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Article

Business Model Innovation Opportunities for the Biopharmaceutical Industry: A Systematic Review

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ABSTRACT

Research on business model innovation for the biopharmaceutical industry continues to be an area of high global interest due to the combination of industry innovation challenges and global macroeconomic pressures. Through the use of a systematic literature review, this research explores academic literature published from 1976 to 2013 that has addressed business model relevant factors and dynamics in the biopharmaceutical industry. 305 relevant publications were identified, analyzed, and inductively categorized based on the similarity of their conversations into twelve categories. The authors find that opportunities for business model innovation in the biopharmaceutical industry lie in five key areas: *External Orientation*, *Learning Capabilities*, *Cluster Participation*, *Qualified Business Management Team* and *Organization Controls*. This research provides not only insight into opportunities for business model innovation specific to this industry but also can be used independently as a valuable reference tool for similar research.

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INTRODUCTION

With its roots in the 19th century, what is known today as the modern biopharmaceutical industry has only within the last 40 years encountered a significant disruption to its historically prevalent business model. The revolution in biotechnologies responsible for this disruption has affected not only biopharmaceutical companies themselves but importantly, also the entire ecosystem of supporting stakeholders.

From the late 1970's, there has been a literal explosion of new biotechnology development and commercialization by thousands of researchers and companies across the world. Though the potential that biotechnology showed as a potential source for new therapies was exciting in its own right, it was the 1976 founding of Genentech as the world's first dedicated biotechnology company[1] and its collaborative 1982, development and market launch of its rDNA based synthetic human insulin with Eli Lilly & Co.[2] that showed would-be new biotech entrants and venture investors that intellectual property (IP) could be packaged and sold independently of having a final product. This key event thus ignited an explosion of thousands of new biotechnology firms[3]

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which have in turn driven hundreds of new biotechnology derived therapies to market approval.[4] Prior to 1976, one would need to go back 32 years, all the way to the 1944 founding of Syntex, to find the previous instance where a new successful research-based pharmaceutical company was founded.[3]

The challenge this presented to the industry was that because this biotechnology knowledge base is both complex and expanding and its sources of expertise are widely dispersed, the locus of innovation is found in networks of learning, rather than in individual firms.[5] Therefore, being adept at operating in a world of external collaboration is critical. However,the full vertically integrated business model (FIPCO) that had dominated the biochemistry based pharmaceutical industry for over 100 years, tends to be internally focused and thus limited in its ability to maintain by itself a needed level of expertise in this new, increasingly diverse and globally dispersed family of technologies.

Therefore, with Eli Lilly generally leading the way, despite the limitations of their vertically integarted structures, pharmaceutical firms soon started seeking opportunities and innovation externally by collaborating with these new diverse sources of technological expertise. In doing so, the industry started to fragment from the traditional silos of internal expertise and in doing the distinction between what is a pharmaceutical firm and what is a biotechnology firm took its first steps down a path to becoming less obvious. Indeed, it is now quite common for pharmaceutical companies to use biotechnologies to either support their own pharmaceutical R&D efforts[6] or even market and distribute a pure biotechnology directly, like Pfizer Inc.'s 2002 agreement with Serono SA to market and co-promote Rebif (interferon beta-1a), a treatment for multiple sclerosis.[7,i]

Unfortunately, despite biotechnology's early promise for more efficient research, productivity and cost remain significant concerns for this $1.2 trillion global industry.[8,9] Indeed, the rate of output productivity for research and development (R&D) is actually decreasing relative to the increase of the productivity of its technological inputs. Like the historical development of computer microprocessors, biotechnologies associated with R&D inputs have also been following Moore's Law, a term for the exponential improvements over time in technological fields.[10] For example, since the early 1980's DNA sequencing has become over two billion times less expensive to perform, it takes 100,000 less man hours to calculate 3D protein structures via x-ray crystallography than it did 50 years ago and high throughput screening has reduced the cost of testing drug-like molecules against protein targets by around 10 times per decade.[11]

However, in contrast to these technological inputs, the therapeutic outputs of this industry follow what Scannell et al.[11] paradoxically coin as Eroom's Law (Moore's Law spelled backward). They point out how the inflation-adjusted R&D spend per molecule brought to market over the last 60 years has risen by over 100 times. Despite the billions of dollars that the industry collectively spends on R&D annually, the rate of output of new therapies is declining versus historical productivity levels. Indeed, the year 2010 saw the lowest number of New Molecular Entities (NME)[ii] applications by major pharmaceutical companies in the previous ten years. Moreover, the number of drugs entering Phase I and Phase II clinical trials fell 47% and 53% in 2010 over 2009. For Phase III trials the number is 55%.[12] Clearly, this lower R&D productivity stresses any company's financial health, especially those whose existing product sales are under threat from patent expiration and the resulting generic competition.

In part due to these issues, with an average R&D spend of 14%-15% of total revenue, it remains one of the most research intensive and costly industries in the world.[13] To the point of marketing approval, a typical candidate therapy costs between USD $559 and USD $672 million (2005 dollars) out-of-pocket over an average period of 8 years.[iii,14]

Unfortunately, the ability for companies to cover these costs will become more challenging due to changing global demographics and market conditions which will force global governments and private third party insurance payers to place increasing pressures on this industry's margins. Key among these will be the large

i Indeed, because of this muddling of technological focus and the consequent plausibility that both industries will eventually become indistinguishably integrated, for this research they are primarily treated as the same industry. As such, the terms biopharmaceutical industry or biopharmaceutical will be used to encompass both the traditional pharmaceutical industry and the medical biotechnology industry. Where it is relevant for clarity to separate them, this will be done.

ii NME – New Molecular Entity applications, a common industry indicator of R&D innovation.

iii Importantly, these calculations do not include full R&D costs. To do so, one would also need to account for the cost of capital over this lengthy period of time, the expected return that the company or its investors forego vs. an equally risky investment. Applying these considerations, the average cost per candidate therapy increases to $1.3 billion.[14]

bubble of the population that is currently entering the elderly demographic in key western markets. In the USA, for example, the first members of this "Baby Boom" generation started turning 65 in 2011. By 2029, when all of the baby boomers will be 65 years and over, more than 20 percent of the total U.S. population will be over the age of 65.[15] Since today this population makes up only 14.5% of the population[16] and due to the fact that this segment are overwhelmingly the predominant consumers of health care resources, currently at 34%[17] not difficult to see that this resulting progressive increase in healthcare utilization will force global government and third-party health care payers to continue to increase their pressure on the biopharmaceutical industry for products with greater marginal innovativeness and at lower prices.

As a result, there certainly exists a need for business models that provide more efficient and less costly ways of researching, developing and bringing life changing medical therapies to market in a commercially successful and sustainable way. Unfortunately, explicit research in this area is lacking. Though business models have implicitly been an important part of economic behavior and understanding for hundreds of years, it has been only recently that they have been an explicit focus of academic research. Indeed, Teece[18] and Osterwalder & Pigneur[19] cite the first appearance of the term "business model" in an academic journal to be 1957[20] and in the title of a paper to be 1960.[21] However it was not until the mid 1990s with the advent of the Internet and information technologies (IT) that the explicit concept of the business model became prevalent in academic and industry journals, where it has since exploded as a focus for researchers.[22] This story is similar for the biopharmaceutical industry.

Thus, there is an acute need to identify and assess key business model dynamics that can be helpful. Toward addressing this need, the focus of this research is to explore the universe of literature published since 1976 that has addressed business model relevant factors and dynamics in the biopharmaceutical industry and inductively mine this literature for insights into the opportunities for business model innovation. More specifically, using the method of a systematic literature review, the objectives of this research paper are:

- to deliver a state of the art report on business model relevant research conducted specifically for the biopharmaceutical industry.
- to suggest a categorization and linked-based mapping of the identified literature by analyzing their respective "conversations" (core findings).
- to identify the evolution of this research, current research gaps and directions for potential future research.

The remainder of this article is structured as follows. A section on research method will provide a rationale for the use of a systematic literature review in this research and subsequently describe the detailed protocol followed. This will be followed by results and categorization which will provide the key results of the review including a detailed categorization and narrative of the captured literature. The findings are then discussed in light of the categorizations. Finally, the implications of our findings for researchers and practitioners are highlighted alongside opportunities for further research in the conclusion.

RESEARCH METHOD

Prior to starting this research, a review protocol for a systematic literature review was developed. This protocol established the research parameters including explicit descriptions and the order of the steps to be followed. The first step explicitly established the key question for the focus of this research: "*How, through the use of business model innovation, can the biopharmaceutical industry continue to drive product innovation while at the same time reduce the time and costs that it takes to get a drug to market?*"

Following this, a specific year range was defined in order to limit the universe of publications to those years most meaningful to answering the key question. In this regard, 1976 was used as the start of the year range since it is the founding year of Genentech, the first fully dedicated biotechnology company.[1] Prior to this date, business models in this industry were relatively stable in that they overwhelmingly followed a fully integrated model (FIPCO).[23] The year 2013 was used as the end of the year range as this was the current year at the time of the start of this research.

After establishing the year range, the third step defined the publication universe that would be included. These publications were limited to those international peer-reviewed academic publications, and leading practitioner oriented journals that are included in the Thomson Reuters maintained Web of Science database. Since the Web of Science is both comprehensive and employs a strict inclusion evaluation processes, it was used as a general proxy for research quality.[24] Once these framing parameters were defined, a specific two level search strategy, first and second level search, was developed to ensure a systematic and comprehensive capture of all relevant publications.

The first level phase of this strategy started with identifying the population of literature that address business model relevant factors and dynamics within the context the medical biopharmaceutical industry. Key issues of definition were first solved since there still remains no clear consensus among researchers and practitioners for the definition of a business model[22] and the definition of a business model in many ways depends on the perspective of an author or how they are using the term.[25] Therefore, a decision was made to encompass all factors along the complete spectrum of the biopharmaceutical value chain that would encompass or be largely associated with the commercial translation of research. This would not be inconsistent with the business model definition used by Al-debei, El-Haddadeh, & Avison: *"The business model is an abstract representation of an organization, be it conceptual, textual, and/or graphical, of all core interrelated architectural, co-operational, and financial arrangements designed and developed by an organization presently and in the future, as well as all core products and/or services the organization offers, or will offer, based on these arrangements that are needed to achieve its strategic goals and objectives."*[26]

Based on this, a list of search terms was developed which were felt to cumulatively provide a sufficiently comprehensive level of inclusion criteria to capture the relevant universe of publications needed. Moreover, a similar definition challenge existed with the terms "pharmaceutical industry", "biotechnology industry" and "biopharmaceutical industry" and what they respectively encompass. Here it was determined to narrow the use of terminology to just biotechnology. Due to the significantly increasing co-dependence of research and commercial activities between the two areas, a sharp and clear distinction between them is now less meaningful for the purposes of business model innovation. As such, it was determined that a focus on the term biotechnology will capture enough of pharmaceutical business model dynamics to be sufficient for the purposes of this paper.

As shown in Table 1 below, all terms were then formatted into 18 separate "search strings" and entered into the EBSCO Business Source Complete publication database search engine and results captured. The EBSCO database was chosen due to it being among the largest and most comprehensive databases for business oriented scholarly full-text journals versus other popular databases.[27,28]

For these search results, clear pre-established criteria for study inclusion and exclusion were applied so as to exclude marginally relevant articles. Inclusion criteria were customized from Zott, et al.[29] and include:

- An article must deal with the concept of business model or its relevant building block dynamics in a non-trivial and non-marginal way.
- An article must deal with the concept of business model as a construct centered on business firms or on a dynamic directly related to the business firm's ability to commercialize its technology or service.

Exclusion criteria were also adopted and included published books[iv], government and NGO reports, editorials and book reviews, conference proceedings and any publication that is not in English. As shown in Table 1, after inclusion and exclusion criteria were applied to the 1,401 publications identified in the first level phase, 163 studies remained for inclusion and review.

Using a combination of Mendeley Desktop Version 1.14.1- dev7 for Mac, Atlas.ti 7.1.7 for Windows 7, and Microsoft Excel for Mac Version 15.17, these 163 publications were then read through completely. During this process, in addition to capturing a panel of bibliographic data and key sensemaking notes, each publication was distilled down to its respective "conversation"[30], or core message and used as a basis for categorizing into like and meaningful similarities. Though the use of "conversation" as a tool for categorizing is limited due to issues of subjective interpretation, for the purpose of this review it proved to be sufficiently robust to be successful.

Following the completion of this first level review, a second level review was undertaken to mitigate any limitations that the subjectively chosen 18 EBSCO search strings might incur on the comprehensiveness of the first level search. This also mitigated any unforeseen limitations of the EBSCO database itself. This second level review was completed by performing a "downstream" literature review of the bibliographies of each of the 163 captured first level search publications using the same inclusion and exclusion criteria. This surprisingly resulted in the inclusion of an additional 141 publications which, after being reviewed, analyzed and categorized, were added to the first level results. After including these 141 to the 1st level search of 163 and including one stochastically discovered

iv Published academic focused books are often much more comprehensive than a single academic study thus complicating the ability to capture a single conversation. However, as many books are built on previously published research papers that were foreseen to be captured within the scope of this paper, it was anticipated that this exclusion decision to be of minimal consequence. This proved to be true.

Table 1: First level search string protocols and search results

Nr.	EBSCO Search Phrase	Total publications	Shortlisted publications
1	"Business model*" AND Biotech*	185	43
2	"Biotech*" AND "Revenue Model*"	0	0
3	"Biotech*" AND "Innovation*"	749	77
4	"Biotech*" AND "Activity System*"	0	0
5	"Biotech*" AND "Business Process*" NOT "except biotechnology"	6	1
6	"Biotech*" AND "Platform*" NOT "except biotechnology"	160	3
7	"Biotech*" AND "Business framework*" NOT "except biotechnology"	0	0
8	"Biotech*" AND "Business structure*" NOT "except biotechnology"	1	0
9	"Biotech*" AND "Infrastructure*" NOT "except biotechnology"	81	5
10	"Biotech*" AND "Institutional framework*" NOT "except biotechnology"	13	4
11	Biotech* AND Hybrid* NOT "except biotechnology" NOT agricultural	44	3
12	Biotech* AND "Value generation*" NOT "except biotechnology (in author keywords) " NOT agricultur*	0	0
13	Biotech* AND "Value creation*" NOT "except biotechnology (in author keywords) " NOT agricultur*	9	2
14	Biotech* AND "Collaboration*" NOT "except biotechnology (in author keywords) " NOT agricultur*	109	18
15	Biotech* AND "Interfirm Cooperation*" NOT "except biotechnology (in author keywords) " NOT agricultur*	5	1
16	Biotech* AND networking NOT "except biotechnology (in author keywords) " NOT agricultur*	24	4
17	Biotech* AND "relationship management" NOT "except biotechnology (in author keywords) " NOT agricultur*	0	0
18	Biotech* AND "value chain" NOT "except biotechnology (in author keywords) " NOT agricultur*	15	2
	Total	1,401	163

publication from some informal exploratory reading, the combined number of publications included and categorized for this systematic literature review was 305.

RESULTS AND CATEGORIZATION

Among these 305 publications, 1986 is the first year that research is identified. These first four papers were focused on a combination of university-industry relations and technology transfer[31–34]. These would have been highly relevant issues at that time due to the recent passing of the Bayh-Dole Act (1980), a key US legislation freeing the way for commercialization for federally funded basic research.

From this time forward, as Chart 1 shows, the activity in academic research of business model related dynamics in this industry increases with a clear explosion in publication activity starting from 1996. From this point, the leading research activity was focused on the dynamics of alliances, collaboration

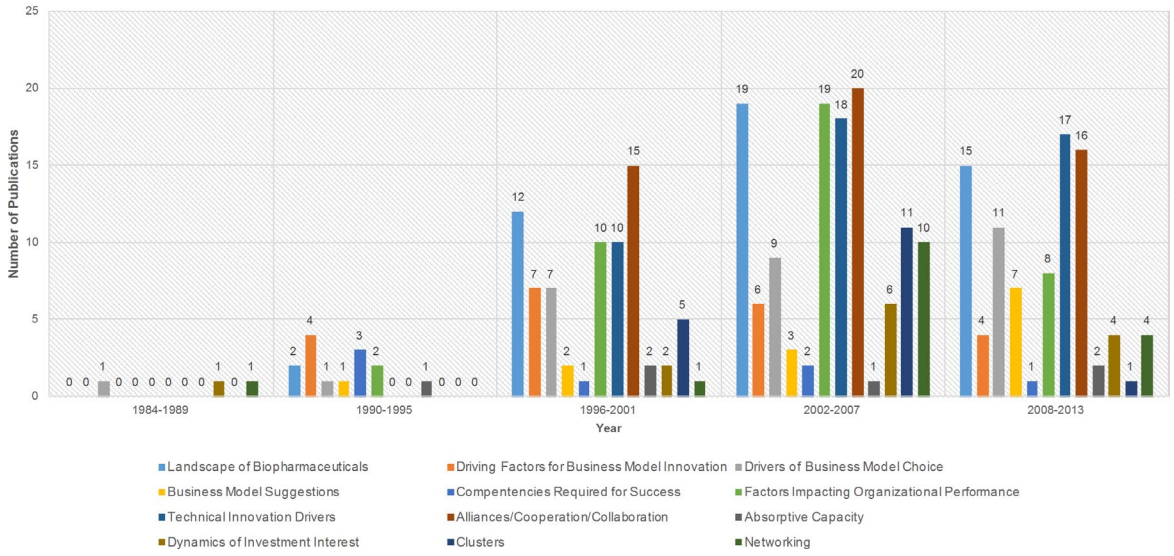

Chart 1: Research categorized by year of publication

Table 2: Ten authors with most publications (lead or contributor)

Nr.	Author (current university)	Number of publications
1	Sharmistha Bagchi-Sen (University at Buffalo)	10
2	Philip Cooke (University of Wales-Cardiff)	9
3	Walter Powell (Stanford University)	9
4	David Deeds (University of St. Thomas-Minnesota)	8
5	Joseph DiMasi (Tufts University)	7
6	David Audretsch (Indiana University-Bloomington)	6
7	Steven Casper (Keck Graduate Institute)	5
8	Gary P. Pisano (Harvard Business School)	5
9	Iain Cockburn (Boston University)	5
10	Rebecca M. Henderson (Harvard Business School)	5

and cooperation as well as what the landscape of the biopharmaceutical industry looked like.

In the years, 2002-2007, though *Alliances/Collaboration/Cooperation* and Landscape of Biopharmaceuticals continue as heavily researched categories, two other categories, *Factors Impacting Organization Performance* and *Technical Innovation Drivers* increase significantly.

Of further interest is the year 2000 when the term "business model" started to appear explicitly in the titles.[35–37] In addition, of the 305 included publications, only 13 are directly focused on some type of specific business model related suggestion. Lastly, Tables 2 and 3 show respectively the ten journals with the most publications and the ten most prolific authors identified in this research. In effect, this is where the academic conversation is occurring about business model innovation in the biopharmaceutical industry.

RESEARCH CATEGORIZATION

After inductively categorizing the 305 publications based on the similarity of their conversations, 12 separate categories were determined and are shown below in Table 4. Though some overlap does exist in their respective

Table 3: Ten journals with most publications

Nr.	Journal	Number of publications
1	Journal of Commercial Biotechnology	33
2	Research Policy	32
3	Strategic Management Journal	14
4	Technovation	14
5	R&D Management	11
6	European Planning Studies	10
7	Industry & Innovation	10
8	International Journal of Technology Management	9
9	Technology Analysis & Strategic Management	9
10	Small Business Economics	8

Table 4: Research categories by conversation similarity

Nr.	Category (Year of first publication) - Primary Focus	Publications
1	**The Landscape of Biopharmaceuticals (1991)** - The structure & history of the biopharmaceutical industry and factors driving its evolution.	48
2	**Driving Factors for Business Model Innovation (1991)** - The underlying issues and dynamics that drive the need and opportunity for business model innovation.	21
3	**Drivers of Business Model Choice (1986)** - Firm specific perspectives of why firms choose the type of business model they do.	29
4	**Business Model Suggestions (1993)** - Suggestions for various business models based on their ability to overcome market challenges.	13
5	**Competencies Required for Success (1991)** - The critical nature that various competencies play in a firm's success and its ability to utilize various business models.	7
6	**Factors Impacting Organization Performance (1990)** - The dynamics that impact organizational market performance.	39
7	**Technical Innovation Drivers (1996)** - The dynamics both internal and external to a firm that drive it's technical innovation productivity.	45
8	**Alliances/Cooperation/Collaboration (1986)** - The benefits, challenges, and dynamics relevant in the formation and managing of alliances and various forms of cooperation.	51
9	**Absorptive Capacity (1994)** - The enabling effects that the breadth and depth of a firm's existing technical knowledge plays on its ability to utilize external knowledge.	6
10	**Dynamics of Investment Interest (1987)** - The various issues and factors that drive investment interest from stakeholders.	13
11	**Clusters (1997)** - The prerequisites and factors important to geographic cluster formation and the benefits associated with participating within them.	17
12	**Networking (1986)** - The key dynamics important for network formation and factors impacting firms utilization of these networks.	16
	Total number of publications	305

concepts and dynamics, they are sufficiently independent of each other to be informative. Following Table 4, each of these 12 categories are addressed both with a summary narrative and a corresponding conversation table. The conversations in the tables have been distilled due to space limitations for inclusion into this paper.

The Landscape of Biopharmaceuticals

The Landscape of Biopharmaceuticals comprises 48 publications related to the structure of the biopharmaceutical industry including its history and the dynamics that led to its development and periodic transitions. It also includes the economics of the industry both at a macro and micro level, the industry topology and interaction workflows among its stakeholders and how all of these dynamics vary by national organizational structure. As shown in Table 5 below, these publications have been split into 5 subcategories.

History and Development contains 12 publications that focus on the history and the evolution of the medical biopharmaceutical industry. It covers its institutions from its inception as a nascent chemistry based pharmaceutical industry in the 19th century following multiple subsequent and overlapping technological paradigms[38] through key respective developmental and transitional dynamics into the modern biopharmaceutical industry. Common among this collection of research are publications focused on understanding what Coriat, et al.[39] describe as this industry's "Division of Scientific Labor", that is, basic research oriented academic and not-for-profit organizations vs. applied research focused for-profit organizations. The interaction of these two divisions of labor and the stakeholders, issues and policies affecting their interaction forms the narrative of the historical development of this industry and indeed is one the keys to understanding its current state and future trajectory. As an example, Hopkins et al.[40] point out that due to their closer relationship with university basic research, pure biotechnology companies have been causing a vertical disintegration of the pharmaceutical FIPCO models.

Topology and Operational Dynamics contains 14 publications that focus on the unique fragmented structure of this industry in terms of the many types of stakeholders and the dynamic information flows between them including the evolutionary adaptive responses leading to its current structure.[41,42] For example, Niosi[43] through his use of Complex Adaptive Systems as a model of analysis, discusses the evolving nature of these dynamics by showing how the biotech industry is an evolving complex system of interdependent institutions. He goes on to highlight that solutions to increasing innovation within this industry are thus a function of lessening the natural resistance that stakeholders within this complex archipelago may exhibit.

National Institutional Structures contains 8 publications that focus primarily on the role that national institutional structures and cultures play on the fertility of their respective national biotechnology industries. These include research comparing relative advantages in a liberal market economy like the U.S.A. vs. a coordinated market economy such as Germany.[44] It also includes comparative differences in academic-industry relations among countries such as the perceptions governing academic careers and also industrial relationships and governmental policies influencing academic relationships with industry.[45,46]

Market Success, Cost and Profitability contains 8 publications that focus on the cost of drug and therapy R&D. Although there is a consensus that this is certainly an expensive industry in which to do business and becoming increasing more so, there is some disagreement on profitability given current approval success rates. For example, though Glick[47] points to the success of current biotech business models, citing industry revenue and profitability figures, Grabowski et al.[48] point to the skewed distribution of profitability in this industry and highlights in his analysis the average mean which is barely above the cost of capital. Despite this, Lazonick & Tulum[49] show how, due to speculative investment, sociology, and government R&D support policies, significant investment will continue to flow into this industry regardless of its profitability.

