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

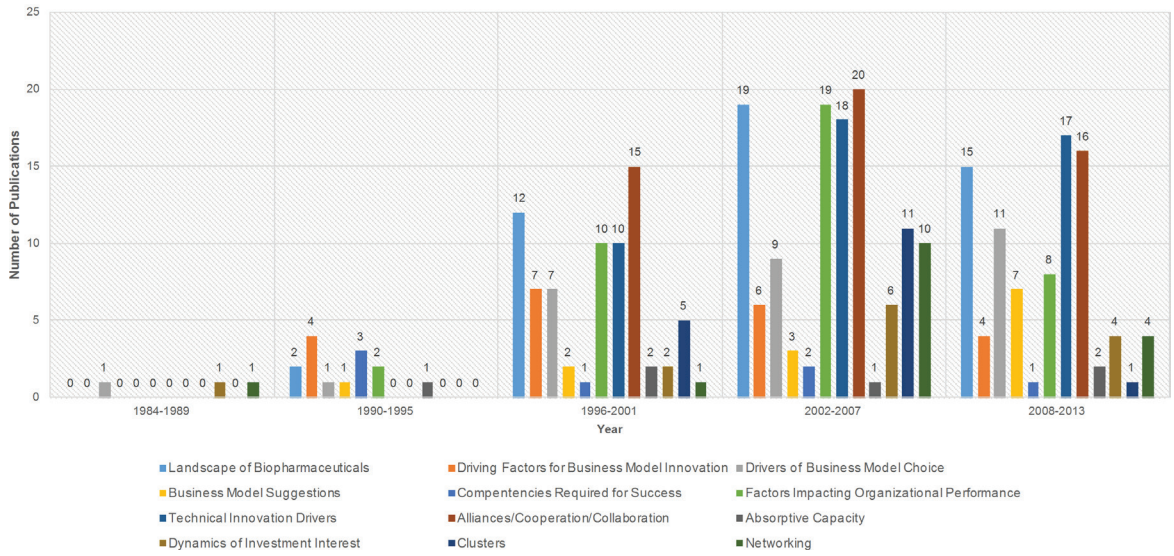

Chart 1: Research categorized by year of publication

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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