; killer experiment design, and project selection and project management via various meetings involving regulatory strategy, IP strategy and financial plan development. In the past 9 years, 24 products have been contributed via the Coulter process.

Dr. Ashley Stevens made a presentation on "The Role of Academic Medicine in Creating New Medical Devices." The medical device market is significantly large in size, is growing and has several segments depending upon the applications. Dr. Stevens provided examples of products that have been approved in various therapeutic categories; the institutions discovering them and current marketers (companies) of those products. There are some key differences between the medical device and drug studies. For example, the PSRIs are contributing to the devices since much longer time than for the drugs; the device discovery is based on the unmet

needs of the medical practice (as opposed to drug discovery that is fueled by basic scientific research); device patents are assigned to multiple entities (as compared to the PSRI as in the case of drugs); devices contain multiple technologies and different components can be enabling (as compared to biopharmaceuticals that can need many enabling technologies), and no equivalent data source is reported for devices (as compared to the FDA Orange Book for drugs). An additional difference is that devices have a shorter life cycle than drugs. The latter's lifecycle is until patent expiration and beyond. Dr. Stevens discussed that the role of academic medicine in creation of new devices is substantially greater than their role in drug discovery and that many key categories of medical devices began with an MD who in turn collaborated with engineers. On the other hand, company-originated devices seem to be in the minority. The preliminary observations shared by Dr. Stevens are: Commercialization pathways typically do not involve the institution (e.g., not all of the teams that developed first stents got patents on them); product generations subsequent to the initial product are developed by device companies. The ownership status for devices seems much less clear-cut than for drugs. Many clinicians do not feel obligated to assign the invention to the institution and instead assign it to an entity that provides financial support for the translational work. An example of this has been of Dr. Julio Palmaz whose idea of stent and the device eventually made it to J&J and contributed to a significant fraction of J&J's total profits.

The panel discussion, "Drug Discovery and Development Primer for More Effective Technology Commercialization" included Isabelle Gorrillot, Ph.D. (Managing Director, Areon Biosciences) and panelists Tom Campi, DVM, MPVM (Elanco); Alan Naidoff, DMD, JD, CLP (InnovationAdventure, LLC); Arundeep Pradhan, M.S. Pharmacy Administration, B. Pharmacy, RTTP (Apio Partners) and Ines Holzbaur, Ph.D. (Amorchem).

In his presentation, Thomas Campi discussed the pros and cons regarding the focus on animal health. The rationale supporting animal studies includes: Feasibility to immediately conduct the studies in target species; monetization of assets in a shorter timeframe and the potential for alternate revenue stream in case the studies eventually fail in humans. These aspects can speed up the road to market. Data from animal models using dogs/cats/cattle/sheep/pigs can enhance predictability of outcomes over mutant rodent models and the IND-enabling studies may be reached faster. In terms of the study quality, the GCP, GLP and GMP regulations are the same for human and veterinary therapeutics. On the other hand, human-focused biotech companies can have objections regarding the potential loss of focus. In addition, there can be concerns regarding potential adverse effects and the possibility that the veterinary product(s) would be prescribed/utilized by human patients although such scenarios have never taken place so far. In terms of therapeutic development, divergence into naturally occurring disease states in animals has facilitated shorter timelines for human drugs. The 2014 sales figures for animal health products show that feline and canine products contributed to about 40% followed by cattle (25%); swine (18%); poultry (12%) and sheep (5%). For animals that are used as food, the animal health market is being driven by factors such as internal and external parasitic infections; infectious diseases and improvement in production efficiency. Drivers for the companion animals market include parasitic infections; pain; chronic progressive diseases and cancer. Transformational oncology products are highly valued.

Inez Holzbaur made a presentation entitled, "Getting your assets across the goal line," which discussed the needs of both, the pharma and the VCs. Pharma's needs include replenishment of an internal pipeline; changing the stage and modality according to different indications, and bringing reimbursable and clinically relevant drugs to market. In addition, the pharma companies look for opportunities and early-stage assets, and may wish to take on pre-IND steps internally. They desire to have access to key opinion leaders (KOLs) and need to know the value proposition that is provided by a potential partner's asset(s). The needs of VCs include; commercial value of an academic invention; a plan for what the next step looks like; and the potential exit through IPO or via sale to pharma. VCs may take on greater risk if a good payoff seems likely. The value of an invention can be maximized by validation of the asset and the protection of the existing or potential IP. Translational research provides value inflection for basic research to clinical research. Venture philanthropy; Venture capital and accelerators can provide financial support; in-kind support and mentorship. The capacity to fund promising assets; strong industry-university interaction; reaching out at an early stage and good understanding of the assets contribute to successful technology transfer.

These various sessions provided insights regarding innovative agreements and partnership models for multiparty alliances; implications for industry-university partnerships and business development relationships. These can help speed therapies to market and decrease the risk threshold of developing products that attend to global health needs. In addition, the path to medical product regulatory approval and aspects surrounding the generation of medical devices by practicing M.D.s were discussed.

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CORRESPONDENCE

Business correspondence and inquiries should be addressed to *editor@CommercialBiotechnology.com* or to thinkBiotech LLC, 1133 15th Street NW, 12th Floor Washington, DC 20005.

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