Role of Government Policy contains 6 studies that focus on the role that government policy can play in improving the fertility of regional biotechnology environments. For these studies, there appears to be a general consensus that government policy plays a key role in the promotion of a healthy biopharmaceutical industry, particularly in promoting the commercial translation of research from academia into industry through policies and legislation. A good example of this is the 1980 implementation of the Bayh-Dole Act in the U.S.A. and the role that it played in motivating universities to commercialize their research.[50]

Driving Factors for Business Model Innovation

Driving Factors for Business Model Innovation comprises 21 publications related to the underlying issues

Table 5: The Landscape of Biopharmaceuticals – Distilled conversations with subcategories

	The Landscape of Biopharmaceuticals	
	History and Development	**Study**
1	By the 1990s, pharma had developed significant capabilities in biotech to work with specialized biotechs to drive innovation.	Galambos & Sturchio, 1998[23]
2	The growth and diffusion of intellectual human capital explains where and when the biotechnology industry develops.	Zucker et al. 1998[51]
3	Key factors stimulated stronger US biotech growth versus Europe.	Prevezer, 2001[52]
4	1992 PDUFA and 1997 FDAMA have led to greater efficiencies in therapy approvals	DiMasi, 2001[53]
5	Specific institutional arrangements of the US scientific system led to the unique dynamic of the biotechnology industry.	Dalpé, 2003[54]
6	Concomitant technological and US legislative developments explain the development and flourishing of the biotechnology industry.	Coriat et al., 2003[39]
7	Biotechnology has spawned greater complexity in the pharmaceutical industry and grows complexly integrated within it.	Quere, 2003[55]
8	Medicinal biotechnology is following a pattern of slow and incremental technology diffusion.	Nightingale & Martin, 2004[56]
9	Evidence shows that the biotechnology industry is following a historical pattern of slow and incremental co-evolutionary change.	Hopkins et al., 2007[40]
10	A strong correlation exists between the collaboration rate of large pharmaceutical firms and their performance.	Gottinger & Umali, 2008[57]
11	Transformation of US pharma from manufacturing apothecaries to research institutions was accomplished through university engagement.	Furman & MacGarvie, 2009[58]
12	Key differences exist between the biogeneric and traditional generic drug business models.	Tucker et al., 2008[59]
	Topology and Operational Dynamics	
1	Evolution of R&D alliance networks is an adaptive response to the emergence of the radically new molecular biology knowledge base.	Orsenigo et al., 2001[41]
2	Patterns of biotech's industrial dynamics explain the patterns of firm behavior and the mechanisms through which they exert their impact.	Malerba & Orsenigo, 2002[60]
3	Knowledge capabilities rooted in specific knowledge domains are producing a new economic geography.	Cooke, 2006[61]
4	In the constellation of alliance relationships in the biotechnology industry, key relationships offer mutual advantages.	Bagchi-Sen, 2007[42]
5	Biotech policy agendas should focus on increasing factor conditions to enhance start-up formation, alliances, and skilled employment.	Ahn & Meeks, 2008[62]
6	Public–private collaborations in biotechnology play significant roles in building firm-based and policy-making capabilities.	Papaioannou, 2011[63]
7	The shift in tacit and exploration knowledge to DBFs signifies a crisis for multinational drug companies.	Cooke, 2004[64]
8	Drug development under today's new institutional arrangements could turn out to be faster and better, but not cheaper.	Cockburn, 2004[65]

9	Changes in the healthcare value chain due to biotechnology are causing governments to change policies to attract bioclusters.	Cooke, 2004[66]
10	Due to lower productivity pharma firms are changing their R&D structure and focus.	Gassmann & Reepmeyer, 2005[67]
11	The previously distinct cultural boundary between university and commercial science is merging.	Vallas & Kleinman, 2008[68]
12	Institutional models help to define optimal linkage structures for understanding industry technology transfer dynamics.	Shohet & Prevezer, 1996[69]
13	Because innovative effort may not be stimulated by demand, biotechnology firms must play an active role in stimulating demand for the resulting technology.	Walsh, 1993[70]
	National Institutional Structures	
1	Availability of venture capital investment in the science base and national culture explain commercialization differences in US vs. UK.	Senker, 1996[71]
2	Differences in basic science exploitation, venture capital, and cluster formation help explain differences between US and EU biotech development	Cooke, 2001[72]
3	US vs. EU organizational differences of academic-industry relations is consequential.	Owen-Smith et al., 2002[45]
4	National technological performance in biotechnology is affected by institutions governing scientific careers.	Gittelman, 2006[46]
5	Changes in the national institutional framework affects industry dynamics.	Lynskey, 2006[73]
6	There exist national structural and policy comparative advantages allowing US to dominate biotech new starts vs. Japan.	Ibata-Arens, 2008[74]
7	Varieties of Capitalism explains how free market economies have advantage over controlled economies in cultivating biotechnologies.	Lange, 2009[44]
8	Though biotech development models used by China have advantages vs. US model, these advantages don't extend into the commercialization.	Zhang et al., 2011[75]
	Market Success, Cost, and Profitability	
1	Out-of-pocket cost per approved NCE is $114 million (1987 dollars). Capitalizing to the point of marketing approval $231 million.	DiMasi, et. al., 1991[76]
2	Though preclinical cost increases stable, overall costs of drug development are increasing at a 7.4% CAGR above inflation.	DiMasi, et. al., 2003[77]
3	Out-of-pocket cost per approved biopharmaceutical was lower vs. pharmaceuticals. Capitalized cost was nearly the same.	DiMasi & Grabowski, 2007[14]
4	Pharmaceutical R&D has highly skewed distribution of returns and a mean industry internal ROI modestly above cost-of-capital.	Grabowski et al., 2002[48]
5	Revenue evidence suggests that biotech business models are successful and strategic alliances are most prevalent model.	Glick, 2008[4]
6	Clinical success rates and phase attrition rates are important indicators of pharmaceutical firm resource utilization efficiency.	DiMasi, 2001[78]
7	Estimates of clinical phase transition and approval probabilities for drugs in the pipelines of the 50 largest pharmaceutical firms.	DiMasi et al., 2010[79]

8	Investment continues into biotechnologies due to Greater Fools theory, govt. funding of R&D and industry access to the results of this funding.	Lazonick & Tulum, 2011[49]
Role of Government Policy		
1	Governmental policy instruments can help technological change by giving prominence to elements of regional innovation systems.	Dohse, 2000[80]
2	Biotechnology is an investment opportunity for future economic development.	Feldman, 2000[81]
3	Inducements to inventors to share in the profit of post development inventions is important to induce inventions out of the university.	Jensen & Thursby, 2001[50]
4	Biotechnology sectors can be promoted through policies focused on the development of the knowledge base and commercialization of it.	Calvert & Senker, 2004[82]
5	Policies that promote access to finance, infrastructure development, IP protection and skilled people are important for biotechnology development.	Rosiello, 2008[83]
6	Government science and technology policy is a key factor in explaining biotechnology performance in central and eastern European countries.	Senker et al., 2008[84]

Table 6: Drivers for Business Model Innovation – Distilled conversations with subcategories

Driving Factors for Business Model innovation		
	Strategic Decision Factors	**Study**
1	Resource factors, national regulation, patent law and government policy all figure prominently in the foreign R&D locational decision.	Taggart, 1991[85]
2	Integrating manufacturing with R&D creates a reinforcing set of capabilities and competencies.	Feldman & Ronzio, 2001[86]
3	Knowledge strategy plays a key role on business model related structural decisions and firm performance.	Bierly & Chakrabarti, 1996[94]
Relationship Orientation		
1	As norms of behavior and policy shift, academic scientists become more involved in research commercialization.	Krimsky et al., 1991[89]
2	Commercial growth of university-developed technology is driven by arrangements that compensate for social constraints on privatization.	Argyres & Liebeskind, 1998[90]
3	Biotech firms are engaged in a learning race where speed is driven by the capability of learning from collaborations.	Powell, 1998[87]
4	Though biotechnology has not delivered on its promise to revolutionize therapy R&D, with sharing-based business model changes it can improve.	Pisano, 2006[88]
5	Biotech entrepreneurs must also invest in understanding organizational and market forces to take full advantage of innovation potential.	Khilji, 2006[95]
Exogenous Market Factors		
1	Recent legislative and technology changes in the biopharmaceutical industry are causing structural changes in the industry.	Grabowski & Vernon, 1994[96]
2	Through population ecology and organizational systematics theory, one can analyze processes within firms to find business model hybrids.	Oliver & Montgomery, 2000[97]

3	Biotech business models must manage risk over long periods of time and foster integration across an array of disciplines and knowledges.	Pisano, 2007[91]
4	Given the dramatic changes in the economic climate and potentially the regulations affecting biotechnology, it is time for a new business model.	Friedman, 2010[98]
5	Business model change must manage and reward long-term risk, integrate across bodies of knowledge, and learn cumulatively over time.	Pisano, 2010[99]
6	When the knowledge base is both complex and expanding, and sources of expertise are widely dispersed, the locus of innovation is in networks.	Powel et. al., 1996[5]
7	Pharmaceutical professionals need to find new competitive—not commercial—models to succeed in the competitive stage of the industry's lifecycle.	Bernard, 2013[100]
8	Universities should adapt their technology transfer policies to conditions in its institution and regional economy.	Breznitz et al., 2008[101]
National Institutional Frameworks		
1	National institutional frameworks affecting technology transfer, finance, labor markets, and company law affect business strategies.	Casper & Kettler, 2001[102]
2	Different features of national institutional frameworks encourage firms to adopt distinctive approaches to developing innovative competencies.	Whitley, 2002[92]
3	National biotechnology policies should distinguish between the different types of biotechnology firms (Platform vs Product focused).	Bagchi-Sen & Scully, 2004[103]
4	Lack of a significant national venture funding infrastructure imposes critical limits on the growth of a biotech and business models types.	Herpin et al., 2005[93]

that drive the opportunity for business model innovation. As shown in Table 6 these publications have been divided into 4 subcategories:

Strategic Decision Factors contain 3 publications that are focused on how strategic decisions play a role in the opportunity for business model innovation. For example, where a firm chooses to place its R&D operations[85] or whether to conduct manufacturing in-house[86] are issues that can affect a firm's proximity to or receptivity toward breakthrough ideas in a novel business model.

Relationship Orientation relates to 5 publications that form a consensus on the importance that sharing and integration across biopharmaceutical industry stakeholders play in the innovation of business models.[87,88] Multiple authors agree that there exists a changing dynamic among university policies toward its relationship with industry[89,90] which in turn identifies an area of opportunity for commercial translation models.

Exogenous Market Factors include 9 publications focused on the macroeconomic, legislative and technological changes with which firms must constantly adapt. In sum, these publications help to understand the various external challenges that could be influencing adaptive business model responses. As a strong example, Pisano discusses the various business models prevalent since the 1970's.[91] Important, to his discussion is that over these 40 years, different types of business models have been prevalent due to a unique set of economic, legislative and technological factors with which they, in each respective era, were best suited to address. As these factors changed, so did the business model.

National Institutional Frameworks make up 4 publications that point to the impact that different features of national institutional frameworks play on the fertility of business model innovation. In essence, factors such as relative access to venture capital, organization of academic research training and careers, labor market regulation and governmental science policy all play a role, either restrictive or promotional, in business models innovation efforts.[92,93]

Drivers of Business Model Choice

Unlike the previous section which is framed on a macroeconomic perspective, this category consists of 29 publications that are focused on a company-specific perspective. That is, why biopharmaceutical firms,

Table 7: Drivers of Business Model Choice – Distilled conversations with subcategories

	Drivers of Business Model Choice	
	Various Dynamics Affecting Business Model Choice	**Study**
1	When imitation is easy, profits from innovation may go to complementary asset owners vs the developers of the IP.	Teece, 1986[34]
2	Due to the asymmetry of appropriation risk, for a small DBF to partner with a large company alternative strategies are needed.	Williams, 1998[106]
3	Different business models have developed to meet specific market needs and overcome specific challenges.	Fisken & Rutherford, 2002[105]
4	Spin-offs and start-ups are different with significantly different risk/reward profiles. Understanding these differences is important.	Persidis & De Rubertis, 2000[35]
5	Business model development is based on many factors including technology, goals, experience, expertise and market characteristics.	Mangematin et al., 2003[113]
6	A flexible business model can be helpful in times of macroeconomic change.	Chaya, 2005[114]
7	With platform technologies a monopoly can exist if the technology is proprietary; otherwise a firm must be active in strategic alliances.	Persidis, 2001[115]
8	There are four types of business models in Italy. These have developed due to specific market factors.	Bigliardi et al., 2005[104]
9	Business models with an attentive technology watch, the right partnership, and a sensible resource allocation policy are key to success.	March-Chorda & Yagüe-Perales, 2008[116]
10	A good business model helps balance relationships with other firms and helps it articulate and finance its activities for future success.	Sabatier et al., 2010[117]
11	Building value is a function of reducing risk. Thus choosing between a project, product or company development strategy is important.	Boni, 2012[118]
	Considerations for Vertical Integration	
1	Knowing when to vertically integrate, when to collaborate, and when to license is a critical skill requited for both new and established firms.	Pisano, 1991[107]
2	Technology platforms that address only a tiny part of the drug discovery process risk becoming optional or redundant.	Papadopoulos, 2000[36]
3	Expanding reach across the value chain is an important strategy due to costs and technological complexity.	Champion, 2001[119]
4	Tradeoffs between vertical integration and collaboration are a function of collaboration content, business planning, investment constraints and IP.	Basile & Faraci, 2013[120]
5	Variability in organization forms is related to the stringency of the regulatory approval, technological risks, and the facility costs.	Luukkonen, 2005[121]
6	Though virtual business models can be beneficial, without a cultivation of trust and commitment they can be thick with problems.	Weisenfeld et al., 2001[122]
	Impact of National Institutional Frameworks	
1	Sector specific government business development strategies are limited by national institutional structures and mentality.	Casper, 2000[37]
2	Italian biotech growth is limited due to lack of government support, low level of academia and industry cooperation and weak equity finance.	Nosella et al., 2005[108]

3	US type business models and structures must be adjusted for the national framework peculiarities of each respective country.	Bower & Sulej, 2007[123]
4	Despite what Chinese government policy is promoting, the strategy that Chinese companies follow may not be sustainable.	Malone et al., 2008[124]
5	Business models in Spain are overwhelming centered on low investment, limited R&D expenditure and incremental innovation.	March-Chordà et al., 2009[125]
6	Developing economies like Estonia have infrastructural and cultural barriers limiting them to service models.	Suurna, 2011[126]
7	Due to differences in infrastructure, dominant logic and resource access DBFs from CME and LME approach business models differently.	DiVito, 2012[109]
8	The availability of investment is a key driver of business model choice.	Hopkins et al., 2013[127]
Business Model Change Dynamics		
1	Genomics platform companies are increasingly adopting product development oriented business models to stay alive.	Rothman & Kraft, 2006[111]
2	There is an increasing business model hybridization toward product development, caused by shifts in business models after founding.	Willemstein et al., 2007[112]
3	R&D productivity/innovation is in trouble. Restructuring pharmaceutical R&D structure can improve this situation.	Garnier, 2008[128]
4	Opportunity recognition drives business model change. Recognizing this is a function of team knowledge and business capabilities.	Brink & Holmén, 2009[110]

themselves, choose the type of business model they do. As shown in Table 7 these publications can be further divided into 4 subcategories:

Various Dynamics Affecting Business Model Choice include 11 publications focused on various factors that influence the choice of business model that a firm engages. Though many factors are studied, the major factors on which authors agree is the impact that funding availability has on the type of business model chosen. For example, Bigliardi, et al.[104] along with Fisken & Rutherford[105] show how low access to investment capital channels business model choice toward service or platform models and away from therapy development based models. The former typically requires less startup capital and reaches revenue generation sooner. Other issues on which authors find consensus are the concerns that a firm has of having its intellectual property appropriated by an alliance partner.[34,106] Thus, choice of business model can be one way of mitigating this risk.

Considerations for Vertical Integration are a group of 6 publications focused on the comparative advantages of and considerations for relative levels of vertical firm integration. This collection of research encompasses the important risks and advantages of pursuing (or not pursuing) a fully vertically integrated business model.[107] For example, Papadopoulos[36] discusses how pursuing full vertical integration mitigates the risk of a platform model firm's technology becoming redundant and obsolete.

Impact of National Institutional Framework includes 8 research publications focused on revealing what impact national institutional frameworks play on business model choice and success. These authors show, for example, how dedicated biotechnology firms (DBFs) in Europe tend to pursue models focused on services and platform technologies due to the relative lack of government industry support, relatively low level of cooperation between academia and industry and weak equity finance infrastructure.[108,109]

Business Models Change Dynamics are 4 publications focused on the dynamics of why biopharmaceutical firms change their business model over time. These dynamics include new commercial opportunity recognition[110], the opportunity to capture more value from their discovery efforts by expanding toward therapy development[111] or even a natural evolutionary trend toward therapy development after founding due to resource constraints.[112]

Business Model Suggestions

Business Model Suggestions are a grouping of 13 publications that address various models for innovation in business models. Throughout these publications, there

Table 8: Business Model Suggestions – Distilled conversations (no subcategories)

	Business Model Suggestions	Study
1	(Adam Smith Model)* - An networked specialized division of labor model would allow greater decentralization and the distribution of costs.	Valle & Gambardella, 1993[134]
2	(BayPat Model)* - Direct private business partnering with public research.	Caples & Grace, 2001[135]
3	(Everybody's Baby Model)* - Network based (grant funded) research consortium to feed networked based virtual commercialization consortium.	Weisenfeld et al., 2001[129]
4	(Virtual business model)*- Focus on core competencies (product development) only. Outsource all else.	Baker, 2003[130]
5	(Patent pooling model)* - Patent pooling as "one-stop shopping" technology license platforms	Horn, 2003[136]
6	(Open innovation model)* - The fully integrated business model is increasingly considered to be unsustainable.	Hunter, 2010[131]
7	(Open sourced R&D model)* - to work, it must be able to demonstrate the same level of expertise in minutiae of R&D details as FIPCO model.	Munos, 2006[132]
8	(Lean connected business models)* – It is time for open sourced interdependency based models that use greater connectivity	Booth, 2009[137]
9	(Academic portfolio collaboration model)* - it is imperative that the public and private sectors coordinate and leveraged their collective expertise.	Melese et al., 2009[133]
10	(Hybrid business models)* - Hybridization possesses important advantages that can help offset the risk inherent in biotech.	Lowe & Gertler, 2009[138]
11	Patient-centered model - Making decisions focused on what is best for the patient will lead to better business utility.	Rao, 2010[139]
12	(Crowd sourcing model)* - Though in its infancy crowdsourcing is potentially a key tool that can be used in biopharmaceutical business models.	Lessl et al., 2011[140]
13	(Abandoned compounds model)* - proactively license out IP that are no longer being pursued.	Chesbrough & Chen, 2013[141]

**(that in parenthesis is nickname give by author of current study, not original author)*

is a consensus that due to the increasing scientific complexity of this industry, some form of sharing or decentralized distribution of responsibility is a key factor for increased productivity and lower costs. Among these is included suggestions for the use of virtual company business models utilizing high levels of outsourcing[129,130] and the use of open innovation models.[131–133]. See Table 8 below.

Competencies Required for Success

No matter the type of business model chosen, each business model requires different firm level competencies for success. As shown in Table 9 below, this category comprises 7 publications that focus on the critical nature that various firm-level competencies play in a firm's success and in its ability to utilize various business models. Specifically, this research includes the importance that experienced managers with business management competencies play in firm's success. Indeed, a firm's ability to acquire or develop these individuals is a key performance differentiator.[142] This is especially so since managers with this experience are in shortage.[143,144] Other publications include research on the importance that a firm's ability to stay aware and adaptive to changing market conditions plays on success.[145,146]

Table 9: Competencies Required for Success – Distilled conversations (no subcategories)

	Competencies Required for Success	Study
1	Strategic managers need to be aware of environmental changes so as to balance an emergent/ adaptive strategy with a deliberate strategy.	Dodgson, 1991[145]
2	High success rates for strategic alliances have been the result of a large amount of time and effort of managerial involvement.	Forrest & Martin, 1992[147]
3	Integrative competence rests on a complex set of interlinked factors that usually evolve only slowly over time. Firms must leverage this.	Henderson, 1994[148]
4	The main differentiators between biotechnology performers is complementary skills outside R&D and effective transfer of organizational learning.	Woiceshyn & Hartel, 1996[142]
5	Start-ups need experienced management, whether it be from mentors, interim managers or fulltime managers, as early as possible.	Rodgers et al., 2002[143]
6	A common feature of successful NBFs is their ability to harmonize the changing scientific and business agendas.	Ireland & Hine, 2007[146]
7	Different business models require different top echelon theory based management competencies.	Patzelt et al., 2008[144]

Table 10: Factors Impacting Organization Performance – Distilled conversations with subcategories

Factors Impacting Organizational Performance		
	Strategy Specific Factors	**Study**
1	In technological discontinuity, success positioning should emphasize technical innovation (R&D vs. Mfg. & Mkt.), external orientation and timing.	Hamilton et al., 1990[149]
2	Location is a significant predictor of firm performance as are products in the pipeline and firm citations - not just patents.	Decarolis & Deeds, 1999[166]
3	Companies should attend to six specific integrated areas to improve on performance.	Myers & Baker, 2001[167]
4	Innovator position, niche operation, and internationalization improve SMTEs' profitability.	Qian & Li, 2003[168]
5	Build in mechanism to reduce therapy candidate attrition rates as early in the development process as possible.	Kola & Landis, 2004[169]
6	Technology and biomedical companies create success cycles by the way they perform four critical business processes.	Cohan & Unger, 2006[170]
7	Making the risk management plan part of the strategic plan and planning process improves a company's ability to manage growth and to compete.	Vanderbyl & Kobelak, 2008[150]
Organizational Competencies		
1	Ability to integrate knowledge both across the boundaries of the firm and across disciplines and product areas is a source of strategic advantage.	Henderson & Cockburn, 1994[151]
2	Key factors that drive knowledge transfer drive firm performance.	Palacios-Marqués et al., 2013[152]
3	Biotech firm competencies are better predictors of market measures of performance.	De Carolis, 2003[171]
4	New pharma products will be more successful when a firm possesses the appropriate stocks of technological and product market experience.	Nerkar & Roberts, 2004[172]

5	Certain firm competencies should not be outsourced.	Mehta & Peters, 2007[173]
6	Marketing issues constitute a problem for biotechnology companies, since many lack marketing capabilities.	Costa et al., 2004[153]
7	Marketing for biotechnology companies encompasses five key challenges unique from other industries.	Rajamäki, 2008[154]
8	Marketers in the life sciences industry face novel and unique challenges.	Stremersch & Dyck, 2009[155]
9	Different types of scientist bring different types of value to a firm.	Catherine et al., 2004[174]
Strategic Alliance Usage and Management		
1	Though a diminishing return exists after some point, a firm's rate of product development is a positive function of the number of its strategic alliances.	Deeds & Hill, 1996[157]
2	The impact of networks on a firm's technological competence and its capacity to construct external linkages is crucial to its success.	Estades & Ramani, 1998[156]
3	Incumbents that focus their network strategy on exploiting complementary assets outperform incumbents that focus on exploring the new technology.	Rothaermel, 2001[158]
4	It is important for firms to maintain close ties with academia in order to maintain a source of innovation.	Nilsson, 2001[175]
5	Intimate links with large pharmaceutical firms and publicly-funded research centers are key to spin-out businesses.	Philip Cooke, 2001[176]
6	Acquisition of knowledge in technology-intensive settings is achieved through mechanisms both formal and informal, both proximate and distant.	Zaheer & George, 2004[177]
7	A strategy of relentless pipeline building appears to enhance relative and absolute performance of biopharmaceutical industry leaders.	Ahn et al., 2009[178]
Various Factors		
1	Market orientation is positively associated with profit margins, growth in market share and overall performance but not in new product success.	Appiah-adu & Ranchhod, 1998[179]
2	New product development capabilities are a function of a firm's location, quality of scientific and technological team, and independent managerial skills.	Deeds et al., 1999[159]
3	Managing corporate reputation through key determinant factors is a key business model success lever.	Grupp & Gaines-Ross, 2002[160]
4	While scientific breakthroughs drive innovation in biotechnology, market demand plays a critical role in business performance of firms.	Hall & Bagchi-Sen, 2002[161]
5	In addition to just alliances, evolutionary milestone based progression also accounts for the success and growth of a biotech firm.	Niosi, 2003[180]
6	Short term pressures to demonstrate performance are not well aligned with the long term business cycle firms need to create investor-attracting value.	Garnsey, 2003[181]
7	Economies of experience gained through alliances increase the probability of success for late stage clinical trials.	Danzon et al., 2005[182]
8	To enhance their knowledge creation capabilities firms increasingly combine internal "core" capabilities with externally acquired "complementary" ones.	Amir-Aslani, 2009[183]

9	Complementing a development portfolio with risk-reduced projects is an attractive way to ensure sustained growth.	Nickisch et al., 2009[162]
10	Due to a significant government focus on biotech science and a recognition of its commercial potential, the US has been a leader versus other countries.	Reiss, 2001[184]
Fertility Factors		
1	There are five key factors underlying regional success in the biotechnology industry.	Walcott, 2002[163]
2	Human and finance resource acquisition are the leading barriers that firms continue to face which impede their success.	Bagchi-Sen et al., 2004[185]
3	Bio-incubators differ in the level of support that they offer across exploration, examination, and exploitation oriented activities.	Cooke et al., 2006[186]
4	Porterian factors affect asset accumulation including asset interdependencies and specifying all factors under rapid technology change.	Thomke & Kuemmerle, 2002[164]
5	The business of biotech in the UK is intimately tied to the national innovation system, which in turn is dependent upon highly localized elite science.	Smith & Bagchi-Sen, 2006[187]
Survival Strategies		
1	Like evolutionary forces causing living organizations to adapt, when the financing markets become hostile, firms still have survival options.	Patzelt & Audretsch, 2008[165]

Factors Impacting Organizational Performance

Factors Impacting Organizational Performance contain 39 publications that are focused on the dynamics that impact how an organization performs in the market. As shown in Table 10 below, these publications are further divided into 6 subcategories:

Strategy Specific Factors are seven publications that focus on the strategic decisions that biopharmaceutical firms can make that affect their success. The areas on which these authors focus are varied but as examples include where in a firm's value chain to place its innovation focus (e.g., R&D, manufacturing or marketing), external vs. internal orientation and timing of key activities.[149] It also includes the role that a risk management plan should play in a firm's strategy.[150]

Organizational Competencies includes 9 publications that are focused on various aspects of a firm's ability to operate successfully in the biopharmaceutical environment. These include publications which support how a firm's competence through its employees to transfer, integrate and manage knowledge drives a firm's success.[151,152] They also include research that explains the unique marketing requirements in this industry and the competencies required for success.[153–155]

Strategic Alliance Usage and Management are a grouping of 7 publications that focus on the importance that alliances at multiple levels play on the success of a biopharmaceutical firm. These authors reach a consensus that the ability to create external linkages especially those with complimentary assets are critical to organizational performance.[156–158]

Various Factors are 10 publications each of which is focused on separate drivers of firm performance. These include the importance of independent management skills[159], the impact that good management of corporate reputation plays[160], understanding the dynamics of market demand for biopharmaceutical products[161] and the use of rNPV analysis in product portfolio risk diversification.[162]

Fertility Factors is a group of 5 research papers that are focused on the underlying dynamics that affect the fertility of the environment in which a firm is trying to succeed. Specifically, these factors include access to an outstanding research university, advocacy leadership, strong risk financing, an entrepreneurial culture, and appropriate real estate, all bound together through an intensive information exchange network.[163] It also includes research on the Porterian dynamics that can affect a firms ability engage this environment to build its firm specific value driving assets.[164]

Survival Strategies includes a single publication by Patzelt & Audretsch[165] in which they address the options that firms have to survive when financing markets become hostile, and venture capital funding dries up.

Table 11: Technical Innovation Drivers – Distilled conversations with subcategories

Technical Innovation Drivers		
	Historical Overview of Innovation Drivers	**Study**
1	Key characteristics of pharmaceutical firms have helped them remain successful innovators.	Galambos & Sturchio, 1996[207]
2	The pharmaceutical industry has gone through 5 Kondratiev type waves of technological innovation.	Achilladelis & Antonakis, 2001[38]
3	The aim of innovation strategies in biopharmaceuticals is to combine the scale advantages of Big Pharma with small biotech flexibility.	Bobulescu & Soulas, 2007[188]
Cooperation and Networking		
1	"Connectedness" to basic research is significantly correlated with a firm's internal organization and performance in drug discovery.	Cockburn & Henderson, 1998[189]
2	The biotechnology industry depends on public science more heavily than large, diversified pharmaceutical companies do.	McMillan et al., 2000[190]
3	A startup's size, access to public equity markets and position in the network of agreements affect its innovation ability.	Shan et al., 1994[191]
4	A firm's networking capability with suppliers, customers, and knowledge-creating organizations asserts a decisive influence on its innovativeness.	Chang, 2003[208]
5	For start-ups, an increase in the number of corporate partners was both positively and significantly associated with products commercialized.	Kim, 2012[209]
6	Understanding the growth dynamics and structure of collaboration networks is critical for building a leading position in biotechnology.	Gay & Dousset, 2005[210]
7	Open innovation moderates the relationship between internal learning and technological innovation capability.	Huang, 2011[211]
8	Cooperation with a competitor is a beneficial strategy that helps to increase innovation.	Quintana-García & Benavides-Velasco, 2004[212]
9	Intrafirm collaborative structures enhance innovation.	Persaud, 2005[213]
10	Strong internal multidisciplinary capabilities drive a firm's ability to form alliances which in turn promotes innovation.	Hall & Bagchi-Sen, 2007[214]
11	Similar partners in a firm's alliance portfolio contribute to firm innovation only up to a threshold.	Luo & Deng, 2009[215]
12	Individual-level collaborations by scientists within a firm positively affect firm-level patented innovation output.	Almeida et.al., 2011[216]
13	IPOs are an effective proxy to observe knowledge spillovers from university to small biotech forms.	Stephan et al., 2003[217]
14	Biopharmaceutical firms can enhance their technological performance by developing R&D activities in multiple technology clusters.	Lecocq et al., 2012[192]
15	Heterogeneity in collaboration is beneficial to innovation.	Raesfeld et al., 2012[218]
16	The preferred balance between internal and external focused innovation is a function of internal and external environment operating factors.	Mittra, 2007[219]

17	Intrafirm collaborative structures enhance innovation.	Chiaroni et al., 2008[220]
Size and Scale of Research Efforts and Corresponding Issues		
1	Large research efforts are more productive due to spillover effects from economies of scale and scope.	Henderson & Cockburn, 1996[193]
2	Increases in the "throughput" of R&D are dependent on organizational and managerial responses to systemic uncertainty.	Nightingale, 2000[221]
3	Involvement in multiscale relationships are important to innovation and development.	Birch, 2008[222]
Human Capital		
1	Success comes down to a small number of motivated extraordinary scientists with vision and mastery of a breakthrough technology.	Zucker & Darby, 1996[194]
2	Intellectual human capital heterogeneity and relationship between innovative activities along the knowledge value chain are innovation keys.	Hess & Rothaermel, 2011[223]
3	A firm's scientists are not homogenous, different types of scientists play different roles in the knowledge production and absorption process.	Subramanian et al., 2013[195]
Organization Controls		
1	Input behavior and output control enhance radical innovation. Input and output controls enhanced incremental innovation.	Cardinal, 2001[224]
2	Project teams break down formal barriers and increase innovation.	Zeller, 2002[225]
3	Stage gates can channel creativity and reduce risk, thus increasing the rate of innovation.	Smith & Schmid, 2005[196]
4	Knowledge management (KM) dynamic capabilities act as a mediating variable between KM practices and innovation performance.	Alegre et al., 2011[226]
5	The process of communication in new product development is essentially an information seeking and uncertainty reduction activity.	Frahm et al., 2007[197]
6	A company should make In-licensing decisions by trading off research time for gradually emerging information on the compound's quality.	Zhao & Chen, 2011[227]
National Institutional Environment		
1	UK corporate governance structure allows firms to more quickly adapt than German firms to rapidly changing external environmental conditions.	Casper & Matraves, 2003[198]
2	Unlike the US or EU, Japanese drug companies rely primarily on in-house drug discovery due to national framework issues.	Kneller, 2003[228]
Proximity		
1	Proximity to new technology anchor firms increases innovation output.	Feldman, 2005[229]
2	Proximity and firm boundary permeability drives innovation.	Zeller, 2009[230]
3	Ties to distant partners are positively associated with scientific impact but negatively to firm patenting.	Gittelman, 2007[199]
4	There exists complementarity of globally distributed analytical knowledge creation and locally oriented synthetic creation.	Moodysson et al., 2008[200]
5	An analytical knowledge base is important for biotech.	Plum & Hassink, 2011[231]

Knowledge Base Coherence and Competence		
1	Two properties of the knowledge base, its scope, and its coherence, contribute positively to a firm's innovative performance.	Nesta & Saviotti, 2005[201]
2	Learning and capability formation follows a co-evolutionary path dependency on successive experiences and endeavors.	Miettinen et al., 2008[202]
3	Technological capability and product innovativeness are linked.	Renko et al., 2009[203]
Models for Understanding and Managing Innovation Processes		
1	A model of innovation can be built on two dimensions and their interactions: Innovation stage and organization construct.	Bernstein & Singh, 2006[204]
2	There are two key requisites for innovation: customer insight to identify unmet need, and awareness to identify the enabling technology.	Fetterhoff & Voelkel, 2006[205]
Innovation Differences Among Firm Types		
1	There are three comparative advantages between large established firms and smaller firms.	Arora et al., 2009[206]

Technical Innovation Drivers

Technical Innovation Drivers includes 45 publications that focus on the dynamics, both internal and external to a firm, that drive its technical innovation productivity. As shown in Table 11 below, these can be divided into 10 subcategories:

Historical Overview of Innovation Drivers includes 3 research papers on the dynamics and drivers of technical innovation in the biopharmaceutical industry. These publications help to understand how this industry has historically organized itself to promote innovation including the use of scale, followed by R&D partnerships and then to industrial biocluster management.[188] Of particular interest is a study by Achilladelis & Antonakis[38], who have analyzed the history of the industry over five consecutive and overlapping technical phases since the industry's inception in the 19th century and shown why these phases came about and what caused them to change.

Cooperation and Networking includes 17 publications that focus on the benefits that cooperation plays on a firm's innovation success. Indeed, as the biggest subtopic within this category, it highlights the importance that researchers perceive cooperation to be in helping a firm to be more innovative. Key areas of consensus among these 17 publications include the benefits on technical innovation that a close relationship with publicly funded basic research institutions has[189,190] and the innovation benefits on various dynamics from collaborating with firms across the value chain.[191,192]

Size and Scale of Research Efforts and Corresponding Issues consist of 3 studies that show the benefit that firm size has on technical innovative output. For example, Henderson & Cockburn[193] make a case for larger research efforts being more productive due to their economies of scale and scope and the resulting increase in spillovers and absorptive capacity.

Human Capital consists of 3 publications that focus on the dynamics that a firm's scientific human resources play on a firm's innovation output. This includes the impact that different scientist types play on the innovation process including the important role of star scientists.[194,195]

Organizational Controls include 6 papers that span various methods of organizational control that firms can use to enhance innovative output. As two examples, it contains research on the use of stage gate controls to channel creativity and reduce risk in innovation management[196] and the management of communication across the firm to enhance innovation.[197]

National Institutional Environment is a subtopic containing 2 publications that, like in previous categories, shows how technology innovation specifically is affected by key underlying national structures and culture.[198]

Proximity is a grouping of 5 publications that help to understand the effect that geographical proximity to certain institutions and bioclusters has on a biopharmaceutical firm's innovation in both basic and applied research.[199,200]

Knowledge Base Coherence and Competence are a grouping of 3 papers which agree about the complementary importance that a firm's scientific and technological competence and experience play in its innovativeness.[201–203]

Models for Understanding and Managing Innovation Processes consists of 2 publications each providing a

model that a biopharmaceutical firm can use to manage its innovation processes.[204,205]

Innovation Differences Among Firm Types is the last in this category and consists of a single study comparing the differences among organizational types showing how vertically integrated firms currently tend to be the most innovative.[206]

Table 12: Alliances/Cooperation/Collaboration – Distilled conversations with subcategories

Alliances/Cooperation/Collaboration		
	Spatial Proximity Factors	**Study**
1	When knowledge is transmitted through formal ties between researchers and firms, geographic proximity is not necessary.	Audretsch & Stephan, 1996[232]
2	Even though functional proximity is facilitative, global knowledge collaboration is indispensable for most DBFs.	Moodysson & Jonsson, 2007[233]
3	Geographical proximity has become less important for inter-organizational collaborations.	Hermann et al., 2012[251]
Benefits of Relationships		
1	University-industry research relationships have both benefits and risks for academic institutions.	Blumenthal et al., 1986[31]
2	Biotech industry support for university research is significant and growing in addition to government still remaining the biggest supporter.	Blumenthal et al., 1986[32]
3	Key reasons that industry engages academia are access to commercially viable innovations, knowledge spillovers and talented people.	Blumenthal et al., 1996[234]
4	Companies with university linkages have lower R&D expenses while having higher levels of innovative output.	George et al., 2002[235]
5	NSF-affiliated university scientists also engage in interactions with industry that are conducive to non-economic knowledge transfer.	Boardman, 2008[252]
6	NBFs rely on their own hierarchies and on external network exchanges for sourcing scientific knowledge.	Liebeskind et al., 1994[253]
7	Motivations for collaboration stretch beyond just financial and new technology acquisition to include the development of tacit knowledge.	Senker & Sharp, 1997[254]
8	Firms adapt to radical technological change via interfirm cooperation with new entrants when the incumbents have complementary assets.	Rothaermel, 2001[6]
9	Strategic research partnerships help small firms with size-inherent disadvantages like deficiencies in control, capabilities, and context.	Audretsch & Feldman, 2003[236]
10	Establishing inter-firm collaborative relationships is considered vital as commercial biotechnology gains independent from academic research.	Suarez-Villa, 2004[255]
11	"Cycle of Discovery" model, shows how exploitation and exploration build on each other in an evolutionary chain of development.	Gilsing & Nooteboom, 2006[256]
12	For a biotech company, partnerships and collaborations can be a key factor for success, especially for new firms.	Marks, 2009[1]
13	Collaboration, specifically with university scientists, is important for continued success in R&D and product/process oriented biotech firms.	Hall & Bagchi-Sen, 2001[257]

14	The M&A activity of firms reveals their needs of achieving improved innovation, increased revenue and product diversification.	Pavlou, 2003[258]
Governance and Relationship Management		
1	Strong relationships between partners is a more effective deterrent to opportunism than the creation of hostage investments or contracts.	Deeds & Hill, 1999[237]
2	Pooling small biotechs together can mitigate against opportunism risks from bigger partners.	Williams, 2005[2]
3	In alliances, an equity link can serve as a trust substitute.	Filson & Morales, 2006[238]
4	The allocation of control rights to the R&D firm increases with the firm's financial resources.	Lerner & Merges, 1998[240]
5	The market tends to favor earlier stage alliances which are consistent with an underlying healthy pharmaceutical research pipeline.	Higgins, 2007[259]
6	Aligning and implementing mechanisms of control are an important part of inter/intra firm project success.	Baraldi & Strömsten, 2009[239]
7	The greater a firm's relative scarcity, superior complementarity, and relative bargaining ability the greater share of control rights it can win.	Adegbesan & Higgins, 2010[260]
8	Due the issue of moral hazard and credence goods, collaborative R&D is at high risk for failure. Control rights can mitigate against this.	Kloyer, 2011[261]
9	In face of a potential collaboration, termination governance can be designed so as to maintain incentive for continued participation.	Panico, 2011[241]
10	Alliance contracting problems are solved through ownership allocation, explicit contractual clauses, and relationally incentivized implicit contracts.	Robinson & Stuart, 2007[262]
11	Managing post-formation alliance dynamics and flexibly adapting partnerships are crucial aspects of collaborative strategy.	Reuer, Zollo, & Singh, 2002[263]
12	Alliance failures in pharma/biotech can be reduced through three key measures.	Laroia & Krishnan, 2005[264]
13	Different inter-organizational governance structures are appropriate for different tasks and environments.	Pisano, 1989[265]
14	A hybrid post-acquisition integration approach is important for pharmaceutical companies acquiring biotechnology companies.	Schweizer, 2005[266]
Dynamics of Relationship Formation		
1	In biotechnology, networks of collaborative ventures have developed as the primary institutional arrangement governing exchange and production.	Powell et al., 1996[267]
2	Motivations for cross-border alliances include manufacturing, supply and market access and equity investment for domestic alliances.	McCutchen et al., 1998[268]
3	Alliances are used as organization opportunities for learning and growth albeit they are used in a non-linear manner.	Oliver, 2001[242]
4	Different types of alliances are motivated by different goals.	Rothaermel & Deeds, 2004[243]
5	Early R&D stages alliances are driven by need for technical competence. Later by the need for expertise in gaining regulatory approval.	McCutchen et al., 2004[269]

6	Continued low productivity from Big Pharma should enhance the ability of biotech companies with high-quality products to attract funding.	Czerepak & Ryser, 2008[270]
7	A firm's appropriation environment and governance capabilities strongly influence portfolio-level collaboration mode choices.	Aggarwal & Hsu, 2009[244]
8	The quality of firm knowledge base, as measured by depth and breadth, has sophisticated influences on technology collaboration.	Zhang & Baden-Fuller, 2010[245]
9	While collaborative arrangements with universities are common, those with such linkages are not always the firms experiencing success.	Levitte & Bagchi-Sen, 2010[271]
10	In partner selection decision making, partners with the ability for value creation might use that ability to appropriate value.	Diestre & Rajagopalan, 2012[246]
11	Firms with an in-house innovation history on one or few products are most likely to be attractive alliance partners with large economy firms.	De Mattos et al., 2013[247]
12	Collaboration should always be observed as coexisting with dynamics of competition.	Oliver, 2004[272]
13	The basic–applied dualism to represent research activity type and the public–private dualism to depict organizational nature are redundant.	Lynskey, 2006[248]
14	The dynamics of university tech transfer offices are changing.	Blakeslee, 2012[249]
15	Most collaborations within Canada are with local universities as well as with foreign universities.	Bagchi-Sen et al., 2001[273]
16	Technological opportunity, market conditions, and innovation policy are key factors driving increase in Japanese firm-university collaborations.	Motohashi, 2007[274]
17	Firms with multiple in-licensing agreements are more likely to attract revenue-generating alliances with downstream partners.	Stuart et al., 2007[275]
18	Dense cluster location, alliances with local research institutes, and a central position in national research network drive int. research alliances.	Al-Laham & Souitaris, 2008[276]
19	Firms use different organizational modes for relationships with different partner types with the aim to exploit technologies and knowledge.	Bianchi et al., 2011[250]
20	Collaboration and the factors that support it are an important factor driving product innovation.	Bagchi-Sen, 2004[277]

Table 13: Absorptive Capacity – Distilled conversations (no subcategories)

	Absorptive capacity	Study
1	Biotechnology firms differ in their ability to benefit from collaborative relationships based on their internal technological knowledge.	Arora & Gambardella, 1994[278]
2	This is a strong correlation between the diversity of firms' development efforts and the success probability of individual projects.	Cockburn & Henderson, 2001[281]
3	Portfolio characteristics and absorptive capacity jointly influence innovation performance.	George et. al., 2001[282]
4	Firms need a certain level of employee skills and R&D continuity to internalize the external knowledge that has been acquired.	Xia & Roper, 2008[279]
5	Absorptive capacity enriches work with experts.	Fabrizio, 2009[283]
6	Knowledge breadth and centrality of R&D structure positively influence its absorptive capacity, its propensity to form alliances.	Zhang et al., 2007[280]

Alliances/Cooperation/Collaboration

Alliances/Cooperation/Collaboration is a collection of 51 publications that focus on various benefits, challenges and dynamics relevant to this industry in the formation and managing of alliances and various forms of cooperation. As shown in Table 12 below, these can be divided into 4 subcategories:

Spatial Proximity Factors are a grouping of 3 publications that focus on the dynamics that govern the functional and geographic proximity in biopharmaceutical firm relationships. In sum, these publications help to understand the relationship between the type of knowledge being shared and its associated need to be geographically close. That is, the sharing of tacit knowledge tends to require closeness whereas encoded knowledge is not as sensitive to this and can be effectively shared between alliances over much greater geographical areas.[232,233]

Benefits of Relationships comprises 14 publications that address the benefits that firms derive from various manner of cooperative relationships. One key area of consensus among these authors is the multiple benefits that an academic relationship can bring to a commercial biopharmaceutical company including access to commercially viable innovations, talented human resources, and lower R&D costs.[234,235] Another, similar to that above, is the general benefit firms derive from formal and informal cooperations with each other including the development of new tacit knowledge and complementary capabilities.[1,236]

Governance and Relationship Management is made up of 14 publications that focus on the how firms that are in alliances manage key important aspects of their relationships with other firms. These include a focus on how to protect against opportunism, where Deeds & Hill[237] find the use of close relationships more effective than contractual means or hostage equity positions and where Filson & Morales[238] find that an equity position serves as an effective trust substitute. It also includes a large grouping of specific research on control rights in alliances, where Baraldi & Strömsten[239], Lerner & Merges[240] and Panico[241] discuss the dynamics of aligning and implementing mechanisms of control between cooperating firms.

Dynamics of Relationship Formation is a grouping of 20 publications exploring various dynamics of alliance formation *(previous categories focus on the benefits, not on the process/dynamics).* These publications include various factors influencing alliance decisions including what key issues influence organizations to enter into alliances such as opportunities for learning and growth or attempts to maximize product development performance[242,243], key internal firm issues and capabilities that influence alliance choice such as governance capabilities or appropriation culture[244,245] and issues affecting alliance partner selection such as a demonstrated history of value creation and in-house innovation.[246,247] This subtopic also includes research on other issues including changing norms in commercial academic relationships[248,249] and a typology of organization mode choice for alliances.[250]

Absorptive Capacity

Absorptive Capacity consists of 6 publications that address the enabling effects that the breadth and depth of a firm's existing technical knowledge plays on its ability to utilize external knowledge. This includes for example research on how absorptive capacity enriches collaborative relationships[278,279] and a publication on the factors that drive a firm's absorptive capacity such as broad knowledge base and centralized R&D organization.[280]

Dynamics of Investment Interest

Dynamics of investment Interest is a grouping of 13 publications that focus on various issues and factors that drive investment interest from stakeholders into biopharmaceutical firms. The largest grouping focuses on factors that drive investment interest from potential alliance partners. These factors may include having a product late in the development stage or approval process[284] or willingness to give the larger partner management control.[285] Other groupings include a focus on what factors drive venture capital investor interest such as close relationships and geographic closeness.[286] See Table 14 below.

Clusters

Clusters is a group of 17 publications that focus on the prerequisites and factors important to geographic cluster formation and the benefits associated with participating within them. These include the co-existence of both world-class scientific resources with the complementary business resources to translate this knowledge into a commercial product.[297] This pooling of resources focused on similar technology development provides firms the advantage of a common labor pool and access to key markets and customers[298] and importantly access to key basic research.[299,300] Moreover, as is present in other categories, this category also includes research on how national institutional frameworks affect clustering[301] and includes research that shows how information flows and relationships within a cluster are a holistic group of interacting and overlapping dynamics.[302,303] See Table 15 below.

Table 14: Dynamics of Investment Interest – Distilled conversations (no subcategories)

	Dynamics of investment Interest	Study
1	Foreign alliance partners are attracted more to products late in the approval process rather than products already approved or early stages.	Coombs & Deeds, 2000[284]
2	Among other trends, collaborations are moving away from buying the golden goose and instead buying the egg.	Belsey & Pavfou, 2005[287]
3	Despite public investment interest in biotechnology waning, venture capital remains steadfast in its interest.	Lee & Dibner, 2005[288]
4	Alliances where the firm has greater management control are associated with greater acquisition of financial capital by the biotech firm.	Gopalakrishnan et al., 2008[285]
5	Different risks attract different investor types.	Champenois et al., 2006[289]
6	Relationship between R&D and finance are based on ties fostered in regions with extensive two-way communication among parties.	Powell et al., 2002[286]
7	Financial markets invest in firm-specific capabilities.	Deeds et al., 1997[290]
8	Companies with deep therapeutic product pipelines protected by sound IP are becoming ever more attractive targets for M & A.	Sowlay & Lloyd, 2010[291]
9	Legally independent affiliates of biotech companies, special purpose entities, once supported the development of several blockbuster drugs.	Schiff & Murray, 2004[292]
10	Venture capital firms play a more pronounced role in fostering successful firm exit than new firm entry.	Burns et al., 2009[293]
11	Founding Angels (vs. Business Angels) could be a financing model solution.	Festel, 2011[294]
12	FDA regulation is preventing innovative firms from economic success in the marketplace. Thus they should seek out a variety of financing options.	Roberts & Hauptman, 1987[295]
13	Though Phase II seems the optimal time for drug licensing, more value may be captured if done earlier.	Kalamas & Pinkus, 2003[296]

Networking

Networking is collection of 16 publications that focus on key dynamics of network formation and factors impacting a firm's utilization of these networks. See Table 16 below. In general, this collection of research makes clear that many factors exist that affect network formation in the biopharmaceutical industry and that network participation drives firm success. Key among these include the role that academic inventor-scientists play, through not only their own direct human capital contribution to a firm, but also through the contribution of their important social capital by which firms gain credibility and access to the greater network.[314] Indeed, the strength of this social capital can be considered an important strategic resource.[315] This collection of research also makes clear that as a firm's network develops, a specialized sub network develops which increase the options and opportunities to firms.[316] Particularly interesting is Owen-Smith & Powell's[317] use of a channel and conduit metaphor to describe the different types of knowledge spillovers that occur through network participation.

DISCUSSION

Through a systematic literature review, this research has identified, reviewed and categorized 305 academic research publications between the years 1976 and 2013 that are highly relevant to understanding the dynamics for business model innovation in the biopharmaceutical industry. Through the 12 separate areas of research identified, key issues for understanding business model innovation have been highlighted, and five specific areas of opportunity have been proposed.

Table 15: Clusters – Distilled conversations (no subcategories)

	Clusters	Study
1	The main agent of attraction to new firms to enter a cluster is the presence of a strong science base at that location.	Prevezer, 1997[304]
2	The generation of a successful regional cluster requires the existence of high scientific talent and factors to commercially translate this knowledge.	Audretsch, 2001[297]
3	Companies active in the same technology, cluster geographically due to easier access to agglomerated resources.	Niosi & Bas, 2001[298]
4	Industries cluster because of difficulty to leverage the social ties necessary to mobilize essential resources when they reside far from those resources.	Stuart & Sorensen, 2003[305]
5	Policies that complement networking initiatives with an analysis predicted on marketplaces may increase the innovative capacity of clusters.	Casper & Karamanos, 2003[306]
6	Due to many factors, biotech firms in Israel tend to cluster around leading research institutes.	Kaufmann et al., 2003[299]
7	Active regional science policy is beginning to prove a key precondition for regional development visions in the knowledge economy.	Cooke, 2004[307]
8	Firm location to a cluster has much to do with access to the frontier of knowledge.	Mytelka, 2004[300]
9	It takes a whole community to build a biotechnology cluster but once built; the cluster can achieve a sustaining life that strengthens itself.	Nelsen, 2005[308]
10	Sustainable clusters are linked to the existence of dense social networks across key personnel supporting career mobility.	Casper, 2007[309]
11	Cluster advantages arise only after some years of existence in a cluster, and the companies have learned ways to "grasp" cluster advantages.	Geenhuizen et al., 2007[310]
12	For multiple reasons, it is advantageous for SMEs in France to cluster around its industrial/academic nexus.	Lemarié et al., 2001[311]
13	R&D localization is highly influenced by the comparative advantages assessed on national institutional framework structures and dynamics.	Jommi & Paruzzulo, 2007[312]
14	The foundation and growth dynamics of biotech firms in the BioRegion Rhine-Neckar Triangle are a function of factors unique to Germany.	Krauss & Stahlecker, 2001[301]
15	Dynamic regions are characterized both by dense local social interaction, knowledge circulation and strong out of region connections.	Gertler & Levitte, 2005[302]
16	Clusters are larger than their core industries and encompasses complementary agents cutting across industry affiliations.	Waxell, 2009[303]
17	Clusters should not be seen as isolated but as integrated into the biosciences research, medical and healthcare systems.	Cooke, 2005[313]

Opportunity for Innovation: Key Issues for Understanding

This research has revealed that a necessary prerequisite to understanding the opportunities for business model innovation in this very complex industry is to first understand the reason for the prevalence of this industry's historic business models and key national level differences that are affecting its innovation and commercialization success.

From its beginnings in the 19th century, the modern biopharmaceutical industry started as an industry using stochastic trial and error oriented research methods based primarily on chemistry and later organic chemistry. During this time a fully integrated business model

Table 16: Networking – Distilled Conversations (no subcategories)

	Networking	Study
1	Academic scientists are a key factor in firms because they mediate social capital which drives embeddedness in the scientific community.	Murray, 2004[314]
2	Geographic propinquity and organizational form alter the flow of information through a network.	Owen-Smith & Powell, 2004[317]
3	The indirect network position of a firm (or the position of the firm within its network of indirect ties) is an intangible strategic resources.	Salman & Saives, 2005[315]
4	Even weak contacts with universities are conducive to transferring technology from research to industry thus enhancing tech innovation.	Roberts & Hauptman, 1986[33]
5	Subnetworks condition the choices available thereby reinforcing an attachment logic based on differential connections to diverse partners.	Powell et al., 2005[316]
6	External sourcing is not always a function of strategy but can also be opportunistic. Moreover, it is not always reliable as a source.	Lane & Probert, 2007[318]
7	The science-technology base, research funding, firms' business models, and competitor strategies account for biotech networking patterns.	Hendry & Brown, 2006[319]
8	The structure of the R&D network in pharmaceuticals is driven by a combination of a purely random and a cumulative process of growth.	Riccaboni & Pammolli, 2003[320]
9	Within the BioNet (Bavaria) regional network, many companies are only loosely connected to the network's dense core. Core-Periphery Structure.	Rank et al., 2006[321]
10	Firms with high exploratory innovation output have short path indirect access to many firms and operate in dense industry alliance networks.	Karamanos, 2012[322]
11	The "open architecture" of biotech firms facilitates product development. However, the lack of a well-developed governance structure poses risks.	Powell, 1999[323]
12	Participation in networks is found to vary according to the firm's size, stage of development and its sector of activity.	Traoré, 2006[324]
13	Interfirm R&D partnerships are increasing in prevalence. Now, pharmaceutical firms dominate the centrality nodal positions.	Roijakkers & Hagedoorn, 2006[325]
14	Exposure factors involved in the network development occur as a result of the firm's existing network and networking resources.	Kaufmann & Schwartz, 2009[326]
15	By staying responsive to developments in networks, firms are ready to act on network resources when windows of opportunity appear.	Tolstoy & Agndal, 2010[327]
16	The coordination of networks can be specialized, with the emergence of Dedicated Coordinating Firms.	Sabatier et al., 2010[328]

(FIPCO) prevailed. Among the key reasons for this were the knowledge accumulation advantages that large economies of scale and scope gave an organization when all of its knowledge was contained and containable "in-house." Indeed, as evidenced through the successive and overlapping Kondratiev type long waves of technological focus, that Achilladelis & Antonakis[38] extensively describe, the FIPCO model was well suited in its ability to allow the pharmaceutical industry to take advantage of its evolutionary accumulated expertise in organic chemistry and channel it toward the discovery of new products and product classes.

Then, starting in the late 1970's everything changed with the appearance of the first biotechnology-based medical therapies. Their presence and utilization represented a conundrum for organic chemistry based pharmaceutical companies. On the one hand, this new technology offered them an opportunity to bring new innovative therapies to market by offering a complementary alternative to their prevailing random discovery

based methods and potentially a way to reduce the time and cost to bring a therapy to market approval. However, it also exposed a disruptively innovative threat since biotechnology companies using these new therapies could themselves develop as an independent and competitive industry. Indeed, this threat was quite real since the prevailing FIPCO models that had been so successful for them for over 100 years would not necessarily prevail in this new fragmented technological environment. FIPCO models were built on the advantages of having a very deep knowledge in predominantly one key technological area, organic chemistry. This R&D was conducted mostly within the walls of their own organizational R&D units with only relatively limited need to be actively engaged with external research centers around the world. However, a shift to an externally focused R&D paradigm was exactly what this new decentralized biotechnology focused world was requiring. Biotechnologies, (initially molecular biology and genomics) were a new complex knowledge base and required such adaptive responses that firms could capture only fragments of the new technologies.[41] In addition, it was dispersed in universities and basic research centers around the world. As a result, small specialized product and service firms were best suited to develop and commercialize these new various biotechnologies, leading to what Pisano[3] would call an archipelago of specialization.

Complicating matters was that all countries were not equally ready to take advantage of these new technologies. Because these new biotechnologies follow a co-evolutionary progression of scientific, technical, industrial, clinical and regulatory changes, the institutions governing these respective changes must coordinate their efforts.[40] However, national institutional structures and national institutional culture play an important role in how scientific institutions and commercial entities coordinate and respond to new technologies. As countries typically differ on welfare systems, employment law and conventions, training systems, financial markets, and legal systems[92], the comparative mix of these factors affect the relative rates of innovation and the fertility of different types of business models.

One key aspect of this is the important role that academics perceive themselves to have in commercializing their technologies and, in turn, how active universities are in seeking commercial opportunities for the science that derives from their personnel. In general, U.S. universities have a strong culture of collaboration with industry, European universities less so.[43] Moreover, the direct involvement of European academic researchers in commercial endeavors is relatively limited versus that of the US researchers.[54] This is an important key in the understanding the opportunities for business model innovation in this industry due to the cultural and structural roadblocks that exist. If an academic scientist has little desire to pursue anything other than his or her own career enhancing publications or the university fails to provide a healthy level of support in pursuing IP protection for its researchers' discoveries, many important ideas and innovations may never see the commercial "light of day. Indeed, this relationship to academia is a particularly important topic of interest due to the changing Mertonian norms and dualisms of relationships caused by traditionally "independent" academia becoming more intertwined with biopharmaceutical commercialization.[248]

Intertwined within these academic perceptions are the national level legislations that influence the private commercialization of publically funded research. In the U.S.A., among many key legislations that have been historically instrumental in the lead-up to its present ability to be a world leader in biopharmaceutical innovation and commercialization are the 1862 and 1890 Morrill Act leading to applied science focused land grant universities[99,329], 1980 Baye-Dole Act which opened the way for federally funded research to be owned and commercialized by the inventor[50], the Diamond vs. Chakrabaty ruling by the US Supreme Court that genetically engineered life forms were patentable[87], and the 1984 NASDAQ listing requirement reforms.[39] Though the U.S.A. has been the leader in enacting these liberalizing governmental actions, other nations are only slowly following suite. These include, for example, Germany's 2002 adjustments to its Arbeitnehmererfindungsgesetz (ArbnErfG), its employee discovery law which attempted to create Baye-Dole Act similarities.[v]

Another key national structure issue affecting the fertility of business model innovation is the relative strength of a nation's private equity investment market. With a relatively weak equity capital investment market, such as those of continental Europe where bank driven forces prevail, new start biopharmaceutical companies are challenged to find the large amount of investment capital needed. This leads to a prevalence of choosing business models that are service or platform based since they require less capital versus a therapeutic development focused model. Lastly, is the role played by differences in national labor markets. From an industrial perspective, small and medium-sized enterprises need flexibility in their labor resources since a company may need to react quickly to an opportunity or threat. Therefore, the relatively protected and less flexible labor markets of the

v Unlike the Baye-Dole Act which moved the ownership of an invention closer to the inventor themselves, the 2002 ArbnErfG changes moved the ownership to the employer with the promise of employee compensation upon successful IP licensing/sale.

world outside of the US can be a challenge to a firm that needs to quickly downsize.

Five Areas of Opportunity for Business Model Innovation

External orientation

By far the most common theme identified in this research is how important an external orientation is as a source of advantage in the modern biopharmaceutical industry. Specifically, this includes openness to sharing and mining for ideas outside of the firm through a focus on collaboration and learning. This is in stark contrast to the historical role that a full vertically integrated business model played as an advantage for success in this industry with its relatively stronger internal focus. Indeed, this body of research is highly focused on gaining the advantages of full vertical integration but as a decentralized entity through optimizing the advantages and efficiency of diverse relationships to attain the same end and at a lower cost. As mentioned earlier, [5] show in their research that when the knowledge base of an industry is both complex and expanding, and the sources of expertise are widely dispersed, certainly the case for today's biopharmaceutical industry, the locus of innovation will be found in networks of learning, rather than in individual firms. Thus, the cumulative data from this review appears to show that a firm's ability to thrive in this network will be influenced by its ability to operate with a business model that competitively excels in its effectiveness to operate with an external focus.

Learning capabilities

Now, key to this ability to operate externally is a capability to recognize and absorb new opportunities when they appear and to learn cumulatively over time.[110] This is driven in part by the scope and coherence of a firm's knowledge base[201] which follows an evolutionary path dependency of successive experiences and endeavors.[202] This absorptive capacity is critical to innovation success. It is a key factor that allows a firm to recognize, assimilate and to exploit different types of knowledge[282] and is often the differentiator for success among firms. Thus, it is not only important to develop broad and deep networks with external experts but more so, it is important to improve absorptive capacity to utilize this expertise. Thus a business model must include a strong network development and maintenance capability. This should include relationships with stakeholders at all levels of the industrial value chain especially with those in academia as it provides a strong source to commercially viable innovations, knowledge spillovers and talented people.[234]

Of particular importance in this ability are policies focused on developing a well networked technical team on both formal and informal levels[177] and a team that is committed to broadening their learning so as to enhance their absorptive capacity to capture knowledge spillovers.[193] Included in these policies, for example, should be assurances that this team consists of the right composition of scientist types, what Stokes[330] and Subramanian[195] call "Pasteur" scientists and "Edison" scientists. "Pasteur" scientists are applied scientists who also have a strong basic research focus. Their higher publication rates give a firm better informal access to university-based academic scientists. "Edison" scientists, on the other hand, are pure applied researchers. They excel at patenting and translating basic research. This recognizes that a firm's scientists are not homogenous and that they play different roles in the knowledge production process and interact differently with the knowledge absorption process. Indeed, the findings of this research have been consistent with how this importance can not be understated since it is a critical dynamic to the virtues of solid network development. The value of a key scientist is not just that of his scientific capital contribution but also that of his social capital. This helps not only with obtaining greater embeddedness within relevant networks and the scientific community [314] but also with conveying a signal of confidence to other relevant stakeholders such as investors and alliance partners.

Cluster participation

Complementary to the development of these learning capabilities is firm location, particularly a location that is close to a strong and technologically relevant biocluster. Such, a cluster is one that is anchored by a strong science base typically represented by a top science university or universities[304] whose gravity attracts the complementary orbit of multiple other stakeholders necessary for commercial success. These stakeholders include finance resources, a local supportive government providing fertility enhancing resources[297], access to markets and customers[298] and generally a dense social network of key personnel that, among other advantages, supports access to a stable common labor pool through its provision of career mobility and sustainability.[309] Thus, the importance of cluster participation will remain particularly critical as the trajectory of business models continues to follow a decentralization pattern of specialized players relying on alliances and outsourcing.

Qualified business management team

Though much of the research revealed in this review is focused on the importance that an external orientation and acumen plays on firm success, including the importance of key characteristics of the technical and scientific team, a clear separate body of work is focused on the importance that a qualified independent management team plays on the ability to commercialize innovations. In this industry, this is indeed of critical importance since, even with an innovative new technology, a company may still fail commercially without the right management expertise on board. However, it can be a significant challenge for a cash-strapped new start biopharmaceutical company to obtain and retain top commercial expertise due to the lack of financial resources and also to the perceived career threat to that person of onboarding such a high-risk endeavor. However, though the research from this review shows that these challenges can be mitigated through the use of strategic alliances and a strategy focused on strong network development[156], the shortage of qualified, experienced business managers remains a problem.

Organizational controls

Lastly, this research reveals that effective organizational controls are critical for any business model to be effective in this highly complex and high-risk industry. These controls will be an important tool to address both internal and external dynamics of survival and success. Internally, they are important to enhance communication and knowledge proximity across the firm.[225] For example, the use of stage gates can be used to channel creativity and reduce risk[196] including prudent resource allocation. Externally, in the increasingly fragmented nature of this industry, many challenges have to be overcome if indeed a firm is to operate at similar economies of scale and scope as would a fully integrated company. They include the tendencies toward opportunistic behavior that exists in alliances and relationships.[2,237] Thus, in addition to formal mechanisms to dissuade this behavior such as the use of contracts or ownership equity positions,[238] companies will need to develop other creative mechanisms to complement these tools.

CONCLUSIONS

This paper systematically captures and inductively explores a defined set of academic literature for insights into how the biopharmaceutical industry, through the use of business model innovation, could continue to drive its technical innovation toward new and innovative therapies while at the same time reduce the significant costs and time to market. What is found is that although no "magic bullet" of a single clever new business model has been revealed, five areas of opportunity have been identified that could be the source of incremental innovation in this area. Continued focus in these five upstream value chain areas have the ability to unleash greater potential value from networked collaboration among the widely scattered sources of expertise in this industry including the ability for a firm to recognize, functionally absorb and utilize the fruits of these collaborations and govern the required process successfully. However, as this research reveals, any innovation must incorporate national institutional structure limitations on these innovations, such as the creation of appropriate incentives for academic researchers to push out their IP while simultaneously addressing their career linked publication needs.

FURTHER RESEARCH

Like explicit research on business models as a standalone concept, business model research in the biotechnology industry is still relatively young. Indeed, this research reveals that only since the year 2000 have business models been an explicit focus in biopharmaceutical research. Moreover, of the 68 publications identified in this systematic review that specifically use the word "Business Model," there remains no clear consensus of what exactly is meant by this term, some implicitly mean revenue model, others mean strategy while others are referring to organizational structure. Therefore, this field could benefit by research focused on the comprehensive defining nature of the biopharmaceutical business model itself versus a specific component or dynamic of it. Also useful would be empirical comparative research on performance dynamics between business models, especially relating to external cooperation mechanisms with longitudinal or geographical components.

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Article

Bioinformatics Patents — The Challenges

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ABSTRACT

This paper examines the problems and complexities created by the patent regime as well as challenges posed by accommodating new technologies like bioinformatics in its traditional patent framework. It examines and analyses the standards of biotechnology and software patents followed in the US, EU and India based on judicial precedents and its implications on bioinformatics patents, analyses bioinformatics patents granted in the United States and European Union and examines the Indian Patent Manual and the patentability standards followed in India.

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INTRODUCTION

The future development of biotechnology depends on bioinformatics. The enormous amount of data or information generated using modern biotechnology techniques needs to be effectively used. Bioinformatics tools can help store, manage, access and process the accumulated information. Thus, it is imperative for the biotechnologist to learn about bioinformatics tools to effectively use them in research. Commercialization of bioinformatics tools like databases, software, hardware and algorithms involves many competing interests since the commercial opportunities in genomics, proteomics, and pharmacogenomics have attracted pharmaceutical, biotechnology and IT giants.[1] Successful protection of innovations in bioinformatics, through intellectual property protection, is crucial to the continued advancement of the field of bioinformatics and the commercial viability of the businesses.

We have already witnessed the problems like denying access to patients for diagnosing cancer because of patents granted to BRCA genes, emerging from lowering of the standards of patentability criteria for accommodating new technologies like biotechnology and computer-related inventions.[1] This paper examines the problems and complexities created by the patent regime and the challenges posed by accommodating new technologies like bioinformatics in the traditional patent framework. In the context of bioinformatics patent applications filed in the Indian patent office it has to be examined how patentability standards been applied by Indian Patent office in case of bioinformatics patents.

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Bioinformatics – A Blend of Biotechnology and Information Technology

Bioinformatics techniques involve the algorithms and programs that run everything from a spot-picking microarray machine (simple), to a genome-wide Blast search (medium), to complex protein modelling software packages (advanced) that distinguish bioinformatics from other scientific disciplines such as biology, computer science, mathematics, etc.[3] PERL, BSML (bioinformatics sequence markup language),[4] BIOML (biopolymer markup language)[5] and PYTHON[6] (which is a complete subject-oriented scripting language) are some of the languages used in the above-mentioned computer program. Super computers are used in bioinformatics for creating algorithmic models that mine databases of DNA sequence information[7] A large number of studies have concentrated on genomic algorithms (GAs) to process microarray data.[8]

A simple bioinformatics technique is a blend of IT and biotechnological techniques. For example, in a given nucleotide sequence, the probable amino-acid sequence of the encoded protein can be determined using translation software. The sequence research technique helps to find the homologues to model the structure of the specific protein on experimentally characterized structures. Finally, docking algorithms could design molecules that bind to the model structure, leading the way for biochemical assays to test their biological activity on the actual protein and finally to development of the desired drug.

Thus, these programs or algorithms as well as software and hardware form the basis of most bioinformatics techniques and they underpin most of the sequencing projects. Patents on bioinformatics are typically those on process or method and, relating in some aspect to computers or software and being typically associated with the catch phrases "data mining" or "predictive modelling."[9] This includes lines of code and algorithms that relate to an application, specially designed hardware, software, data structure and the user interface.

Importance of Bioinformatics and its Applications

Bioinformatics is a computer-assisted interface discipline dealing with the collection, compilation, storage, management, access, processing and representation of information in order to understand life processes in healthy and diseased states and find new treatment techniques or better drugs.[10] If most of the preliminary data can be gathered via bioinformatics research efforts the cost involved in DNA sequencing can be substantially reduced, along with the need for testing on cells and animals.[11]

The field of genomics and proteomics relies on bioinformatics, i.e., automated protein and DNA sequencing technologies that enable life scientists to transform an enormous amount of complex biological data into useful information.[12] In addition to gene prediction (genomics) and genome architectural analysis, bioinformatics resources and tools have been applied to understand pathogen genomes for the discovery of virulence factors and effective drug targets, for the identification of human disease genes, for the general understanding of the genome expression, as well as for the realization of the concept of personalized medicine (pharmacogenomics).[13] Thus, genomics,[14] pharmainformatics, pharmacogenomics and proteomics, as well as other emerging areas such as metabolomics, transcriptomics and computer-aided drug design research,[15] are the products of bioinformatics and have transformed this field of life science from an academic undertaking to a massive commercial endeavour. Thus, bioinformatics contributes significantly to the field of medicine, agriculture, drugs and pharmaceutics.

Converging Nature of Bioinformatics Patents – Concerns of USPTO

As inventions through bioinformatics are basically software tools and related methods, they will be dealt with in the same manner as computer-related inventions. However, the problem lies in the fact that these inventions are basically biological/genomic data or structural patterns in a computer readable medium. The software helps to process and analyse these genomic data and integrates them into useful information to find solutions in the biomedical sector, such as for developing drugs. Hence, the guidelines related to biotechnological inventions are also applicable. So far, no guidelines related to bioinformatics patents have been developed. However, the USPTO has responded to the challenge of examining applications for bioinformatics patents by establishing in 1999 a new Art Unit (1631) to deal with such claims. They developed a collection of bioinformatics patents by searching prior art in likely classes and provided specialised training for examiners in the field.[16] This newly established Art Unit 1631 sought to identify prior art in bioinformatics patents by more specific selection of subclasses (for example, patents related to data structure) relevant to bioinformatics to avoid irrelevant patents.[17] In 1998 the USPTO published "interim written description guidelines" for the purpose of providing a general, systematic legal analysis for examiners to review applications. This was superseded by the 2001 Guidelines for Examination of patent application under 35 U.S.C s.112 on written description requirements. At present USPTO is following the 2008 revised written description training materials for examining bioinformatics patent applications. By using all these guidelines USPTO is trying to tackle the problems facing bioinformatics patents. However, there is no guarantee that bioinformatics patents will be assigned to Art Unit 1631; sometimes it may be assigned to the computer Art unit 1600. Thus, no consistency is assured in examinations, which depends on the nature of the claims.[18]

Bioinformatics Patents: The US Approach

As inventions in bioinformatics are basically computer applications – implemented protocols or software for

collecting, storing, processing or analysing biological data converging with biotechnology – one has to determine to what extent the guidelines related to computer-related inventions are suitable for determining the standards of patentability for bioinformatics inventions. The US courts and the patent office have struggled with the changing technological landscape that computers and biotechnology have introduced in the patent regime in the US since the decision in *Diamond v. Chakrabarty* and later in *Diamond v. Dier*.[19] However, later numerous patents were granted in the US even for patents pertaining to business methods. The increasing number of patents on incremental innovations affected the public interest. The US courts on realising the danger reaffirmed the TSM Test in the KSR case. Again in In rebilski[20] the court affirmed the 'machine or transformation' test. The implication of this test is that it will invalidate all patents on incremental innovations, like business method patents, software patents and advanced biological method patents, and thus, inevitably, bioinformatics patents too.

Algorithms, which consist basically of instructions, are not patentable.[21] Although claims relating to computer-related processes[1] were rejected by the court on the grounds that they were directed at the method in the abstract without regard to a particular physical substance in the cases of *Gottschalk v. Benson*[22] and *Parker v. Flook*[23], in *Diamond v. Dier*[24] the Court adopted a strange interpretation and held that if a claim describes a structure or process for implementing or applying a formula and the structure or process performs a patentable function such as transforming an article from one form to another then it could be patentable by appreciating the claim as a whole[25]. The Court further held that inclusion of mathematical algorithms in claims per se will not preclude them from being treated as a subject matter for assessing the standard of patentability[26]. This means that functions of basic software tools like algorithms could be patented if one could transform an article from one form to another using an algorithm. The test adopted by the patent office following the above decisions is generally known as the Freeman-Walter-Albele Test. According to this test, in a computer-related invention involving a mathematical algorithm in which the mathematical algorithm is directly or indirectly found in a claim, the claim is then further analysed as a whole to determine whether the algorithm is applied in any manner to physical elements or process steps. In essence, claims relating to computer programs are patentable, if they are able to show a special purpose/feature of a computer rather general purpose and are capable of giving useful, tangible and concrete results The application of this test opened the flood gates, which resulted in expanding the scope of protection in *In Re Alappat*[27] & *Arrhythmia Inc v Corazonicx Corp*[28]. This principle was further diluted by the *State Street bank case*[2] to include anything that can cater to practical use, leading to business method patents. Thus, the Court expanded the judicially created statutory subject matter to include laws of nature, natural phenomena and abstract ideas while confirming the use of the invention to derive a concrete, tangible result. The patents were granted even for biological databases, which comprise DNA sequences.[30] This led to granting unnecessary monopoly, resulting in narrowing down of the public domain and stifling further innovations. Reacting to this the Supreme Court of the US reaffirmed the TSM Tests and set higher standards of patentability[31]. Since the 2007 decision in KSR[32] the USPTO has been applying the restated TSM tests to bioinformatics inventions. Later in *In re Bilski*[33] a machine transformation test was laid down as the governing test for determining the patent process, but the US Supreme Court held MOT as a useful test and not as the sole test. Thus, application of the TSM test[34] and the transformation test[35] sets higher standards in determining the 'non-obviousness'.

The expansion of the subject matter of patents[36] to accommodate biotechnology resulted in lowering of the patentability standards. The *Grahams* test[37] was diluted and the USPTO started granting patents for 'discovery' by the justification that human intervention makes natural things nonnatural. As a result, an increasing number of patents on EST, SNP and other research tools started creating problems and the USPTO fell into a dilemma[38]. This compelled the USPTO to apply more rigorous examination guidelines in this field, like "The written Description Examination Guidelines for biotechnology in 1996"[39] and the "2001 Utility Examination Guidelines and DNA patents of the USPTO". The conditions for satisfying utility are that the subject matter to be patented must be (a) specific[40], (b) substantial[41] and (c) credible[42]. The Kirin Amgen case[43] is a reflection of the problems faced by biotechnology patents, mainly the different methods to reach the same product, which are really nonobvious to a person skilled in the art. Unlike chemical patents, in biotechnology even a small change will result in drastic results, which are really nonobvious.

Bioinformatics Patents – The Challenges

The method usually followed by the USPTO to determine patentability in the case of data structure encoded in a computer readable medium is based on guidelines on computer-related inventions. The USPTO had distinguished data structures that are not patentable[44] from a computer readable medium encoded with a data

structure that was considered patentable[45]. However, mere arrangement or compilation of data or facts stored so as to be read, or stored data that do not create any functional relationship (that is, nonfunctional descriptive material), is not patentable.[46] This was based on the reasoning that the encoded medium 'defines structural and functional relationships between the data structure and the medium, which permit the data structure's functionality to be realized'. There seems to be no rationale for such a distinction, because an isolated DNA that encodes a specific protein is patentable provided it satisfies novelty and nonobvious criteria. At the same time, the same sequence embodied as a novel and nonobvious data structure per se is not a patentable subject matter even though, in essence, both are the same. Accordingly, USPTO has issued a patent for a computer readable medium encoded with a computer program for processing and analysing biological data based on the guidelines on computer-related inventions.[47] In the 1996 USPTO Examination guidelines on computer-related inventions, the criteria for patentability are that the invention should produce a useful, concrete and tangible result and that it must have technical effect/technical contribution.[48] In the case of claims for data structure in computer readable medium, the structural and functional relationship between the data structure and the medium has to be satisfied. As most of the bioinformatics inventions have technical applications, they can easily satisfy these conditions. In the case of bioinformatics patent claims for new methods or processes, which generally involve a practical application such as capturing 3-D images of protein structure and prediction of a protein structure using data mining technology[49], it is possible to show a structural and functional relationship between the data structure and the medium. Thus, the eligibility criteria for the patent can be satisfied.

Another challenge faced by bioinformatics patents is the requirement of nonobviousness and the test of a person skilled in the art – that is, a bioinformatician. As bioinformatics inventions involve more than one technology, difficulty lies in determining nonobviousness. The prior art may include both computer-related references and those involving the life sciences. As bioinformatics is a combination of computer science and life sciences, the prior art references could be both biotechnology- and computer-related patents, which have to be strictly complied with. However, the decision of whether a data structure on a computer readable medium is a functional or nonfunctional descriptive material depends ultimately on the examiner. In bioinformatics, naturally occurring biological sequences are converted into digital sequences or can be said to be a mere discovery of existing sequences using a computer program. Thus, fixing the inventive step in the case of bioinformatics patents becomes crucial for the patent examiner.

The application of the Machine Transformation Test helps to preempt the use of fundamental principles such as business methods. However, how it could be applied to bioinformatics patents is unclear – whether a change in a single base of the digitized genetic sequence will come under the term 'transformation'? Thus, the application of standards of nonobviousness in bioinformatics patents is yet be established by the USPTO. In addition, the lack of judicial precedents in bioinformatics patents makes it more challenging.

Another challenge faced by patent examiners is with regard to the application of biotechnology- or computer-related invention guidelines in bioinformatics patents, which depends on the drafting of the claims, either independently or in a combination of software and sequence claims. The nature of language used may be related to either biotechnology or computer, or both. The prior art reference in computer inventions relating to biological data seems inadequate to be applied for bioinformatics inventions. Gene sequences are thus patented as gene sequences stored in a computer readable medium using the software patent standards. Thus, bioinformatics opened a way for patenting gene sequences.

Now care has to be taken not to repeat the problems like allowing 'reach through' claims i.e., (claims attempting to obtain protection for something which has not yet been invented). In bioinformatics the research tools are created using automated process and they are used as bioinformatics products as well as research tools.[50] The claims for downstream developments are called reach-through claims, i.e., the extent to which the patentee is entitled to derive benefit from downstream developments that result from use of the research tool.[51] Usually, genomics-related claims are too general to meet the written description requirements. Therefore, the requirement for patent specification must describe the claimed invention in sufficient detail that a person skilled in the art can reasonably conclude that the inventor had possession of the claimed invention under the guidelines for the written description.[52] The interpretation in *University of California v. Eli Lilly*[53] will help the patent examiners insist on the applicants clearly describing the bioinformatics invention.

As a result of the light of guidelines on computer-related inventions, bioinformatics patents become eligible for patenting, which otherwise may not have been if stringent conditions of nonobviousness and utility, such as substantiality, specificity, credibility and recent biotechnology patentability standards, are applied. This helps to narrow down the claims and the use of general terms. Another important fact is the way of drafting the claims and examining the same in the case of

bioinformatics patents. The analysis of some bioinformatics patent applications reveals these problems.

Bioinformatics Patents in the US – An Analysis

United States Patent 6023659[54] is a bioinformatics patent granted in 2000. This patent is related to a method of using a computer system to present information pertaining to a plurality of biomolecular sequence records stored in a database. It is an indirect way of monopolizing the genomic database, which comprises basically natural biological sequences that have already been discovered and stored in a biological database in a digital form.

The databases are for storing and retrieving biological information. They are never considered as having any substantial inventive step. In the US, patents were granted mainly to protect the investment involved in developing the database. However, in the EU, a sui generis protection for databases was developed. Therefore, the claim for the database itself does not satisfy the patentability criteria. However, the database must have special technical features. In the case of biological databases, if we apply the machine transformation test on the basis of the DNA's nucleotide sequence to both its natural biological function and the utility associated with DNA in its isolated form, no markedly different characteristics can be seen. Thus, it can be said that in the case of bioinformatics patents only the nature of the sequence is changed; that is, it is converted to an electronic form. Therefore, the claims are directed at unpatentable products of nature in the case of bioinformatics patents as well.[55] On the basis of the DNA's nucleotide sequence to its natural biological function and to the utility associated with DNA in its isolated form there are no markedly different characteristics. Another problem is similar to that faced by business method patents: how can the machine transformation test be applied to bioinformatics patents?

Some of the biomolecular sequences are grouped into a first hierarchy of protein function categories, with their biological functions corresponding to the biomolecular sequences and matching one or more selected protein biological function categories with one or more biomolecular sequences. A computer system and a computer readable medium must have program instructions to automatically categorize biomolecular sequence records into protein function categories in an internal database. The new sequences may be continuously compared (e.g., using a BLAST algorithm) against external (e.g., public, such as GenBank) databases.

This claimed invention is only an improvement in relational database systems, and their content will help accelerate biological research for numerous applications. By examining the prior art reference of US patent 5706498 relating to the "Gene database retrieval system", it could be seen that a dynamic programming device for comparing key sequences with database sequences and a dynamic programming operation unit for determining the degree of similarity between target data and key data by utilizing the sequence data from the gene database has been claimed already. Thus, the application of the TSM Test to the said patent claims, that is, claims 14[56] and 41, shows that there is a motivation or suggestion in the prior art, obvious to a person skilled in the prior art, and can be said to be an improvement rather than an inventive step.[57] Hence, through the method of using a computer system a database having no inventive step gets patented. It would pass the technical contribution test but would not satisfy the nonobviousness requirement.

The US seems to have lowered the patentability standard and granted patents. Later, this approach by the patent office was strongly criticized by the US court in *KSR v. Teleflex*.[58] The result of granting such patents is that basic tools such as the biological database, which is highly indispensable to unravelling the mysteries of biological science, were monopolized. This may affect further research and innovations in this field, by creating numerous right holders (.anti-commons problems).[2] Moreover, the genomic database contains the DNA sequence that must be kept in the public domain. It seems that the nature of the investment made in developing such a database and the commercial benefits that may be derived from licensing information from it prompted patent claims.

Implications of the Decision of Bilski's Case[59] & Association for Molecular Pathology v. USPTO[60] on Bioinformatics Patents

The decision taken in Biliski's case that the machine transformation test is not the only test to decide process patents had posed challenges to bioinformatics software patents, advanced biological method patents and diagnostic and other method claims. On one hand it helps invalidate all patents on incremental innovations such as business method patents and software patents, but on the other hand there is another possibility of interpretation of the US Supreme Court decision whereby considering the conversion of biological data into useful information using bioinformatics techniques as 'transformation' is a threshold question to be answered. The recent decision taken in the *Association for Molecular Pathology v. USPTO*[61] case is yet another important decision of the US Supreme Court that has implications on bioinformatics

patents wherein certain Myriad Genetics' patents related to BRCA 1 and 2 breast and ovarian cancer susceptibility genes were invalidated. Here the claim was for isolated DNA sequences and for methods of comparing or analysing gene sequences to identify the presence of mutations corresponding to a predisposition to breast or ovarian cancer. The court rejected the claims based on the fact that purified DNA sequences must be new and useful in order to be eligible; that is, they must possess 'markedly different characteristics'. Here, the existence of DNA in an 'isolated' form alters neither this fundamental quality as it exists in the body (ie., natural biological function of its ability to carry the information sufficient and necessary to code a protein as well as the utility associated with it) nor the information. Thus, the court came to the conclusion that claims are directed at unpatentable products of nature;[62] that is, genes are not just chemicals, precisely because they carry information. Thus, the recent decision of the US Court on gene patenting shows the setting of higher standards by the judiciary irrespective of the nature of the technology involved. Recently US courts especially in three cases ruled in favour of patients holding that a lower ourt's decision that the diagnostic tests claims are ineligible for patenting under Supreme Court precedent. It reflects re thinking of judiciary's earlier decisions and the way patentability applied by patent office. These cases are In re BRCA1- and BRCA2-based Hereditary Cancer Test Patent Litigation (Myriad III; 2014), Ariosa v. Sequenom(2015) and Genetic Technologies Ltd v. Merial (2016); each case extends the reach of the Mayo decision for invalidating genetic diagnostic method claims. In the Myriad III case, the Federal Circuit held that Myriad's claims — which recited the specific mutations, primers and methods for detecting breast cancer-related mutations in the BRCA1 and BRCA2 genes — were invalid for reciting a law of nature (the association of specific BRCA mutations with cancer predisposition) that was detected by "routine, well-understood and conventional" methods (PCR, sequencing and hybridization). This was followed by the Ariosa case, which involved claims to a blood test for detecting paternal DNA amongst cell-free fetal DNA (cffDNA) in maternal bloodNevertheless, the district court invalidated these claims for reciting patent-ineligible subject matter and the Federal Circuit affirmed that decision. The rationale was the same as in Myriad III: the existence of cffDNA in maternal blood was a natural phenomenon, and the claim recited only conventional methods for detecting it. (Kevin noonan, Nature Review Drug Discovery, 2016) This kind of interpretation will satisfy the legislative intent without compromising the patentability standards.

Bioinformatics patents: Emerging Issues in EPO

Unlike the US there is no special examination unit for examining bioinformatics inventions in EPO. The standards of patentability are the same for all subject matter. Even though Article 52(2)(c) read with article 52(3) specifically excludes computer programs "as such" from being patentable subject matter,[63] the EPO granted many software patents based on whether the invention possessed the proper "technical character'.[64] According to the case law of the Boards of Appeal, a technical contribution typically means a *further technical effect* that goes beyond the normal physical interaction between the program and the computer.[65] However, later there was a shift in the contribution approach and the technical effect approach from the following decisions. In Vicom/Computer-related invention[66] the claim relating to a method of digitally filtering data performed on a conventional general purpose computer was rejected, as the claim was held to define an abstract concept not distinguished from a mathematical method.[67] However, claims on the method of image processing that used the mathematical method to operate on numbers representing an image were allowed on the reasoning that the image processing performed was a technical (i.e. nonexcluded) process related to the technical quality of the image and that a claim was for a technical process in which the method used does not seek protection for the mathematical method as such.[68] The Board stated that a technical process alters a physical entity and reasoned that the patent was sought for a technical process as the invention altered a physical entity, which was the image in question. With regard to the preemption argument, it stated that the use of a computer program to control the steps in a technical process was also patentable because protection was not sought for the program "as such". 'Therefore, the allowable claims as such went beyond a mathematical method.'[69] This type of interpretation was extended to the IBM/Data Processor Network[70] where the Board of Appeal held that the invention was of sufficient technical character, and it supported its patentability because the invention was concerned with the internal working of processors and the way in which the particular application programs operate on the data.[71] In IBM/Computer-Related Invention (text processing),[72] the Board held that the signaling of conditions prevailing in a machine (word-processing machine) was a technical problem and was therefore patentable subject matter. In the Koch and Sterzel/X-ray Apparatus,[73] the board went on to state that "when in time the technical effect occurs is irrelevant to the question of whether the subject matter claimed constitutes an invention under article 52(1) EPC.

The only fact of importance is that it occurs at all''. Thus, it could be seen that even though the EU guidelines are restrictive in approach the contrary interpretation given to the "technical effect" or "technical contribution" by the board resulted in expansion of limits of patentability falling within the lines of the US.[74]

The EU Biotechnology Directive was implemented in European patent law. The EPO has introduced four new rules, Rules 23b to 23e, that set out general matters and define the meaning of biotechnological inventions, biological material, plant variety, microbiological process and patentable biotechnological inventions, including biological material isolated from their environment, even if known in nature. In Plant Genetic Systems application,[75] the European Board of Appeal held that microorganisms would include not only bacteria, yeast, fungi, algae, protozoa, plasmids and viruses but also animal or plant cells and generally all unicellular entities with dimensions beneath the limits of human vision. In the light of the above interpretation, the standard of patentability of bioinformatics patents may be gauged. Bioinformatics inventions are mainly software tools and screening methods.

IMPLICATIONS OF THE DECISION OF *ELI LILLY V. HUMAN GENOME SCIENCE* ON BIOINFORMATICS PATENTS: The recent decision of the UK court in *Eli Lilly v. Human genome project*[76] seems to be the first case in which the UK courts had to consider the circumstances under which patents on gene sequences could be allowed and laid down the principles to be followed to determine whether a given patent possesses industrial applicability.[77] This decision seems to be only a beginning and had a direct impact on bioinformatics patents. The decision highlighted the importance of knowing the function of the gene and amino-acid sequences at the time of filing the patent in order for the patent to be valid.[78] Here the therapeutic protein discovered by bioinformatics tools was really a breakthrough invention. However, mere prediction or speculation of the biological activity of the protein on the basis of the commonality of the family to which it belongs was insufficient to satisfy the test of industrial application. No one can accept such contentions, because a protein belonging to a particular family may have some specific function or characteristics, other than the common features, that others may not have. This nature of the biological material differentiates biotechnology or bioinformatics invention from other mechanical or pharmaceutical inventions. In short, it could be said that the decision in the Eli Lilly case is very helpful in deciding the claims for bioinformatics patents where gene sequences are discovered without spending considerable time using special super computers. Thus, the claims for such sequences through computer-related methods such as screening methods are usually made for bioinformatics patents and for biotechnology inventions. In the light of the advancement in technology and similar demanding situations, strict application of the utility/industrial application criteria is the need of the hour. Therefore, the care and caution taken by the judiciary in applying the patentability requirements in their true spirit is really appreciable for maintaining the balance between private interest and public interest.

This could be illustrated by an example of the bioinformatics patent claims granted in the EPO. In the EPO patent EP 2052087 (A2),[79] the said invention provides a genome-wide methodology for identifying single-nucleotide polymorphisms and mutations related to disease conditions, such as cancer. Specifically, the invention provides methods for detecting genome-wide mutations by successively amplifying sequence differences between two sample populations. From claim 1[80] and claim 2 it is clear that the diseased cell used is a cancer cell.[81] Here, the invention provides methods for detecting genome-wide mutations by successively amplifying sequence differences between two sample populations but takes only cancer cells as the disease cell, which is evident from claim 2. Moreover, general terms like "genome-wide mutations", which means mutations in all genes. These are mere predictions of biological activity rather than specific claims[82] as pointed out in *re fisher's case*[83] There is a serious need to invalidate general claims and strictly apply specific and substantial utility criteria in biotechnology patents, which is the case in bioinformatics patents too. From the above-analysed bioinformatics patents it can be seen that the problems plaguing these patents persist even now. The implications of such patents in the case of emerging technologies like bioinformatics affect further research and healthy competition by allowing to monopolize natural biological materials under the guise of methods of identifying mutations by using general terms and the like.

Claim 2 of the said patent tries to cover mutations in every gene other than the gene responsible for cancer, which should not be allowed. The invention also provides methods for diagnosing, treating or preventing disorders associated with such genome-wide mutations. Methods for diagnosing, treating or preventing disorders resulting from such mutation are also covered. Thus, by way of claim formulation, even the subject matter that is excluded under patents becomes eligible for being patented.

It is true that it takes years to find out the specific DNA sequence of a gene, as well as its characteristics, nature and qualities, but allowing such claims without any requirement of a description of a particular gene and specifying its function is granting of unnecessary monopoly, as held in Eli Lilly's case. The same holds good for the claim for a software program in the guise of a

computer-related method. In the case of DNA patents it is difficult to establish specific utility. Also if a new and useful purified and isolated DNA compound described by the sequence is eligible for patenting, in bioinformatics it gives rise to complex issues like whether one has a right over digitized genetic information and so on. Precedents in computer program patents and biotechnology patents without solving their inherent problems in bioinformatics patents could prove disastrous, resulting in monopolizing the basic tools in unravelling the mysteries of biological science where these software tools are indispensable.

In the above analysed granted patents it seems patent office is following the reasoning given in *vicoms case*. Without identifying the inventive step involved in the computer program and without considering the legislative intent, granting patents may be as based on the Hence, the examination of an application for a bioinformatics patent, which involves the claims of a multidisciplinary field like biotechnology and computer technology, is challenging.

BIOINFORMATICS PATENTS – THE INDIAN SCENARIO

Scope of Bioinformatics Patents in India

India is the first country in the world to establish a nationwide bioinformatics network (BTIS network) under the Department of Biotechnology (DBT).[84] Large-scale IT organizations, both global and Indian, are also breaking into this sector. Many biotech companies entered into a partnership with IT companies – eg. Lead Invent Technologies Pvt. There are over 200 companies in Bangalore, Hyderabad, Pune, Chennai and Delhi that are in one way or another involved in bioinformatics.[85] The Indian Government is extending full financial support to this industrial sector. In India more than 100 patents have been granted to both software and biotechnology.[86] Bioinformatics patent applications filed in the Indian patent office are under process. The standard being followed for bioinformatics patents is the same as that for software or biotechnology patents. Let us analyse the patentability standards of software and biotechnology inventions followed in India.

Patentability Standards of Software and Biotechnology Inventions in India

In light of the TRIPS Agreement, the Patent Act of 1970 was substantially amended in 2002 and again in 2005. The introduction of the definitions of "new invention" "inventive step" and "capable of industrial application" gives a good indication. But it could be seen that for satisfying the inventive step there should be technical advances or economic significance, or both, in the features of the invention and it should 'not be obvious to a person skilled in the art'.[87] The requirement for 'technical advancement' could be construed to exclude incremental innovations. But there is a probability of misinterpreting the intention of the legislature. It gives an impression that inventions having economic significance are considered to fulfill the criterion of inventive step. Even in *Graham's case*[88], commercial success was considered only a secondary condition.

Thus, the definition of inventive step is very crucial in determining the level of inventiveness.[89] Therefore, a mere improvement or innovations, especially in the case of a computer program, that may not have adequate 'technical advance compared to the existing prior art' may achieve significant commercial success and can easily claim patents. Hence, there is a serious need to replace the term "or" with "and" in the definition of "inventive step."

In the definition '*capable of industrial application*' the term "in relation to an invention" has placed a higher threshold; it means an inventive application rather than one of mere utility.[90] Here industrial application means practicability. The test of utility laid down in the 2008 Manual is whether the invention will work and whether it will do what is claimed for it.[91] Hence, rather than insisting on practical utility just claiming the invention capable of industrial application may harm the legislative intent. Unlike in the US, in India there is no requirement that utility must be credible, specific and substantial. The judiciary has laid down a high patentability standard in *M/s. Bishwanath Prasad Radhey Shyam v. M/s. Hindustan Metal Industries*[92] according to which, in order to claim patents, the improvement or the combination must produce a new result, or a new article or a better or cheaper article than before and must independently satisfy the test of invention or an 'inventive step'.

The 2002 Amendment of the Patent Act expressly excluded 'computer programme per se' and plants and animals from patentability.[93] Sec.3 (k) excluded 'a mathematical or business method or a computer programme per se' or algorithms from being patentable. However, to understand the meaning of '*per se*' the Patent Manual

has given the case laws and precedents in the U.S, U.K. and the E.U. The Patent Manual of 2008 has retained the definition of "computer-related invention"[94], which is a serious concern. Here it has ignored the concept of invention as having novelty and inventive step in technical advancement because of the effect of the program[95] and has given a broad and vague definition. Hence, the evaluation of a computer program as a whole as followed in the US may lead to granting of patents for mere advancement in computer programs per se.[96] Clause 4.11.6 of the patent manual says that a claim orienting towards a "process/method" that contains a hardware or machine limitation and technical applicability of the software claimed as a process or method is defined in relation to the particular hardware components. However, it is not clear from the guidelines as to where such technical effects must be in relation to the invention. It further states that a claim directed at a technical process in which the process is carried out under the control of a program (whether by means of hardware or software) cannot be regarded as being related to a computer program as such.[97] This statement has added further confusion to whether the approach in determining the novelty and inventive step should reside in the program that controls the product or process or in the product or process caused by the effect of the program.[98]

In the case of an apparatus, claims should clearly define the inventive constructional hardware features and must define the specific application and not the general application.[99] The statement in the Patent Manual that a novel solution to a problem relating to the internal operations of a computer, although comprising a program or subroutine, will necessarily involve technological features of the computer hardware or the manner in which it operates and hence may be patentable tries to cover a program or subroutine involving technological features solely of such a computer program and the effect created by it in the way it operates. Thus, it could be seen that the interpretation given in the draft manual, which was based heavily on the interpretation of UK courts, cannot be relied upon as a basis for arguments in favour of the patentability of software in India. Thus, the patent manual has brought in the claims that the legislation tried to exclude. Section 2(k) has excluded claims relating to a computer program invention for a business method. Hence, care must be taken to ensure that only those having a very high degree of both form and function satisfy the requirements of the Indian Patent Act.[100]

Therefore, it could be seen that, even though the Patent Act had laid down higher patentability standards, one can lower the threshold using the available loopholes and the contradictions and misinterpretations furthered by the computer-related invention guidelines in the 2008 Patent Manual. It is the consequence of such interpretations that the US is currently facing. In the US the application of lower patentability standards for computer-related inventions opened a flood gate of questionable patents. The ultimate result was narrowing down of the public domain, which seriously affected the competition in the software industry. Currently, the patent system of the US is under serious revision at the legislative, administrative and judicial level.

On the basis of the requirements of Article 27.3[101] of the TRIPS the provision Section 3 (j) was included in the Indian Patent Act. It excluded from the patentable subject matter plants and animals other than microorganisms, and essentially biological processes for the production of plants or animals. Gene sequences or DNA sequences are naturally occurring biological materials that inherently lack an inventive step. That is the reason why legislation excluded it from patentable subject matter. Thus, there is a legislative ban on patenting gene sequences. What is allowed for patents are genetically engineered microorganisms. In the absence of a definition for the term microorganism there is a need to formulate strict guidelines for examination of patent applications involving microorganisms from the point of view of substantial human intervention and utility.[102] In Examination Guidelines relating to biotechnology inventions in the 2008 Patent Manual, clause 7 excluded genetically modified plants and animals and biological materials such as organs, tissues, cells, viruses, etc from being patented as they are only mere discoveries of things existing in nature. If biological material like recombinant DNA is produced by substantive human intervention, it is patentable. It indicates that DNA isolated using recombinant DNA technology by substantive human intervention is allowed.

The draft manual 2008 even allowed the patenting of protein, antibodies, diagnostic kits and amino-acid sequences without mentioning human intervention and utility. For example, take the case of genetically modified plants; it is the genetically modified DNA sequence that is responsible for the development of transgenic plants. Hence the claim for a genetically modified sequence amounts to indirectly claiming that plant itself, which is against legislative intent as it is excluded u/s 2(j). The patent manual allows gene patenting if the function of the DNA sequences and their industrial application are given and satisfy the inventive step.[103] Thus, Patent Manual 2008 diluted the legislative intent. Thus, despite the exclusion provision in S.3, the guidelines allow patenting gene sequences, thereby blurring the legislative intent. Presently, 2013 guidelines for examination of biotech applications has been issues by patent office so as to provide clarity on biotech patentability

The term "microorganism" can be subject to different interpretations, like cells or genetic material, as there

is no clear-cut definition for the term "microorganism" or "biological material" under the Patent Act of 1970. The Patent Manual too is silent on this front. Thus, gene sequences can be patented under the guise of microorganisms. Another loophole for claiming gene sequences is by way of declaring it as a chemical entity.[104] Hence, care must be taken to ensure that such claims do not defeat the purpose of the legislation.

Analysis of Bioinformatics Patents On the Basis of Indian patentability standards

In the light of the patentability standards given in the Patent Act, Patent Manual, 2008 and the judicial precedents let us analyse bioinformatics. Whether bioinformatics patented in the US would enjoy the benefits of patenting in India based on Indian patentability standards has to be analysed. The United States Patent 6023659[105] is a bioinformatics patent granted in 2000. This patent is related to a method of using a computer system to present information pertaining to a plurality of biomolecular sequence records stored in a database. In India, a database does not satisfy the inventive step concept. Hence, it is not patentable. Claim 14 relates to a method of using a computer system to present information pertaining to a plurality of biomolecular sequence records stored in a database, the method comprising the display of a list of the said records or a field for entering information identifying one or more of the said records. Also mere presentation of information is excluded u/s 3(n) of the Patent Act.

Here the inventive constructional hardware features that make the system patentable and their relation to the particular hardware components are not defined. A computer system and a computer readable medium having program instructions to automatically categorize biomolecular sequence records into protein function categories in an internal database are computer programs *per se* simply expressed on a computer readable storage medium and as such are not allowed. As the novelty or inventive step is not satisfied the claim is not patentable. Even by examining the prior art reference of US patent 5706498 relating to the "Gene database retrieval system" it could be seen that a dynamic programming device for comparing key sequences with database sequences and a dynamic programming operation unit for determining the degree of similarity between target data and key data by utilizing the sequence data from the gene database has been claimed already. Therefore, according to the decision taken in *Biswanath Prasad*[106], the inventive step must show massive improvement and mere workshop improvement is not patentable. In the above-mentioned case, when compared with prior art the claimed invention was only a mere improvement and hence was not patentable. However, one has to wait and see how the decision in the case of Biswanath Prasad is going to be applied to bioinformatics patents. By the application of the Patent Manual guidelines, ESTs, which are used as research tools, will easily satisfy the inventive step criteria because of their specific functions and industrial applications such as in gene therapy and chromosomal mapping. In the case of research tools like EST and SNP, irrespective of biotechnological or bioinformatics tools, there is no express exclusion in the Patent Act. However, the guidelines in the Patent Manual says that if the genetically modified sequence is new, inventive and has industrial application it is patentable, which is against the intent of the legislature. Therefore, there is a probability that despite the exclusion provision in s.3 the guidelines in the Manual allow patenting of gene sequences. These guidelines may lead to patenting of even digital sequences, for which a novel, inventive step and industrial application are the only criteria to be satisfied.

CONCLUSION

The threshold of the patentability requirements in the Patent Act gets diluted by the patent manual guidelines. For example, in the biotechnology guidelines, DNA sequence claims are allowed. Hence, application of the patentability standards in new technology like bioinformatics may result in granting patents in such frontier technologies. The 2013 guidelines for the examination of patent applications involving microorganisms from the point of view of substantial human intervention and utility has thrown clarity on the patentability of biotech subject matter, still requires clarity on bioinformatics applications.

The Patent Manual is only a guide and does not have any force and effect of law. This may set bad precedents from the Indian patent office. Such tendencies must be discouraged to prevent bad patents. It is high time that the Indian patent office consider the policy considerations and the legislative intent of incorporating the s.3 (k) and the implications of decisive interpretation of computer-related invention guidelines given in the patent manual 2008. Bioinformatics patents granted both in the US and EPO do not answer many of the questions plaguing the existing software and biotechnology patent applications. It took more than 25 years for the US and EPO patent office and for the judiciary to realize the consequences of the innumerable patents granted for incremental inventions in computer programs and biotechnology and to reconsider their patentability standards. The time has come for us to give serious thought to the patentability standards to be followed in the case of bioinformatics

patents in India. Thus, in short, I suggest strict application of the patentability standards; as bioinformatics tools are basically computer software, only such inventions having substantial inventive step should be granted patents.

1. An invention that consists of hardware along with software can be patented, provided the hardware in itself performs the function that is novel and carries an inventive step due to the effect of the program. 2. Avoid granting patents to databases, as they inherently lack substantial inventive step or novelty. 3. Strictly follow the criteria of industrial application; that is, utility must be credible, substantial, or specific in the case of bioinformatics inventions. 4. Claims for computer program products must be excluded as they lack novelty and inventive step. 5. Embedded systems can be patented provided the inventive step and novelty reside in the corresponding apparatus. 6. Invalidate broad and general terms used in the claims, especially relating to DNA sequences. 7. Bioinformatics patent applications must be examined by a bioinformatician – a person well versed in biotechnology and information technology. 8. In the light of public interest exclude patents on methods of treatment, therapy or diagnosis. 9. Invalidate claims relating to patenting of EST, which is used as a bioinformatics tool. 10. To distinguish the invention from prior art, relevant prior art relating to both biotechnology and computer technology is required to be given in the specification. 11. It is essential to analyse the part of the invention that is claimed for apparatus/process and compare it with prior art in order to identify the contribution to the art and determine whether there is an inventive step involved. 12. Invalidate claims for DNA sequences in a computer-related medium. A better option would be to adopt open-source software or free software.

INDIAN CONTEXT

The absence of a definition for computer programs and microorganisms and lack of judicial precedents have resulted in lack of clarity on patenting of software and microorganisms. Even by the application of software guidelines and biotechnology guidelines what is not intended by the legislature gets covered in patent claims. As bioinformatics applications are pending in our patent office the crucial question is what factors should be taken into account by the Indian patent office while considering applications for bioinformatics patents. Apart from the suggestions given above, the following are also worth considering by the Patent Office:

1. It should strictly ensure that the subject matter is not couched in such a manner so as to indirectly relate to the method of treatment, therapy or diagnosis.
2. Claims relating to a computer program invention but directed towards business methods should not be entertained.
3. A clear definition for microorganism, biological material and chemical entity is required so that DNA sequences are not covered under patent claims.
4. Apply the industrial application criteria to satisfy the intention of the legislature.
5. Claims relating to computer program products must be invalidated as they lack novelty and inventive step.
6. Claims addressed through "means plus function" or claimed through equivalence, etc. are to be specifically avoided.
7. Invalidate claims indirectly relating to research tools like ESTs.
8. As we have no prior art relating to bioinformatics patents, international search will help to compare the prior art in bioinformatics with the said claim.

The Indian Patent Office should give assurance that its guidelines do not lead to the grant of questionable patents. In the light of the experience of developed countries and the consequences they are facing currently as a result of dilution of patentability standards, our patent office must be highly cautious and careful while framing the Patent Manual for procedure and practice. Otherwise it will defeat the purpose of the legislation. Hence, rather than following the lines of the US or UK it must develop a balanced patent system so as to ensure that quality patents are protected in new emerging fields like bioinformatics.

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6. It has quick and easy generation of graphical user interface, a library for structural biology also for numerical methods.
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20. 545 F, 3d 943 (Fed Cir. 2008) (en banc).
21. 409 US 63 (1972).
22. 409 US 63 (1972).
23. 1978. 437 US 584, 198 USPQ 193 the claim was for the method of updating alarm limits which contain new mathematical formula in a Programme to do some catalytical chemical reaction. The court held that since mathematical formula has no substantial practical application except in connection with the digital computer it was not patentable.
24. 450 US 175 (1981).
25. 450 US 175 (1981).
26. 450 US 175 (1981).
27. 27.33 F.2d 1526 (Fed Cir.1994).
28. 958 F, 2d 1053 (Fed Cir. 1992).
29. 149 F, 3d at 1371, 47 U.S.P.Q.2d at 1599.
30. Database system including computer code for predictive cellular bioinformatics, Vaisberg, Eugeni A, U S Pat No 5706, 498 (to Cytokinetics, Inc.) 18 November 2003.
31. 550 US 398 (2007).
32. 550 US 398 (2007).
33. 545 F, 3d 943 (Fed Cir. 2008) (en banc). Under this test, a claim is patent-eligible if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing. Federal Circuit affirmed the USPTO Board of Patent Appeals and Interferences decision upholding the examiner's rejection of U.S. patent application Serial No. 08/833,892, which related to a method of hedging risk in the field of commodities trading, as not directed to patent-eligible subject matter under 35 U.S.C. § 101.
34. 550 US 398 (2007).
35. 545 F, 3d 943 (Fed Cir. 2008) (en banc).
36. *Diamond v. Chakraborthy, 1980*. 447 US 303, 206 USPQ 193.
37. *Graham v. John Deere co.,* 383 US 1 (1966).
38. Mathew Rimmer (2008) *Intellectual Property and Biotechnology.* Edward Elgard publishers Inc.
39. Sufficient relevant identifying characteristics such as The claimed invention Reduction to Practice Actual reduction to practice not always required. Deposit of biological materials not a substitute for written description. Clear depiction of the claimed invention in detailed drawings Weigh factual considerations in view of level of skill and knowledge in the art. The less mature the technology, the more evidence is required to show possession. Level of skill and knowledge in the art increases over time.

40. Specific means that utility must not be general that would be applicable to the broad class of the invention. It must be specific to the subject matter claimed.

41. "Substantial utility" means current "real world" use. To illustrate substantial utility of a protein that would be coded by any gene found by the probe. This makes it clear that in the absence of such knowledge patent cannot be granted. If the only utility of a compound is for scientific research, then there is no substantial utility.

42. Credibility refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. To illustrate this consider a claim for a DNA fragment whose use is disclosed simply as a "gene probe" (pieces of DNA that can be used to find new genes by hybridizing to them), would not be considered specific in the absence of a disclosure of a specific DNA target (means particular site of DNA were these fragments hybridize). This specific DNA target will be different for other "gene probe." For example a particular gene probe is used for cancer gene mutation, the specific, real world use of probe is to be given than its general use.

43. [2004] UKHL.

44. In re Warmerdam 33 F, 2d 1526 (Fed Cir. 1994) and In re Lowry, it was held that claims to data structures per se do not constitute patentable subject matter pursuant to 35 USC §101. However, a machine (such as a computer) or a computer-readable medium (such as a CD-ROM or floppy disk) encoded with a data structure is patentable. These rulings are consistent with the USPTO's guideline for patentable subject matter in computer-related inventions.

45. In re Lowry, 958 F, 2d 1053 (Fed Cir. 1992).

46. In re Gulack, 703 F, 2d (381 217 USPQ 401, 404 Fed Cir. 1983, it was held that If the difference between the prior art and claimed invention is limited to descriptive material stored on or employed by a machine, office personnel must determine whether descriptive material is functional descriptive material or non functional descriptive material. Functional descriptive material is a limitation in the claim and must be considered and addressed in assessing patentability. So rejection of a claim is in appropriate unless functional descriptive material would have been obvious.

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52. Guidelines for Examination of Patent Applications under the 35 USC 112, "Written Description" Requirement, 66 Fed. Reg. 1099, February, 2003.

53. *University of California v. Eli Lilly,* 119 F.3d 1559, 1568 (Fed Cir. 1997). The federal district court in *University of California v. Eli Lilly* held that merely naming a type of known material, without any knowledge as to what that material consists of, is not a description of that material.

54. US Pat No. 6023659, Title: Database system employing protein function hierarchies for viewing biomolecular sequence data.

55. See, *Association for Molecular Pathology v. USPTO,* 569 U.S. June 13, 2013.

56. The claim 14 reads as follows – A method of using a computer system to present information pertaining to a plurality of biomolecular sequence records stored in a database, the method comprising: displaying a list of said records or a field for entering information identifying one or more of said records; identifying one or more of said records that a user has selected from said list or field; Then matching said one or more selected records with one or more protein function categories from a first hierarchy of protein function categories into which at least some of said biomolecular sequence records are grouped; and displaying the one or more categories matching said one or more selected records, wherein said protein function categories specify biological functions of proteins corresponding to said biomolecular sequences and said first hierarchy includes (i) a first set of protein function categories specifying biological functions at a cellular level, and (ii) a second set of protein function categories specifying biological functions at a tissue level.

57. US Pat No. 5706498.

58. 550 U.S. 39 (2007).

59. 561 U.S. 2010.

60. Ibid.

61. *Association for Molecular Pathology v. USPTO* (569 U.S. June 13, 2013).

62. *Association for Molecular Pathology v. USPTO* (569 U.S. June 13, 2013).

63. The European Patent Convention (EPC), Article 52, paragraph 2, excludes from patentability, "in particular discoveries, scientific theories and mathematical methods; aesthetic creations; schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; [emphasis added] presentations of information. Paragraph 3 then says: "(3) The provisions of paragraph 2 shall exclude patentability of the subject-matter or activities referred to in that provision only to the extent to which a European patent application or European patent relates to such subject-matter or activities as such."

64. The EPO has granted at least over 30,000 patents for computer program-related inventions. Many of these patents were in the core areas of information technology, i.e. digital data processing, data recognition, representation and storage. Others were granted in different technical areas such as automotive and mechanical engineering, e.g. for program-controlled processors.

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68. Ibid.

69. Id.

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71. See, infra n. 67.

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73. Koch & Sterzel/X-ray Apparatus, T26/86, EPO Journal [1998]. Where the claim was for computer control of a known X-ray apparatus.

74. Yogesh Anand Pai (2007) Patent protection for computer programs in India: Need for a coherent approach computer programs. *The Journal of World Intellectual Property* 34.

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76. 2010 EWCA Civ 33, Kitchin, J. Set out the following guidelines which essentially summarise EPO jurisprudence: a. the capability of industrial exploitation must be deliverable by the skilled person from the description read with the benefit of the common general knowledge; b. the description, so read, must disclose a practical way of exploiting the invention in at least one field of industrial activity. That is to say, it must disclose in definite technical terms the purpose of the invention and how it can be used to solve a given technical problem; c. the requirement will not be satisfied if what is described is merely an interesting research result without any specified application. A speculative indication of possible objectives is not sufficient. The patent should not leave the skilled person with a research programme to carry out in order to exploit the invention; e. if a substance is disclosed and its function is essential for human health, the identification of the substance having that function will immediately suggest a practical application. If the function of that substance is not known or is incompletely understood and no disease has been identified which the substance is implicated in, and no other practical use is suggested for it, then the requirement of industrial applicability is not satisfied (even if there is a scientific achievement of considerable merit in the disclosure); and it is no bar to patentability that the invention has been found by homology studies using bioinformatics techniques but this may have a bearing on how the skilled person would understand the disclosure.

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80. A method for identifying a genome-wide mutation, comprising:
(a) providing DNA from two sample pools of a subject, wherein a first sample pool is obtained from an diseased cell and a second sample pool is obtained from a normal cell;
(b) digesting each DNA sample pool to generate at least two DNA fragments;
(c) ligating *a s*hort oligonucleotide adapter to each fragment at a site of mismatch cleavage; and
(d) selectively amplifying and identifying the sequence

differences between the two sample pools to identify a mutation.

81. The method of claim 1, wherein the diseased cell is a cancer cell.
82. *Eli Lilly v. Human genome science, (emphasis by the Author).*
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93. The Indian Patent amendment Act, 2002.
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99. Clause 4.11.7 p. 74. For example, in a computer comprising means for storing signal data and a first resistor for storing data, the clause starting with "for" describes the function or process carried out by the apparatus, and form the part of "process limitation" here.
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Article

Prospects and Challenges for the Commercialization of Biosimilars: Perspectives from the EU, Japan, and the US

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ABSTRACT

With many blockbuster biologic drugs coming off patent in the next couple of years, biosimilars are making significant breakthroughs in cost-effective biologic therapies. The global market for biosimilars is expected to increase nearly 30 fold from $1.3 billion in 2013 to $35 billion by 2020. To promote biosimilar development and commercialization in the U.S., the Biosimilars Act was signed into law in 2010 to establish an abbreviated pathway by which the FDA could approve biosimilar versions of previously licensed biological products. Since its enactment, two biosimilars have been approved in the U.S. This Article will discuss key aspects of the U.S., the EU and Japanese approval pathways and will explore their likely impact on the commercialization of biosimilar medicines.

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With many blockbuster biologic drugs coming off patent in the next couple of years, biosimilars are poised to make a significant breakthrough in cost-effective biologic therapies. In fact, it is estimated that the global market for biosimilars will increase nearly 30 fold from $1.3 billion in 2013 to $35 billion by 2020.[1]

One hurdle to biosimilar development in the U.S. has been the lack of an abbreviated or expedited pathway for regulatory approval. The lack of an abbreviated pathway means that manufacturers of biosimilars had to go through the same lengthy and costly FDA process as developers of brand-name biologics, or innovators, to obtain approval for their product. Due in part to these hurdles, only two biosimilars have been approved in the U.S. including Teva's tbo-filgrastim (Granix).[2] This is in contrast to the European Union (EU) and Japan. In the EU, twenty-three biosimilars have been approved through an established biosimilar approval pathway that has been in place since 2005.[3] Additionally, in Japan, eight biosimilars have been approved since the Japanese guidelines for biosimilars were published in 2009.[4]

To promote biosimilar development and commercialization in the U.S., the Biologics Price Competition and Innovation Act (the "Biosimilars Act") was signed into law on March 23, 2010 by President Obama as Title VII of the Patent Protection and Affordable Care Act.[5]

1 "Global Biosimilars/Follow-on-Biologics Market (Technology, Types, Applications, Services and Geography) – Research Report, 2013–2020, July 2014. Accessed at www.researchandmarkets.com.

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2 Andrew F. Bourgoin and Beth Nuskey, "An Outlook on US Biosimilar Competition," April 2013. Accessed http://thomsonreuters.com/products/ip-science/04_013/anoutlookonusbiosimilarcompetition-cwp-en.pdf

3 Generics and Biosimilars Initiative, Biosimilars Approved in Europe. Accessed http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

4 National Institute of Health Science, Biosimilars approved in Japan. Accessed at http://www.nihs.go.jp/dbcb/biosimilar.html [Japanese]

5 Patient Protection and Affordable Care Act, Pub. L. No. 111–148, 124 Stat. 119 (2010). The Patient Protection and

The Biosimilars Act established an abbreviated pathway by which the Food and Drug Administration ("FDA") could approve biosimilar versions of previously licensed biological products.[6] The U.S. biosimilars pathway shares common features with its EU and Japanese counterparts but also has some striking differences. This Article will discuss key aspects of the U.S., the EU and Japanese approval pathways and will explore their likely impact on the commercialization of biosimilar medicines.

OVERVIEW OF BIOLOGICS AND BIOSIMILARS

The Biosimilars Act and its EU and Japanese counterparts provide expedited approval pathways for biosimilars.[7] A biosimilar is a biologic that has similar structural and pharmacokinetic properties to the innovator biologic, and is capable of providing the same therapeutic effect. Biosimilars can be considered follow-on or generic versions of an innovator biologic. It is important to note that biosimilars differ from biobetters. Even though biobetters are also biologic products, a biobetter has molecular or chemical modifications that constitute an improvement over the originator biologic. A biobetter, therefore, is a modified version of the innovator biologic that performs better than the innovator.[8]

In contrast to small molecule drugs, which consist of small-molecule compounds produced by chemical means, biologics are large and complex molecules that are produced by living biological systems. Biologics can include various types of products. The Public Health Service Act ("PHSA"), for instance, defines a biologic as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings."[9]

Originally, biologics tended to be products produced primarily from purified extracts of animal blood and tissue.[10] However, due to scientific advancements, particularly in the area of recombinant DNA technology, biologics are now increasingly being produced from modified cell lines genetically reprogrammed to mass produce a particular biological product. Accordingly, the definition of biologics has been expanded to include products such as immunoglobulins, monoclonal antibodies, antisense polynucleotides, stem cells, and molecules for gene therapy.[11]

SAFETY AND CLINICAL CONSIDERATIONS IN REGULATORY APPROVAL

Due to their structural and physical properties, biologics face different challenges during development than their small-molecule counterparts. These challenges impact not only how biologics are manufactured, but also when and how biologics ultimately reach the market.

Biologic products are comprised predominantly of proteins,[12] which are, in turn, comprised of multiple amino acids.[13] Regardless of the size of the biologic, the precise three-dimensional structure of proteins is crucial to their biological function. Even the slightest alteration in the amino acid sequence can have a dramatic effect on its function. For example, the removal of a single amino

Affordable Care Act was previously H.R. 3590, 111th Cong. (2009).

6 Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111–148, §§ S 7001–7003, 124 Stat. 119, 804–821 (2010).

7 Id.

8 http://www.financierworldwide.com/competitive-strategies-in-life-sciences-biobetters-versus-biosimilars/

9 PHSA § 351 (i), 42 U.S.C. § 262(i) (2006).

10 David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 Food & Drug L.J. 143, 143 (2005).

11 Edward L. Korwek, *What Are Biologics? A Comparative Legislative, Regulatory and Scientific Analysis*, 62 Food & Drug L.J. 257 (2007). For a chronology of product class developments, see BIO's Timeline, http://bio.org/speeches/pubs/er/timeline.asp (last visited Apr. 22, 2008).

12 Increasingly popular therapeutic biological products even more complex than single proteins are monoclonal antibodies. Antibodies, which consist of multiple chains of individual proteins, are made by cells of the immune system and are designed to recognize and tightly bind to a specific target. Recombinant monoclonal antibodies are biological products made by the fusion of a beta cell of the immune system to an immortal cell such as a tumor cell. Dianne M. Dinnis & David C. James, *Engineering Mammalian Cell Factories for Improved Recombinant Monoclonal Antibody Production: Lessons from Nature?*, 91 Biotechnology & Bioengineering 180, 180 (2005).

13 Lehninger, David L. Nelson and Michael M. Cox, *Biochemistry* (5ed. 2008).

acid from the 574 amino acid protein hemoglobin has been shown to cause sickle cell anemia.[14]

Due to their size and complexity, there are increased safety concerns associated with biologic products that may increase the time and cost needed for obtaining regulatory approval.[15] One such safety concern is immunogenicity. Immunogenicity refers to the potential for a substance to be recognized by the body as foreign, thereby causing the body to produce antibodies and launch an immune response against the substance.[16] Since changes may occur in the conformation of a protein, the propensity to become immunogenic is a special concern for biologics that does not generally affect small molecule drugs.[17]

The immunogenicity of a biologic is best seen in the case of Epogen® and Eprex®, a biologic used to treat anemia in the United States and Europe, respectively.[18] Epogen® and Eprex® had identical amino acid sequences and were produced by cells utilizing the same recombinant DNA technology.[19] However, slight differences in the way each biologic was formulated (i.e., Epogen® was formulated in human serum albumin and Eprex® was formulated in glycine and Polysorbate 80) caused patients taking Eprex® to develop antibodies to epoetin alpha at much higher rates than patients taking Epogen®. The antibodies developed by patients taking Eprex® were cross-reactive not only to the epoietin active ingredient in both Eprex® and Epogen®, but also to the patients' own endogenous erythropoietin.[20] As a result, some patients taking Eprex® not only became unresponsive to the treatment, but also suffered worsened anemia.[21]

To mitigate the risk of the potentially harmful effects associated with immunogenicity, biologics are required to undergo additional clinical studies prior to approval to ensure safety and efficacy of the biologic.[22] Because of the additional testing required, the process for obtaining regulatory approval for biologics in the U.S. as well as in Europe and Japan is often longer and more expensive than that for small molecule drugs.[23] As such, the development costs of biologics in the US is estimated at around $1.24 - $1.32 billion on average, per drug, compared to about $800 million for small molecule drugs.[24]

The regulatory requirements are equally burdensome when it comes to developing biosimilars. Since biologics are larger and more complex than small molecule drugs, they are also generally more difficult to replicate.[25] In contrast to small-molecule drugs, which can be synthesized in a number of different ways, a biologic product is closely tied to its manufacturing process. As the example with Epogen®/Eprex® above demonstrated, even minor deviations in the manufacturing process of

14 Vernon M. Ingram, *Sickle-Cell Anemia Hemoglobin: The Molecular Biology of the First "Molecular Disease"- The Crucial Importance of Serendipity*, 167 Genetics 1, 3 (2004).

15 Zuñiga L, Calvo B. Biosimilars: pharmacovigilance and risk management. Pharmacoepidem Dr S 2010;19:661–9; Nowicki M. Basic facts about biosimilars. Kidney Blood Pres Res 2007;30:267–72; and Roger SD, Mikhail A. Biosimilars: opportunity or cause for concern? J Pharm Pharmaceut Sci 2007; 10:405–10.

16 *Safe and Affordable Biotech Drugs: The Need for a Generic Pathway, Hearing Before the House Comm. on Oversight and Gov't. Reform*, 110th Cong. (2007) (statement of Janet Woodcock, Deputy Comm'r, Chief Medical Officer, Food and Drug Administration) *available at* http://oversight.house.gov/documents/20070326104056-22106.pdf [hereinafter Woodcock Statement].

17 Michele Kessler et al., *Immunogenicity of Biopharmaceuticals*, 21 Nephrology Dialysis Transplantation (Supp.) v9, v10 (2006).

18 *See* Charles L. Bennett et al., *Long-term Outcome of Individuals with Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Epoetin: A Follow-up Report from the Research on Adverse Drug Events and Reports (RADAR) Project*, 106 Blood 3343 (2005).

19 *See* Huub Schellekens & Wim Jiskoot, Letter to the Editor, *Eprex-Associated Pure Red Cell Aplasia and Leachates*, 24 Nature Biotechnology 613, 613–14 (2006). Each product was manufactured by divisions of the same pharmaceutical company, but changes were made to Eprex® at the request of European regulatory agencies. *Id.*

20 Charles L. Bennett et al., Long-term Outcome of Individuals with Pure Red Cell Aplasia and Antierythropoietin Antibodies in Patients Treated with Recombinant Epoetin: A Follow-up Report from the Research on Adverse Drug Events and Reports (RADAR) Project, 106 Blood 3343 (2005).

21 Sahr, Robert, N., The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition Boston College Intellectual Property & Technology Forum. Accessed at http://www.bciptf.org

22 Biologics Revolution: The Intersection of Biotechnology Patent Law and Pharmaceutical Regulation. Georgetown Law Journal. Tam, J.W.Y. 2010, volume 98, page 535; Tam, Joyce, W.Y., Biologics Revolution the Intersection of Biotechnology Patent Law and Pharmaceutical Regulation_The Georgetown Law Journal_2010_vol98 p535.

23 Id.

24 Katheleen R. Kelleher, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway,* 14 Mich. Telecom. & Tech. L. Rev. 245, 252 (2007).

25 Natasha Singer, *In Pursuit of a Pipeline of Biological Treatments*, N.Y. Times, January 27, 2009.

biologics can lead to variations that may significantly alter the molecule's properties and may result in an ineffective or unsafe product.[26] As a result, the regulatory process for developing biosimilars is often longer, more complicated, and more expensive than that for generic small molecule drugs.[27] According to the Federal Trade Commission ("FTC"), the development of biosimilars takes between eight and ten years and costs between $100 million and $200 million, compared to three to five years and $1 million to $5 million for small-molecule generics drugs.[28]

REGULATION OF BIOLOGICS IN THE EUROPEAN UNION

In the European Union ("EU"), biosimilars are centrally regulated by the European Medicines Agency ("EMA"). The EU was the first region in the world to establish an approval pathway specifically for biosimilars. This approval pathway was adopted in 2004 and came into effect in 2005.[29] In 2006, Omnitrope® became the first biosimilar to be approved by the EMA and since then, a total of 22 biosimilars have been approved by the EMA.[30]

While the EMA's biosimilar pathway directive does not specifically define what constitutes a biosimilar, guidelines published by the Committee for Medicinal Products for Human Use ("CHMP")[31] state that a biosimilar is a drug which has a "known biological active substance" that is similar to an already authorized drug, referred to as a "reference medicinal product."[32] The guidelines further state that the biosimilar and the reference medicinal product "are expected to have the same safety and efficacy profiles and are generally used to treat the same conditions."[33] To substantiate the similar nature of the proposed biosimilar product to the reference medicine product, the EMA requires the biosimilar applicant to provide evidence from comparability studies. These comparability studies may show data related to purity, physiochemical properties, biological activity, preclinical studies (including *in vitro* and *in vivo* studies), clinical trials and immunogenicity.

In addition to the general guidelines on biosimilarity, the EMA also provides product-specific guidelines that address different types of biosimilars. For example, monoclonal antibodies,[34] somatropin,[35] and low molecular weight heparins[36] each have their own individual guidelines that focus on aspects specific to the category of biologic dug. The determination of interchangeability is outside the scope of the EMA's authority and is determined separately by each member state of the EU.[37]

In terms of exclusivity, the EMA follows the "8+2+1" rule. Under this rule, an application for a biosimilar in Europe may not be submitted until the reference medicinal

26 Biotechnology Industry Organization, How Do Drugs and Biologics Differ?, http://bio.org/healthcare/followonbkg/DrugsVBiologics.asp (last visited Nov. 1, 2010).

27 Anthony D. so & Samuel L. Katz, *Biologics Boondoggle*, Op-Ed, N.Y. Times, March 7, 2010

28 Jessica Dye, "Obama Wants To Limit Biologic Protection In Health Bill," Law 360, January 15, 2010. http://www.law360.com/topnews/articles/143763/obama-wants-to-limit-biologic-protection-in-health-bill

29 Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC.

30 *Biosimilars approved in Europe,* Generics and Biosimilars Initiative http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe (last updated Nov. 14, 2014). Although 22 biosimilars have been approved since the European biosimilars pathway was created, two biosimilar approvals have been withdrawn. As a result, only 20 biosimilar drugs are currently approved for use in Europe.

31 *Biological Guidelines,* European Medicines Agency, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000082.jsp (last visited Nov. 14, 2014).

32 *EMA Procedural advice for users of Centralised Procedure for Similar Biological Medicinal Products applications*, European Medicines Agency (Oct. 2014) at 5, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

33 *Id.*

34 *Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues*, European Medicines Agency (May 30, 2012), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf

35 *Guidance on Similar Medicinal Products Containing Somatropin*, European Medicines Agency (Feb. 26, 2006), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003956.pdf

36 *Guideline on Non-Clinical and Clinical Development of Similar Biological Medicinal Products Containing Low-Molecular-Weight-Heparins,* European Medicines Agency (Mar. 19, 2009), http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003927.pdf

37 *EMA Procedural advice for users of Centralised Procedure for Similar Biological Medicinal Products applications*, European Medicines Agency (Oct. 2014) at 34, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/04/WC500125166.pdf

product has received eight years of data exclusivity,[38] ten years of marketing exclusivity,[39] and one additional year of marketing exclusivity if there is a new therapeutic indication. Accordingly, a biosimilar cannot be approved until the reference product has been on the market for 11 years.[40]

REGULATION OF BIOLOGICS IN JAPAN

In Japan, biosimilars are regulated by the Ministry of Health, Labour, and Welfare (MHLW), while the review process itself is conducted by the Pharmaceuticals and Medical Devices Agency (PMDA). In 2009, Japan published guidelines for quality, safety, and efficacy of follow-on biologics,[41] which is similar in concept to the EMA in the EU. In the same year, Sandoz's somatropin became the first drug to be approved as a biosimilar by the MHL. To date, eight biosimilars have been approved by the MHLW, including the biosimilars of Epogen®/Eprex®, Genotropin®, Lantus®, Neupogen®, and Remicade®.[42]

According to the guidelines, biologics are defined as a biotechnological drug product that is comparable to an approved biotechnology-derived product (reference product approved in Japan).[43] The term "comparable" is further characterized by the guidelines, noting that "[c]omparability does not mean follow-on biologics have to show identical quality attributes as the reference product, but it requires demonstration of high similarity in quality attributes with the reference product."[44] Since certain information concerning the innovator's product is generally not disclosed, the guidelines recommend biosimilar applicants to consider a comprehensive approach incorporating all available information and conducting clinical trials. Further, the required data package for the application can be abbreviated, because safety data is accumulated after approval of the innovator product.[45] For example, genotoxicity, carcinogenicity, and reproductive toxicity studies are not required for toxicology studies. In addition, the MHLW provided questions and answers (Q&As) three times in 2009,[46] 2010,[47] and 2015,[48] to promote an accurate interpretation of the guidelines.

There is no specific rule for market exclusivity for biosimilars in Japan. New drugs and biologics have eight years of data exclusivity (ten years for orphan drugs), without distinguishing between small molecule and biologics drugs, and also without distinguishing between innovator and generic/follow on products.[49]

REGULATION OF BIOLOGICS IN THE UNITED STATES

In the U.S., regulation of biologics is governed by the Public Health Service Act ("PHSA"), namely Section 351 (42 U.S.C. § 262). Under PHSA Section 351, a biologic must first be approved by the FDA before it can be commercialized and released onto the market. In order to be approved, the applicant must submit a Biologics License Application ("BLA") showing that the biologic is sufficiently safe, effective, and pure. To satisfy these requirements, the biologic must undergo extensive and lengthy testing.

The Biosimilars Act sets forth several requirements for biosimilars, which are discussed in turn below.

Biosimilar vs. Interchangeable

The Biosimilars Act establishes two categories of follow-on biologics – biosimilars and interchangeable biologics. According to the Biosimilars Act, a biosimilar is "biosimilar" to the brand-name drug if the two are "highly similar" notwithstanding minor differences in clinically

38 Directive 2001/83/EC, as amended by Directive 2003/63/EC and Directive 2004/27/EC, Article 10(1).

39 *Id.*

40 *Id.*

41 Ministry of Health Labor and Welfare, Pharmaceutical and Food Safety Bureau, Guideline for Ensuring Quality, Safety, and Efficacy of follow-on biologics, Notification No. 0304007 (March 4, 2009) [Japanese]

42 National Institute of Health Science, Biosimilars approved in Japan. Accessed at http://www.nihs.go.jp/dbcb/biosimilar.html [Japanese]

43 Ministry of Health Labor and Welfare, Pharmaceutical and Food Safety Bureau, Application for follow-on biologics, Notification No. 0304004 (March 4, 2009) [Japanese]

44 Ministry of Health Labor and Welfare, Pharmaceutical and Food Safety Bureau, Guideline for Ensuring Quality, Safety, and Efficacy of follow-on biologics, Notification No. 0304007 (March 4, 2009) [Japanese]

45 Id. No. 0304004.

46 Ministry of Health Labor and Welfare, Pharmaceutical and Food Safety Bureau, Q&A for the Guideline for Ensuring Quality, Safety, and Efficacy of follow-on biologics No. 1 (July 21, 2009) [Japanese]

47 Id. No. 2 (March 31, 2010) [Japanese]

48 Id. No. 3 (December 15, 2015) [Japanese]

49 Article 14-4 of the Pharmaceutical and Medical Device Act (Law No.145 in 1960)

inactive components and have no clinically meaningful differences with respect to safety and efficacy. [50,51] In addition, the applicant must show that the biosimilar has the same mechanism of action, same condition of use, same route of administration, same strength, and same dosage form as the brand-name biologic.[52] Furthermore, the biosimilar applicant must show that the manufacturing facility used to produce the biologic creates a "safe, pure, and potent" product.[53]

Alternatively, a biosimilar can be "interchangeable" if that biological product is biosimilar to the brand-name product, is expected to provide the same clinical result in a given patient,[54] and can be switched for the brand-name drug without diminished safety/efficacy.[55] Unlike a showing of biosimilarity, a showing of interchangeability permits the follow-on biologic to be substituted for the innovator biologic without consulting the prescribing healthcare provider.

To satisfy the requirements for "biosimilarity" or "interchangeability," a biosimilar applicant must show data from several studies including, (1) analytical studies showing that the follow-on product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; (2) animal studies assessing toxicity; and (3) one or more clinical studies sufficient to assess immunogenicity and pharmacokinetics or pharmacodynamics and to demonstrate safety and efficacy for each proposed indication.[56] Even though the FDA has the discretion to waive any of these studies if it deems them unnecessary,[57] it is unlikely that the FDA will use its discretionary power because of the complex and unpredictable properties of biologics.[58]

Exactly which data and how much data is required to satisfy a showing of "biosimilarity" or "interchangeability" has been the source of much debate. In May 2014, the FDA issued guidance advocating for a "totality of the evidence" approach.[59] Under this approach, the FDA evaluates data from different analytical studies and places the biosimilar product into one of four classifications: *not similar*, *similar*, *highly similar* and *highly similar with fingerprint-like similarity*. Of the four classifications, *highly similar* and *highly similar with fingerprint-like similarity* appear to satisfy the requirements of the Biosimilars Act, while a classification of only *similar* requires further data to support the application and a classification of *not similar* requires a change in the manufacturing process in order to even continue with the biosimilar application.

Exclusivities for Biologics

As a way to allow manufacturers of brand-name biologic products time to recover the substantial costs incurred in developing and obtaining approval for the biologic, the Biosimilars Act provides certain exclusivity periods. Section 351(k)(7) provides that licensure of an application for a biosimilar or interchangeable product under the Biosimilars Act may not be made effective until 12 years after the reference product was first licensed.[60] This form of exclusivity, often referred to as market exclusivity, provides developers of reference products the assurance of a minimum of 12 years of exclusivity on the market without having to face competition from biosimilars. Section 351(k)(7) further provides that an application for a biosimilar may not even be submitted for review to the FDA until 4 years after the reference product was first licensed.[61] This form of exclusivity, often referred to as data exclusivity, prevents applicants for a biosimilar from using the data generated by the reference product in submitting an application to the FDA. Together, these two time periods are known as reference product exclusivity.

The Biosimilars Act further provides for an extension of the market exclusivity period by an additional six-month period if the biologic is tested and approved for pediatric use. As a result, the Biosimilars Act can provide up to 12.5 years in market exclusivity.

Not every licensure of a biological product under 351(a), however, is considered a "first licensure" that gives

50 Public Health Service Act § 351(k)(2)(A)(i)(I), 42 U.S.C.A. § 262(k)(2)(A)(i)(I) (West 2010).

51 Section 7002(b) of the Biosimilars Act amends PHSA § 351 (i) to define "biosimilar" to mean "(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111–148, § 7002(b), 124 Stat. 119, 814–15 (2010).

52 Id. § 351(k)(2)(A)(i)(II)-(IV).

53 Id. § 351(k)(2)(A)(i)(V).

54 Id. § 351(k)(4)(A

55 Id. § 351(k)(4)(B).

56 Id. § 351(k)(2)(A)(i)(I).

57 Id. § 351(k)(2)(A)(ii).

58 Follow-On Biologics, Data Exclusivity, and the FDA. Berkeley Technology Law Journal. Tzeng, L. Jan 2010, volume 25, Issue 1, Article 6, Page 135; Tzeng, Linfong, Follow-On Biologics, Data Exclusivity, and the FDA Berkeley Technology Law Journal_2010_vol25 p135.

59 FDA Guidance for Industry, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" May 2014

60 PHSA § 351(k)(7)(A).

61 PHSA § 351(k)(7)(B).

rise to its own exclusivity period. On August 4, 2014, the FDA released its new industry guidance about determining exclusivity for biological products filed under Section 351(a). The guidance is intended to assist developers of biological products and the FDA in determining the date of first licensure for reference products, which is important in determining when reference product exclusivity ends and when biosimilars and interchangeable products may enter the market. According to the guidance document, the date of first licensure does not include:

1. a supplement for the biological product that is the reference product; or
2. a subsequent application filed by the same sponsor or manufacturer of the biological product (or a licensor, predecessor in interest, or other related entity) for:
    a. a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength; or
    b. a modification to the structure of the biological product that does not result in a change in safety, purity, or potency.

Exclusivities for Biosimilars

The Biosimilars Act additionally establishes market exclusivity periods for the first biological product approved as interchangeable with the brand-name product. This interchangeable exclusivity period may range from 12–42 months. Pursuant to the Biosimilar Act, the first biosimilar applicant to earn interchangeable status will be granted one year of market exclusivity from the date of its first commercial marketing.[62] However, this one year period of exclusivity may be extended in the event of litigation against the first licensee. In the event of a final court decision or dismissal on all patents-in-suit against the first approved biosimilar, for example, the first biosimilar may receive 18 months of market exclusivity.[63] Moreover, in situations where the patent infringement action is ongoing, the first biosimilar may be granted up to 42 months of exclusivity before a subsequent biosimilar may be approved.[64] If no patent infringement suit was brought against the first applicant, then the first biosimilar may receive 18 months of exclusivity.[65]

Patent Dispute Resolution of the "Patent Dance"

The Biosimilars Act also provides a dispute resolution scheme to resolve patent disputes arising out of applications for approval of a biosimilar or interchangeable product. Under the Biosimilars Act, the applicant of the biosimilar is required to provide legal representatives of the reference product a copy of the application as well as additional information regarding the process used to manufacture the biological product within 20 days after acceptance of an application for a biosimilar by the FDA. The representatives of the reference product then have 60 days to (1) provide the biosimilar applicant with a list of all patents for which the reference product sponsor believes a claim of patent infringement could reasonably be asserted against the biosimilar applicant, and (2) identify which of these patents it would be prepared to license to the biosimilar applicant. The biosimilar applicant then has another 60 days in which to provide its own "counter-list" of patents that it believes a claim of patent infringement could be based on and reasonably be asserted against the biosimilar applicant. For each patent on both the reference product sponsor's list and the biosimilar applicant's list, the biosimilar applicant is required to provide either a "detailed statement that describes, on a claim-by-claim basis, the factual and legal basis of the opinion of the [biosimilar] applicant that such patent is invalid, unenforceable, or will not be infringed by the commercial marketing of the biological product" or a statement that is does not intend to begin commercial marketing before the date of patent expiry." Within 60 days of receiving the biosimilar applicant's list, the reference product sponsor is required to provide a "counter-detailed statement" explaining, for each patent listed, "the factual and legal basis of the opinion of the reference product sponsor that such patent will be infringed by the commercial marketing of the biological product" as well as a response to the biosimilar applicant's statements of invalidity and unenforceability. Once the above exchanges have been completed, the Biosimilars Act requires both parties to negotiate, within 15 days, which patents, if any, will be the subject of an infringement action.

62 PHSA § 351(k)(6)(A).

63 PHSA § 351(k)(6)(B).

64 Id. § 351(k)(6)(C)(i).

65 Id. § 351(k)(6)(C)(ii).

GLOBAL OUTLOOK FOR BIOSIMILARS

Due to the increasing demand for treatments for debilitating diseases such as autoimmune diseases, metabolic disorders, degenerative diseases, blood disorders, and cancer, biologics are becoming ever more prevalent and may overtake small molecule drugs in the pharmaceutical marketplace in the near future.[66] In fact, seven of the top eight best-selling drugs on the global market in 2013 were biologics and eight of the top 15 were biologics.[67] The top selling biologics in 2013 were rheumatoid arthritis drugs Humira® ($10.7B) and Remicade® ($8.9B). Other top selling biologics in 2013 include Rituxan® (($8.9B), Enbrel® ($8.3B), Lantus® ($7.8B), Avastin® ($7.0B), Herceptin® ($6.8B), and Neulasta® (4.4B), which are used to treat Non-Hodgkin's lymphoma, plaque psoriasis, diabetes, colorectal cancer, breast cancer, and neutropenia, respectively.[68]

While biologics are increasing in popularity, they also tend to be quite expensive for the patient. On average, the cost of a biologic is over $16,000 per patient per year.[69] However, the commercial price of any given biologic treatment can reach up to several hundred thousand dollars per year. To demonstrate how costly biologics can be, the annual cost for the cancer treatment drug Avastin® is approximately $60,000[70] and Cerezyme®, which is used to treat Gaucher Disease, is over $300,000[71] per patient per year. Other annual costs per patient of top biologics are equally expensive, including Enbrel® at $26,000, Herceptin®, a drug used to treat breast cancer, at an average of $37,000, and Humira®, which costs more than $51,000.[72] To put into perspective aggregate amounts spent on specific biologics, the Centers of Medicare and Medicaid Services reportedly spends approximately $2 billion each year on the anemia treatment Epogen®.[73]

In 2013, the global market of biosimilars was estimated to be $1.3 billion, and it is expected to increase to around $35 billion by 2020.[74] While brand-name biologic drugs have certainly generated significant sales in recent years, the expiry of patents covering popular biologics paves the way for biosimilars to enter the pharmaceutical market. Over the next four years, ten biologic drugs with over $60 billion in combined sales will face key patent expirations.[75] The biologics approaching this so-called "patent cliff" include market titans such as Humira®, Remicade®, and Enbrel®. With the expiration of the patents protecting these major biologic drugs looming, it is expected that more biosimilars will seek approval and enter the market.

The future of biosimilars is only enhanced by the fact that the first two biosimilar products have been approved by the FDA, and several more have been accepted for review. The first biosimilar approved under the Biosimilars Act is Sandoz' Zarzio®, which is a biosimilar version of Amgen's Neupogen® (filgrastim), a biologic used to prevent infections in cancer patients getting certain treatments that result in a decrease in infection-fighting white blood cells. The reference product, Neupogen®, generated $1.4 billion in sales in 2013.[76] Sandoz's biosimilar is the first biosimilar application known to have been accepted by the FDA for review since the enactment of the Biosimilars Act in 2009 and also the first biosimilaar approved under the new pathway.[77] Prior to its approval in the US, Sandoz's biosimilar had already been approved in more than 40 countries outside the US, with approvals in Japan and Europe.[78]

66 Biologic medicines have been marketed to treat a number of diseases including multiple sclerosis, diabetes, rheumatoid arthritis, anemia, sepsis, and various cancers. For a catalog of currently approved biologics and their therapeutic indications, see FDA's Therapeutic Biological Products, http://www.fda.gov/cder/biologics/default.htm (last visited Apr. 22, 2008).

67 Biologics Still on Top in Best Selling Drugs of 2013, http://cellculturedish.com/2014/03/top-ten-biologics-2013-us-pharmaceutical-sales-2/ (last visited Nov. 5, 2014).

68 *Id.*

69 Andrew F. Bourgoin, *What You Need To About The Follow-On Biologic Market in the U.S.: Implications, Strategies, and Impact* at 1, Thomson Reuters (January 2011), http://thomsonreuters.com/products/ip-science/04_013/newport-biologics.pdf.

70 Paula Trioni, "Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs," 19 *Annals of Health Law* (2010), 311.

71 Anna Edney, *Sanofi Wins U.S. Approval for New Gaucher Disease Pill,* Bloomberg, (Aug. 19, 2014, 4:45 PM ET), http://www.bloomberg.com/news/2014-08-19/sanoif-wins-u-s-approval-for-new-gaucher-disease-pill.html.

72 The Generic Pharmaceutical Association. Generic Drug Savings in the U.S. Fourth Annual Edition: 2012

73 Schacht, Wendy H., and Thomas, John r. "Follow-On Biologics: The Law and Intellectual Property Issues." Congressional Research Services, December 6, 2012.

74 *Biosimilars/Follow-on-Biologics Market is Expected to Reach $35 Billion, Globally, by 2020*, PR Newswire, (July 21, 2014), http://www.prnewswire.com/news-releases/biosimilarsfollow-on-biologics-market-is-expected-to-reach-35-billion-globally-by-2020-267947471.html.

75 *Id.*

76 *Id.*

77 *Id.*

78 *Id.*

The second biosimilar approved by the FDA was for Celltrion's biosimilar version of Johnson & Johnson's Remicade® (infliximab), a monoclonal antibody used to treat autoimmune diseases such as rheumatoid arthritis.[79] While Celltrion's Remsima® application was the second biosimilar application known to be filed under the Biosimilars Act, it was the first application that has been filed for a biosimilar monoclonal antibody.[80] Prior to its approval in the US, Celltrion's infliximab biosimilar was already marketed in over 50 countries worldwide under the brand name of Remsima®.[81] In fact, Remsima® remains the world's first and only biosimilar monoclonal antibody to be approved by the European EMA, Japan MHLW, Health Canada, and now the US.[82]

IMPLICATIONS FOR THE HEALTHCARE INDUSTRY

While the Biosimilars Act, the EMA, and the Japanese guidelines pathways are intended to promote development of biosimilar products, questions remain about whether these regulatory regimes can, in fact, promote the development of safe and affordable biosimilars and ensure continued development of novel biologic medicines.[83] This is, in part, due to the strict standards for achieving "biosimilarity" and "interchangeability," safety considerations, the uncertain exclusivity timelines that undermine biosimilar market exclusivity, and potential loopholes that allow agreements between reference product sponsors and biosimilar manufacturers to extend their market exclusivity periods.

A major obstacle presented by these regulatory regimes for biosimilars is the uncertainty, difficulty, expense, and risk associated with the development of a biosimilar.[84] As previously mentioned, biosimilars may need to qualify as either "biosimilar" or as "interchangeable" to be approved under the Biosimilars Act. Despite FDA guidance on the subject matter, it is still unclear exactly what qualifies as "highly similar" or how much safety and efficacy data is required for the various studies, and since no company has yet successfully navigated through the new approval process, there is no clear definition of the requirements needed to satisfy these various standards.[85]

On the other hand, the EMA provides several guidelines for specific products, and the Japanese MHLW gives supplemental notifications that improve the clarity of the guidelines. Although the pathways for biosimilars were created at almost the same time in the U.S. (2010) and Japan (2009), more biosimilars have been approved in Japan during this time. This shows that the uncertainty of the standards in the US is creating a more difficult barrier to approval for applicants as compared to Japan.

The limited guidance that may be available from the biosimilars that have been approved under the BLA process illustrates how difficult it may be for a biosimilar product to attain the higher and more desired classification of "interchangebility." Omnitrope®, for example, received FDA approval in 2006 only as a biosimilar, but not as a substitutable, or interchangeable, product for Pfizer's reference product, Genotropin®. In support of its application, Sandoz submitted extensive clinical data to demonstrate the biologic's pharmacokinetic, pharmacodynamic, physiochemical, and bioavailability similarity to Genotropin®, in addition to new pharmacology, toxicology, and safety data specific to Omnitrope®. Even though the supporting data was not as extensive as required for a new drug, Sandoz still invested a significant amount of time and resources developing the product. Lacking clear guidelines for attaining biosimilarity and interchangeablity, manufacturers of biosimilars could find themselves expending time and resources on studies that may fail to reach the threshold of FDA approval.

Concerns about immunogenicity further compound apprehensions about developing biosimilars. Even minor changes in one amino acid or in the formulation of the biologic can affect the safety of the drug. Problems surrounding the safety of the biologic, however, may not be fully understood until post market surveillance when more patients are exposed to the drug. Even if only a few patients are negatively affected by a biosimilar after it has reached the market, that biosimilar may be pulled off the market and the company manufacturing it may not only fail to recoup the investment of developing the drug, but may also be responsible for potential liability. As a result, the difficulty and risk in developing biosimilars

79 *Celltrion files for US FDA approval of Remsima®*, Celltrion, (Aug. 11, 2014), http://www.celltrion.com/en/COMPANY/notice_view.asp?idx=456&code=ennews&intNowPage=1&menu_num=&align_year=all

80 *Id.*

81 *Id.*

82 *Id.*

83 Joanna T. Brougher and David A. Fazzolare, "Will the Biosimilars Act Encourage Manufacturers to Bring Biosimilars to Market?" Food and Drug Policy Forum, Vol.1, No. 5, March 8, 2011.

84 Will the Biosimilars act encourage manufacturer to bring Biosimilars to Marker? FDLI's. Brougher, J. March 2011 Volume 1, Issue 5.

85 FDA Guidance for Industry, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product" May 2014.

may consequently deter manufacturers from engaging in biosimilar development.

Another hurdle produced by the Biosimilar Act is the uncertain exclusivity timelines awarded to first interchangeable biosimilars. Unlike under the Hatch-Waxman Act, which provides the first approved generic drug applicant with a 180-day period of market exclusivity, the Biosimilars Act provides no set period of time to the first interchangeable biosimilar. As currently written, the Biosimilars Act includes four provisions concerning timelines that effectively prohibit the FDA from approving subsequent interchangeable biosimilars. As a result, the period of exclusivity granted to the first interchangeable biosimilar may vary depending on a number of factors and can range anywhere between 12 and 42 months.[86] This is in contrast to the EU and Japan, which have a distinct market exclusivity period. Without a clear understanding of what the market exclusivity available to the first interchangeable biosimilar will be, manufacturers may not undertake the increased expenditures and risks associated with developing interchangeable biosimilars if there is a chance that they may not receive the exclusivity that they are promised for undertaking such risks.

Another impediment presented by the Biosimilar Act is the possibility of authorized interchangeable settlement agreements. These agreements are arrangements between the reference product and biosimilar manufacturers to forgo patent infringement litigation in the interest of sharing the statutory exclusivity awarded to the first biosimilar applicant.[87] As seen with the Hatch Waxman Act, these authorized settlement agreements help the reference product obtain an additional period of market exclusivity, which ultimately delays biosimilar competition by up to 18 months.

Under the Biosimilars Act, settlement agreements are permissible since litigation of the innovator's patents is not a prerequisite of obtaining exclusivity as it is with the Hatch-Waxman Act. Pursuant to Paragraph (4)(A) of the Biosimilars Act the reference product and biosimilar manufacturers are required to engage in good faith negotiations in order to agree upon which, *if any*, patents covering the brand-name biologic are to be litigated.[88] If the reference product and biosimilar manufacturers agree under Paragraph (4)(A) that none of the patents covering the brand-name biologic product will be litigated, then the reference product manufacturer could elect to enter into a licensing agreement with the biosimilar manufacturer, which could subsequently delay biosimilar market entry beyond the exclusivity provided for in the Biosimilars Act.

A further concern presented by the Biosimilars Act is that the Biosimilars Act may fail to provide the necessary incentives, specifically financial motivations, to promote continued development of novel biologic products. Reduced innovation among reference product companies to develop and commercialize biologics will result in fewer novel biologics on the market and, in turn, fewer available treatment options.

For instance, there are concerns that the market exclusivity period provided under the Biosimilars Act may be insufficient to ensure a large enough financial return to justify the risk and expense in connection with developing a biologic.[89] Specifically, the 12 years of exclusivity currently awarded under the Biosimilars Act may not be long enough to successfully encourage continued biotechnology innovation. Under the Hatch-Waxman Act, the average market exclusivity period that brand manufacturers receive is about 11.5 years.[90] Nevertheless, even with almost 12 years of effective exclusivity, brand manufacturers continued to focus their resources on incremental innovation and competition for a share of the generic market with the result being a decrease in new pharmaceuticals being developed and commercialized. If 11.5 years is insufficient to produce the level of pharmaceutical innovation needed to produce a significant number of novel small molecule drugs, known as New Chemical Entities, then 12 years may not be a long enough exclusivity period for biologics. In fact, in Japan, where only eight years of market exclusivity is provided for both small molecule drugs and biosimilars, brand companies develop fewer novel biologics as compared to the U.S companies.

Due to the aforementioned challenges of developing biosimilars, the Biosimilars Act may encourage manufacturers to develop "biobetters" rather than lower cost biosimilars. Biobetters are improved versions of existing biologic drugs and can improve upon the original in a number of ways, such as reducing the side-effect profile of the drug. Since biobetters are regulated as innovative drugs, they are approved by way of the existing BLA route, which is clearly defined, better understood, and provides a proven pathway to approval. Moreover, the BLA route awards 12 years of exclusivity for structural

86 PHSA § 351(k)(6)(A).- (C)

87 Fazzolare, David A. "Gaming the Biosimilars Act: Loopholes Allow Authorized Interchangeable Settlement Agreements to Delay Authentic Generic Competition up to 18 Months," *FDA Update*, July/August 2010.

88 Biosimilars Act, § 351(l)(4)(A).

89 Brougher, J. "Intellectual Property and Health Technologies: Balancing Innovation and the Public's Health" Springer Publishing, 2014 ed.

90 Manheim BS, et al. 'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry. Biotech Industry. March/April 2006, 394–403.

changes to existing biologics that result in enhanced safety, purity, or potency.[91]

Because of the reduced risk associated with developing biobetters, companies are directing their attention to pursuing them. Biobetters have also proven themselves to be extremely profitable. Amgen's biobetter Neulasta®, used for the treatment of neutropenia, for instance, generated more than $3.3 billion in annual sales compared to only about $900 million a year for the original product Neurogen®. Similarly, Roche's biobetter Pegasys®, which is an improved treatment for hepatitis C, generated $1.58B in 2010, more than double the amount that Roche's original product PegIntron® generated. Therefore, while the route established by the Biosimilars Act to bring biosimilars to market is, at least at the moment, filled with uncertainly, biobetter development under the BLA route may be a preferred alternative for companies when faced with deciding between little to no market exclusivity and the possibility of 12 years of market exclusivity.

SUMMARY

With biosimilars poised to make a major breakthrough, much attention has turned to if and how they will be approved, particularly under the new approval pathway established by the Biosimilars Act. The Biosimilars Act creates numerous challenges that may impact biosimilar development and ultimately commercialization. Although the Biosimilars Act, like the EMA and Japanese pathways, is intended to promote development of biosimilars, questions remain about the uncertainty created by the Act. While it is unclear exactly how biosimilar approval will play out under the Biosimilars Act, what is clear is that a significant amount of discussion will ensue surrounding interpretation of the Biosimilars Act and how the FDA implements it.

91 Biosimilars Act, § 351(k)(7)(C).

From the Board Room

Industry Partnerships, Key Success Factor to Win in the Biosimilars Space

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ABSTRACT

Over the past few years, biosimilars became the promised land of the pharmaceutical industry. Seven out of the top ten drugs are biologics. And all are about to lose patent protection by 2020, representing an underlying pool of $60bn branded sales. While it looks like the next Eldorado is in front of us, the biosimilars market is also a challenging opportunity, where the players have to deal with high R&D costs, unclear regulatory pathways, and uncertainty around business models. To make the biosimilars opportunity a sustainable market, it has to be profitable. In this article, I would like to discuss how innovative business models can help biosimiliars players to de-risk and ensure profitability. Looking at the example of the airline industry and analyzing the development chain for biosimilars, I would like to propose options to de-risk investments, optimize costs, and maximize sales.

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Keywords: biosimilars; biologics; risk; de-risking; business models; profitability; sustainable

In this article I discuss biosimilars of monoclonal antibodies and focus specifically on mature markets.

Over the past few years, biosimilars became the promised land of the pharmaceutical industry. Seven out of the top ten drugs are biologics. And all are about to lose patent protection by 2020, representing an underlying pool of $60bn branded sales. While it looks like the next Eldorado is in front of us, the biosimilars market is also a challenging opportunity, where the players have to deal with high R&D costs, unclear regulatory pathways, and uncertainty around business models. To make the biosimilars opportunity a sustainable market, it has to be profitable. In this article, I would like to discuss how innovative business models can help biosimiliars players to de-risk and ensure profitability. Looking at the example of the airline industry and analyzing the development chain for biosimilars, I would like to propose options to de-risk investments, optimize costs, and maximize sales.

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BIOSIMILARS, A CHALLENGING OPPORTUNITY

First, important investments are required to play in the biosimilars space. On average to develop a biosimilar, you need to put down an initial investment in the range of $150m to $300m over an 8 year time period. And this is just to come up with a compound. Additionally, as competitive manufacturing costs and supply reliability are prerequisites for any biosimilars player, there is a need for reliable manufacturing capacity. Which may be another $50m to $100m additional capex investment. Unless the player can leverage its existing biologic manufacturing capacity.

Then, there are still many regulatory uncertainties, especially in the US. The US accounts for half of the opportunity today, but regulatory pathways are still being clarified. For example, there is no clearly defined provisions for interchangeability or substitution. On the other side, originators are filing law suits to block biosimilars and to delay their entry. There is evidence of substantial pushback from innovator companies to delay biosimilar entry and hinder competition in the US market.

Next, there are many uncertainties around the business models for biosimilars. For the first wave of monoclonal antibodies biosimilars, not only there is an increased need for clinical data to justify biosimilarity, there is also a high need to educate the medical profession about biosimilars, as well as mastering payer contracting to ensure access to patients.

Finally, no player will be able to offer a one-stop shop with a complete portfolio of all the biosimilars. This fragmentation will force hospitals to source from many players, which means duplicative efforts to source the biosimilars versus if a player could offer all the biosimilars at once.

THE EXAMPLE OF THE AIRLINE INDUSTRY IN 2000

Before 2000, each airline was going solo across the entire value chain of the airline business. Each company had their own procurement, their own maintenance and repair, their own booking system, and their own frequent flyer program. In the year 2000, the airline industry got hit by a major crisis. Oil prices were skyrocking. The advent of the internet allowed for price discovering, which eventually led to a price war and a downward spiral of profitability. Finally 9.11 brought 'le coup de grace' as traffic drastically decreased in a matter of months with public fear of flying.

How did the airline industry survive? First by pin-pointing the problem. There was a big waste in the airline industry with many duplicating efforts. So what was the solution? The solution was to improve efficiency. The number of players decreased through industry consolidation. Many of the underperforming companies went bankrupt. There was a major stream of collaboration with the advent of partnerships and alliances. American Airlines led the initiative with the creation of One World comprised of 16 permanent partner airlines. Lufthansa led the second biggest alliance, Miles & More, comprised of 13 permanent partner airlines. Each alliance offered its partners shared procurement where pooled purchase of airplanes allowed to get bulk discounts. Each alliance also offered shared center of excellence which led to substantial economies of scale in maintenance, repair, and booking systems. Finally each alliance offered a pooled frequent flyer program which incentivized passengers to fly with the airlines within the alliance.

Before looking at the potential translation of the lessons learnt from the airline industry, let's quickly review the development chain for biosimilars. In this way, we can pin-point exactly where the investments are needed and where the costs occur.

THE BIOSIMILAR DEVELOPMENT CHAIN

There are five areas of investment for any biosimilar player:

Step #1 is R&D. It includes cell-line & process development, reference material sourcing, and analytics, and manufacturing scale-up.

Step #2 is Manufacturing. This step is directly linked to step #1 as the process development and the manufacturing scale-up should preferably be done in the final manufacturing plant.

Step #3 is Regulatory. It is critical to get FDA and EMA green light. Note that US and EU5 account for over 70% of the total biosimilar potential.

Step #4 is Market Access. It is not sufficient to put a product on the market. The drug also needs to be made available from the payers. Establishing strong payer relationships is key to ensure the drug gets on the formulary and gets reimbursed.

Step #5 is Marketing. There is a need to adopt a branded mentality to win stakeholder trust. Which is an expensive commercial approach to build from scratch. Unless the player has biologic experience to build upon.

As a base across all these steps, clearing the IP landscape is of paramount importance. It implies to have an in-house legal team to ensure no infringement on valid patents through the development stages. It also implies significant investment in legal battles to neutralize originators defense strategies against biosimilars.

In my opinion, the players who master these 5 steps – as depicted in Figure 1, including IP, will be best equipped to master the biosimilar environment.

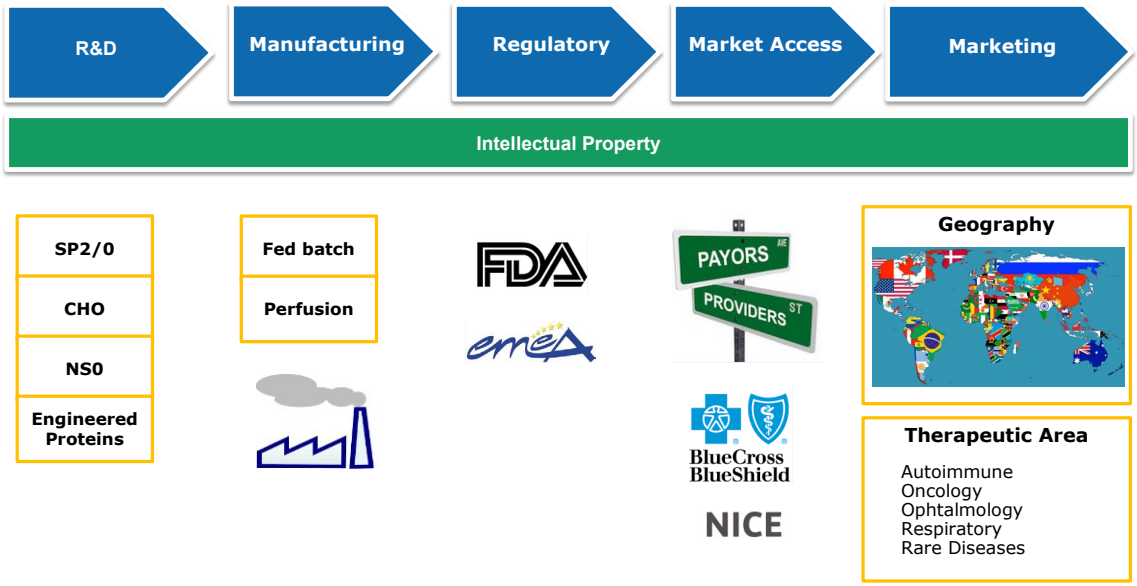

Figure 1 : The Biosimilar Development Chain

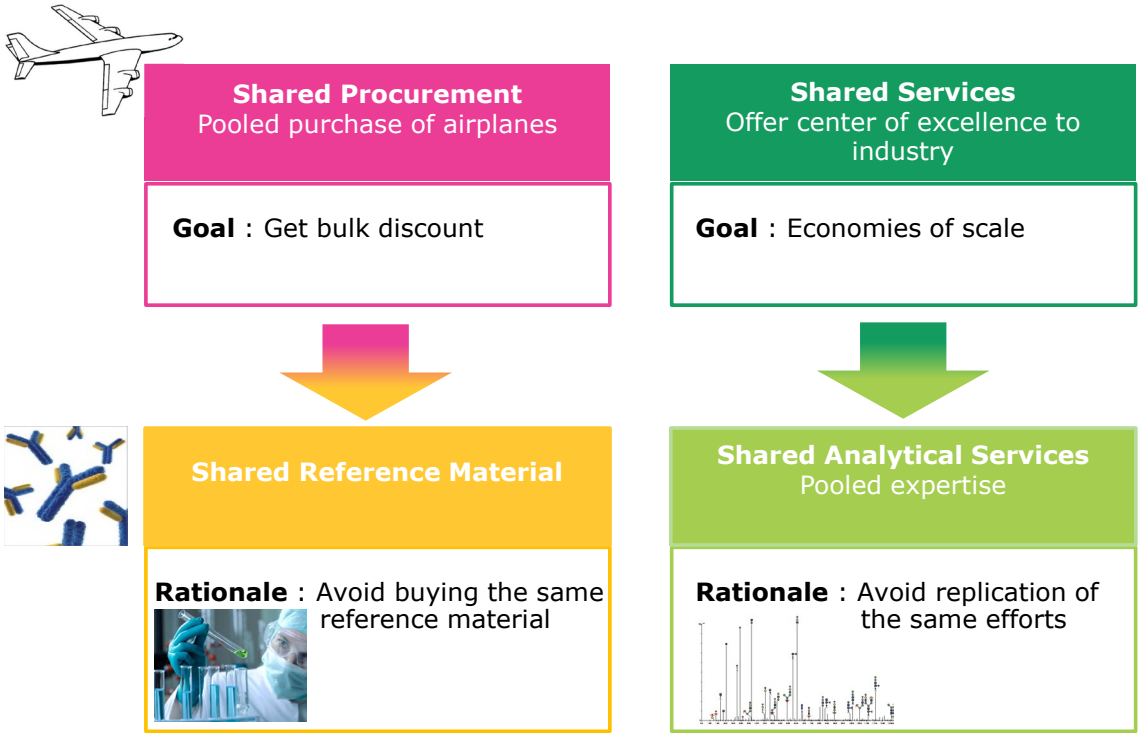

Figure 2 : Potential Translation from Airlines to Biosimilars

POTENTIAL TRANSLATION FROM AIRLINES TO BIOSIMILARS

Just like in the airline industry before 2000, we are duplicating efforts and under-utilizing assets. For example, there are over 20 companies working on a biosimilar of Adalimumab. Each player is working in silos, buying the same reference material and doing the same analytical work. Just like in the airlines industry, we could build alliances and partnerships to better leverage asset utilization. We could collaborate

on sourcing reference materials and align on standards for analytics. How could such a collaboration look like? First we need to have at least three companies in the cooperation. Then data needs to be shared not as package, but when available and everybody should only have access after the overall fee had been paid. Finally, outsourcing of general analytical characterization for each partners' compounds would be helpful to such a collaboration because it decreases the amount of cross-validation. In this context, a firewall between the participating companies would be crucial in order to not destroy the competition and to equalize the timing. In Figure 2, you will find an illustration of the potential translation from airlines to biosimilars.

DISCLAIMER

The views and opinions expressed in the above article are those of the author and should not be attributed to, or considered as reflecting the position of EMD Serono or its management.

From the Board Room

Biotechnology, a Strategic Planning Orphan: Towards an Effective Strategy Framework for Biotechnology Firms

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ABSTRACT

Drug development biotechnology firms are most appropriately conceptualized as intermediaries in the pharmaceutical R&D value chain. Because they generally do not launch products themselves, generate significant revenues or compete in traditional markets, the established strategic planning frameworks and tools, such as SWOT, PESTLE and Gap analysis, have little utility. Porter's Five Forces Model (FFM) is a strategic planning framework that is prominent in texts, but has not been applied to biotechnology firms to any significant extent. This study reports on its application in one drug development biotechnology firm and concludes that, like the other techniques, FFM also fails for biotechnology firms. This is because it is rooted in traditional, highly-competitive markets, where profit maximization is the goal, and not the world of the R&D intermediary, where value creation is the measure of success. Despite the misfit of the FFM for biotechnology firms, the notion that strategy can be derived by consideration of the forces that influence success may provide the basis for a new strategy framework relevant to the business of biotechnology.

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Keywords: strategy; five forces model; biotechnology

INTRODUCTION

While biotechnology has application in a number of fields, including biofuels, biocrops and industrial applications, drug development is the standard bearer in the business of biotechnology, not only because cures for diseases capture public imagination and have profound societal value, but because the financial rewards for successful drug development are so substantial. Indeed, Pisano ignores all other applications and defines "biotechnology" as all those technologies that could be applied to pharmaceutical drug research and development, including biology, chemistry and computer science.[1] He further defines a biotechnology firm as "any firm founded after 1976 that has the principle purpose of advancing, developing, or commercializing these technologies for drug discovery" (p. 16).

Pisano characterizes these biotechnology firms principally as 'middlemen' in the R&D supply chain that take on projects at an early stage, develop them to some point, and then license them to pharmaceutical partners for final development and commercialization.[1] Figure 1 shows the pharmaceutical R&D value chain, in which biotechnology firms operate.[2]

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Figure 1: Pharmaceutical R&D Value Chain

Source: "Unleashing Pharma from the R&D Value Chain", 2013 report by A.T. Kearney, Inc.

The drug development process starts with identifying and validating a disease target, typically a protein, which could act as a locus for intervention in a disease pathway. Typically, this is carried out by universities and other public research organizations. The next step is finding lead compounds that will interact with that target, and once these are optimized, they undergo preclinical development in anticipation of entry into human studies. As the drug enters human clinical studies, it is referred to as a 'candidate drug' and proceeds through three phases of clinical evaluation, starting with safety testing (Phase I), dosage, safety and preliminary efficacy testing in a small number of patients (Phase II) and finally, a large scale, pivotal study (Phase III).

If the candidate drug survives all this, the sponsoring pharmaceutical company will apply to the U.S. FDA (Food and Drug Administration), or equivalent authority elsewhere, for approval to market the drug. The entire process may span 10-15 years and at the Phase I stage, a candidate drug has only a 19% chance of gaining approval, on average.[3] Most biotechnology firms focus on the preclinical stage through to Phase II clinical development, with Phase II generally being the optimum point for licensing to a pharmaceutical partner.[2]

In summary, biotechnology firms typically in-license advances in basic science, usually patents or lead compounds from universities, progress them to candidate drugs,[4] take them through early clinical development and push them towards the market, usually via a pharmaceutical partnership. The fact that biotechnology firms are intermediaries in a long and risky development pathway and may not launch products themselves or compete in traditional markets, makes strategic planning for such firms uniquely challenging.

STRATEGIC PLANNING IN BIOTECH

Surprisingly, not much has been written about the specific challenges of strategic planning for biotechnology firms, with most of the planning approaches proposed being no different to other industries. According to one author,[5] the starting point for strategic planning for biotechnology firms is the long-term objectives of management, i.e., the vision, as shown in Figure 2.

That paper asserts that, because the business of biotechnology is so complex and uncertain, a vision is critical to driving the strategic planning process for biotechnology firms. But what if the long term vision of the founder is wrong or unrealistic?

Because of the uncertainties and complexities of the drug development business, along with the turbulence in the regulatory and funding environment, the chances of setting an inappropriate goal upfront are greater than in any other business. Forced to arrive at a vision to seed the strategic planning process as prescribed, a biotechnology firm founder might decide that his/her vision is to build a global, fully-integrated pharmaceutical company (FIPCO), which is an utterly unrealistic goal for a start-up biotechnology firm that may have one or two preclinical-stage candidates, each with a 90% chance of failure before reaching the market.

Even a generic goal or vision, such as "to create value for our investors" offers no insight as to the pathway and is hollow as a strategic guide. A vision aimed at a particular therapeutic area, such as cancer, ignores the reality that many biotechnology firms will grow a portfolio of candidate drugs, perhaps from the same technology platform, which could span multiple therapeutic fields. With the rapid evolution of technology, a vision focused on a specific technology platform may be equally inappropriate, because the technology may become obsolete or the biotechnology firm may in-license or discover alternative or improved technology approaches. To a large extent, therefore, the future evolution of a biotechnology firm may be unknowable and attempting to prescribe early boundaries in the form of a vision is likely to be counter-productive.

According to the same author, once the vision is laid down, the planning process for biotechnology firms follows the same overall steps as for other industries (Figure 2), namely: conduct an internal and external situation analysis using SWOT and an external auditing analysis similar to a PESTLE analysis. This allows the company to establish strategic goals and conduct a gap analysis to assess variance between projected revenues and the strategic goals. This is followed by assessment and selection of strategy alternatives that emerge.

Techniques such as PESTLE and SWOT are internal and external auditing tools rather than strategy

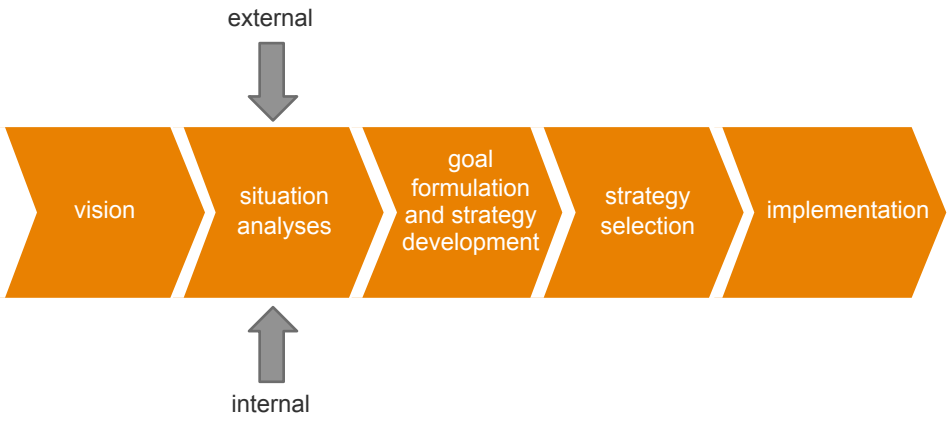

Figure 2: Biotechnology Strategic Planning Process

Source: Muller, C. 2002. Strategic management: A tool for growth in the biotechnology sector. Journal of Commercial Biotechnology, 8(3): 226-234.

forming or directing tools. Without the context of a strategic goal and pathway, they offer little utility. In the case of SWOT, analyzing strengths and weaknesses presupposes a goal for the business, but this is not explicit in most cases and may be unknowable for an early stage biotechnology firm. Analyzing opportunities and threats assumes a market or competitive arena, but this is not defined.

PESTLE analysis is an additional auditing tool that seeks to analyze the environment within which the firm operates, but the lenses offered are not particularly relevant to the business of biotechnology firms and lack strategic context. An environmental audit may help management manage risk and adjust the company's current direction accordingly, but it fails to provide a goal-relevant framework for *de novo* strategy formation.

Gap analysis comprehensively fails for biotech, because there are no sales,[6] from which to build a revenue trajectory, on which a gap analysis might be constructed, in order to arrive at non-organic strategies for growth; virtually everything to do with the value proposition of the biotechnology business is *organic*. Similarly, portfolio analysis tools such as the BCG model and similar models do not work, because biotechnology firms, as defined, have no marketed products and do not operate in product markets in the traditional sense. Moreover, most biotechnology firms often do not have a lot of choice about what product markets they may enter or exit, as these are mostly predetermined by the therapeutic indications for the candidate drugs that they have in development.

In summary, none of the traditional strategic planning models or frameworks offers much utility as a strategy formation tool for biotechnology firms. One technique that is not used as frequently as the above approaches, but has strong support in management texts as a strategic planning framework, is Porter's Five Forces Model of strategic analysis. It is also a model that has been applied to the pharmaceutical industry.[7–9]

THE FIVE FORCES MODEL

For several decades, Porter's Five Forces Model (FFM), as shown in Figure 3, has shaped the strategy thinking of managerial academics and to some extent, practicing managers. Indeed, recently, Porter provided an update on the model re-emphasizing its potential to help practicing managers understand strategic implications for their firms.[10]

The FFM asserts that there are five competitive forces that determine the long term profitability of an industry and that should be the drivers of strategy. Basically, the stronger the five forces, the lower the profitability for the existing competitors, because strong forces attract profit in their direction leaving less for other players. Where all the forces are strong, then the profitability for the competitors will be very low.

One way in which the model can be used to shape strategy is to help decide what industries to enter and which to avoid. For players already committed to a specific industry and where the forces are strong, they can use it to find niches where one of the forces may be lower

Figure 3: Porter's Five Forces Model

Source: Porter, M. (2008) "The five competitive forces that shape strategy." Harvard Business Review. 2008. 86(1):78-93, 137

or use tactics to neutralize or diminish one or more of the forces. Porter's overarching premise is that by understanding the structure of the industry in terms of the drivers of profitability, competitors can stake out positions that allow them to achieve sustainable profitability. Porter asserts that despite the apparent superficial differences between industries, the underlying drivers of profitability as identified in the model are the same for all industries.

FFM has been the subject of both praise and criticism in the literature, which has been summarized and reviewed by others.[11–13] From a practitioner's perspective, one notable criticism is that, while prominent in texts and business schools, FFM has not achieved great traction with practising managers. One study[11] estimates that only 15-20% of practising managers are familiar with the model and as few as 5% actually use it, compared with the awareness and usage of SWOT analysis, estimated at 90-95% and 50%, respectively.

Given FFM's lack of use in most markets, and given the poor utility for biotechnology of those approaches that are widely used, the present authors considered that FFM might offer hidden and as yet, unexplored, utility as a strategic planning model for biotechnology firms.

FFM IN BIOTECHNOLOGY: CASE STUDY

FFM has been applied by some consultants, companies and researchers in the pharmaceutical industry.[7,9] It has also been applied in the biotechnology industry by consultants[8] in reports produced and marketed by consulting firms that use FFM as part of a global or country-specific overview of the industry. In these cases, the analyses tend to be descriptive summaries of each of the five forces as they apply to the overall biotechnology sector in a particular country and to the extent that there are any strategic inferences made, they tend to be broad and industry-level. Further, by inference, they are oriented towards larger, revenue-generating firms, rather than biotechnology firms, according to the present definition.

In one case,[14] consultants did apply FFM to a specific biotechnology firm, ostensibly to guide strategy formation. Again in this case, the output of the FFM process was merely a descriptive summary of the forces at play in the industry as a whole, and these summaries did not appear to be connected to the specific strategic

recommendations made for the company. The present study sought to explore whether FFM could be applied usefully to a pre-commercial drug development biotechnology firm and whether it had utility in deriving strategy drivers or recommendations for a specific firm, rather than simply at an overall industry level.

To this end, we selected a four year-old, privately-held, US-based biotechnology firm with 17 employees, which was engaged in discovering and developing small molecule cancer drugs. The firm's technology comprised patents it had licensed from three academic institutions, in addition to patents its own scientists had filed on specific candidate drug molecules that they had discovered. The company's compounds were all in the discovery or preclinical stage of development. In many ways, this was a typical, early-stage drug development biotechnology firm.

The FFM application process entailed a half-day planning session, in which the senior managers of the biotechnology firm participated. The FFM framework was briefly described to the management team and then they were asked to review each of the five forces and examine their relevance and impact on the company and its future. For each force, the team was asked to identify important issues that emerged. At the end of the session, the management team was asked to comment on the usefulness of the model as a strategic planning tool for their company.

Overall, the FFM planning exercise was not regarded by the firm's management team as useful in assisting the strategic planning of their business. The reasons are summarized below.

1. Profit was not a Relevant Driver of Success

One of the fundamental problems encountered was that FFM is premised on profitability as the driver of strategy selection. The management team of the firm stated that this had little relevance to their company, since their goal was not to achieve profitability, at least in the foreseeable future, but to build value for investors and secure pharmaceutical partnerships. In order to proceed with further application of the model, it became necessary to substitute 'success' for 'profitability' as the criterion for consideration and analysis of the forces, where success was deemed to be (or include) long-term value creation for investors.

2. Government was not Included as a Force

Another important observation by the team was that FFM omitted government as a force. It was felt that the impact of legislation and regulation was a crucially important force in determining the success of a biotechnology firm. Changes in regulations or interpretations by the FDA and other regulatory authorities could change the probability of a company's candidate drugs gaining marketing approval or could increase the costs of drug development by imposing new safety or other hurdles. Changes in patent law or court rulings around patents could also have a significant impact in some cases. New federal legislation could have positive or negative effects. As a recent example, the Biologics Price Competition and Innovation Act of 2009 introduced 12-year market exclusivity for biologic drugs in the US, effectively guaranteeing a pharmaceutical partner a healthy protected commercial life regardless of patent status. This significantly changed the relative attractiveness, in terms of value creation potential, of biologic drugs compared with small molecule drugs for development and partnering.

3. Rivalry Amongst Existing Competitors

The management felt this force was not meaningful to their business, because it was hard to identify any competition. It was felt that the technology space in which this and other biotechnology firms operate are often relatively uninhabited and most biotechnology firms rarely interact with or encounter rival firms, at least not in the frequent and systematic way envisaged by FFM. One reason is that patents are crucial for a biotechnology firm and it cannot garner initial investor funding without a robust patent position. Therefore, from the outset, each biotechnology firm moves in a slightly different technology stream to other biotechnology firms and there are rarely direct competitors in the sense anticipated by FFM. In the case of their firm, they could not identify any direct or current rivals and to the extent that there were indirect rivals, they did not affect the company's prospects for success. Other factors, such as funding and garnering partnerships, were considered much more important to success.

4. Threat of New Entrants

The management team saw this force as having no real strategic relevance, either. Again, this is because patents represent solid barriers to entry of any direct technology

rivals. If there are new entrants, they rarely become direct competitors in the sense anticipated by FFM, because their genesis requires a clear patent position, which by its nature, means that they operate in different technology streams.

5. Threat of Substitute Products

Similarly, it was difficult to see this force as relevant unless conceived very broadly as substitute technologies, in which case and especially in the cancer field, there were very many potential substitute products and technologies that existed or could emerge. All of these could compete for funding and for pharmaceutical partnerships and thereby constitute substitutes or competitors. However, none of the identifiable substitute technologies was thought to represent an immediate threat that might impinge the success of the biotechnology firm in the medium term.

6. Bargaining Power of Buyers

This force needed to be interpreted as the bargaining power of pharmaceutical partners with respect to partnerships, for it to be relevant to biotechnology firms. While it was agreed that such 'buyers' had very substantial influence on the success of a biotechnology firm, abstraction of the notion of buyers to include pharmaceutical partnerships seemed fallacious, because pharmaceutical partnerships are not a competitive threat, but rather are cooperative arrangements that provide valuable funding, investor value accretion due to the commercial affirmation that such a deal represents, and a potential pathway to an exit for investors if a trade sale ensues. In any case, the nature of the buyers anticipated by FFM is very different to such partnerships.

7. Bargaining Power of Suppliers

To be relevant to the firm, 'suppliers' needed to be interpreted as technology licensors, which in this case, would be academic institutions. However, the relationships with the company's three licensors had little operational or strategic relevance to the biotechnology firm, because once the license deals were struck, the license terms simply represented a relatively static, long-term obligation to the company and the licensor had little influence on the day-to-day company operations or direction. It was acknowledged that if a poor bargain had been struck with the licensor in the first place, then it could affect the prospects of attracting a pharmaceutical partnership. For example, if the institution had the right to a substantial royalty on sales, then this could impinge the in-market profitability of the pharmaceutical partner and make a partnership with the biotechnology firm less attractive. In fact, this firm had had this experience with one of its institutional technology providers and recently renegotiated the terms of the license, precisely for this reason. Unlike the 'suppliers' in FFM, the institution was receptive to this, because it was in its interest to see a pharmaceutical partnership executed or the technology would never be commercialized.

In terms of output from the exercise, the list of issues or factors generated from the examination of each of the four external forces was short and provided no new insights to strategy formation in the view of the management team. The fifth force, 'internal rivalry', was considered largely irrelevant, but if conceived as factors internal to the company – a conception that seemed more useful to the management team – then it generated a productive list of issues that were relevant to strategy, notably competency gaps, funding issues, investor relations, facilities and location decisions.

DISCUSSION: TOWARDS A NEW MODEL OF STRATEGY PLANNING

Biotechnology firms are not well-served by widely-used strategy tools, such as SWOT, PESTLE and gap analysis. The present case study demonstrates that Porter's Five Forces Model also fails as a strategic planning tool.

An obvious limitation of this study is that it is based on a single case. However, the misfit of FFM was so profound, it is hard to envisage that it would fare any better in a larger sample of drug development biotechnology firms, given the inappropriateness of the traditional marketplace model and the focus on profitability as the goal.

Biotechnology firms are not driven by profitability as a strategic or operational goal. Rather, their goal is to create value, which is achieved by progression of candidate drugs along the development pathway.[15] This value is affirmed and amplified by a pharmaceutical partnership, and ultimately monetized by a trade sale of the firm to a pharmaceutical partner or an IPO[16], either of which provides a potentially valuable investor exit.

On the other hand, Porter's FFM is deeply rooted in traditional, highly-competitive markets and not the world of the R&D intermediary. Porter's FFM is also inescapably tied to profit maximization as its measure of strategic success. As a result, FFM does not have utility as a strategy framing or forming tool for individual biotechnology firms.

However, given the high praise accorded FFM as a theoretical model for strategic insight and strategy formation, the opportunity may exist to borrow the concept of 'forces that drive strategy' while substituting those forces relevant to the business and goals of biotechnology firms. Such a transformation would also require substituting the primary measure of success, from profitability to value creation. This would then provide a model that retains a core idea of FFM, which is that success, however defined, is derived from the interplay of forces and that by consideration of this interplay, strategic alternatives may appear and strategy formation can take place.

In the case of biotechnology firms as defined in this study, success is the maximization of value creation over time. Value is created by moving candidate drugs along the development pathway[15,17] and amplified by value-affirming licensing deals with a pharmaceutical partner.[16,17]

As to the applicable forces that affect a firm's ability to create value, some are identified or implied by this study. They include government regulation, patent position and licenses, technological substitutes, location, availability of funding and the availability of skills to both maximize pipeline progression and optimize partnering outcomes. Further study could refine these forces and reveal other forces that influence value creation for biotechnology firms. Such a model would also need to consider the interplay of these forces as well. For example, location of the firm could affect its access to funding, its available pool of people and skills, and its competitive position in attracting pharmaceutical partners.

Such a model also needs to consider those uncontrollable forces that are external to the firm's strategic decision-making environment, such as: economic fluctuations that can affect funding availability and overall sentiment towards biotechnology firms; government regulation that could impact patent strategy and pipeline decisions; and demographic and social evolutions, such as an aging population, which may affect the attractiveness of the medical needs pursued by the firm's pipeline.

Finally, any effective model needs to be able to conceptualize and measure what constitutes 'value creation' for biotechnology firms. Without an unambiguous and effective measurement of this success goal, the core of the model will be hollow and biotechnology firms will risk remaining strategic planning *orphans*.

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