BIOSIMILARS: A NEW LOOK ON PROCESS INNOVATION AND THE IMPACT OF COMPETITIVE DYNAMICS

A Dissertation Submitted to the

Temple University Graduate School

In Partial Fulfillment

of the Requirements for the Degree

DOCTORATE OF BUSINESS ADMINSTRATION

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May 2018

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ABSTRACT

As healthcare costs are rising globally and biologic treatments are a growing segment of the cost, governments have created biosimilar regulatory pathways in attempt to lower the costs of biologics. Biosimilars may be viewed as a "pure" or distinct type of process innovation completely separate from product innovation due to the Regulatory requirements and this novel phenomenon allows, perhaps for the first time, process innovation to be studied independently from product innovation.

This phenomenon is researched using the competitive dynamic Awareness-Motivation-Capability (AMC) model structure. Since biosimilars are still relatively new, the impact of the biosimilars from a practical and academic viewpoint is emerging and in particular within the US market. This research creates a biosimilar model and metrics, filling a current gap in the literature, and quantitively evaluates the actions that firms face regarding entering into the biosimilars market due to key metrics such as patent / portfolio risk, prior biologics or generic experience, strength of the R&D pipeline, and the firm's R&D intensity. The biosimilar construct due to the strict regulatory pathway definition provides this unique and novel opportunity to study process innovation and the impact on competitive dynamics without the interference of product innovation. This research is anticipated to contribute to the practical and academic understanding of process innovation via the biosimilar phenomenon and the competitive dynamics of market entry as well as to promote further managerial research into this area of biosimilars.

DEDICATION

This work is dedicated to my wife, Jen, and my son, John Daniel, who sacrificed and supported me over many weekends permitting me to complete my classes and this doctoral research. And to my parents, who have always believed in education as the key to success.

ACKNOWLEDGEMENTS

I would like to acknowledge my excellent Dissertation Committee (Dr. Anthony DiBenedetto, Dr. Charles Dhanaraj (external reader), Dr. Ram Mudambi, and Dr. David Deeds) who have guided me through this process. In particular, I would especially thank and acknowledge Dr. David Deeds and Dr. Ram Mudambi as my mentors and chairs, who have lead me through this research and provided great insights over the past few years. Also, I would like to acknowledge my managers at Janssen R&D, Dr. Basant Sharma and Dr. Georgia Keresty, who helped to make this possible and in believing in me.

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CHAPTER 1.0
BIOSIMILAR RESEARCH MOTIVATON & INTRODUCTION

How does process innovation, separate from product innovation, impact the competitive dynamics of market entry? It is this question that is the motivation from a practical and academic perspective to study the novel phenomenon of biosimilars' impact on competitive dynamics and process innovation. Unlike product innovation, process innovation focuses on the operational side of the product, e.g. the administrative and production process to make, distribute, or market the product, and is often studied along with product innovation (Piening & Salge, 2015). Biosimilars provide a unique opportunity to study process innovation distinct from product innovation. Due to the regulatory requirement for biosimilars to be "as similar as possible", the innovator biologic modifies the traditional Utterback & Abernathy's innovation model of mutual relationships between the product and process innovation by separating the product innovation from the process innovation.

From a practical view point, globally, healthcare costs are increasing due to an aging and a growing population, and biopharmaceuticals are a growing percentage of the total cost. In the U.S., biosimilars were approved by the U.S. Congress as part of the 2009 Biologics Price Competition and Innovation Act under the biosimilar pathway 351 (k) package to create competition for innovative biologics in the pharmaceutical market to combat the increasing costs and expand access to payers and patients (Ryan, 2015). It is due to this pathway that biosimilars are defined and create a unique opportunity to study process innovation separate from product innovation. Prior to this legislation, there was not a

defined pathway in the U.S. for a "generic-like" biologic except by the normal innovative drug approval process.

It is currently estimated a biosimilar will be priced approximately 25% less as compared to the innovator drug (Grabowksi & Guha, 2014; Rompas et al., 2015). And, this pricing estimate is rapidly changing. For example, in November 2016, Pfizer announced that their Remicade biosimilar will be priced at a modest 15% discount as compared to the branded product and this landscape continues to evolve as more companies enter the market (Fortune, 2016). However, in July 2017, Merck with its' partner Samsung Bioepis announced that Renflexis (a biosimilar for Remicade) will be priced at a 35% discount as compared to Remicade (Mukherjee, 2017).

This biosimilar market is increasingly becoming more active. In 2016, two biosimilar monoclonal antibody products were filed in the US for approval including products to compete with Johnson & Johnson's Remicade and AbbVie's Humira. Both products are multi-billion dollars per year products (Udpa & Million, 2016). In June 2016, Sandoz, a subsidiary of Novartis announced that by 2020 the company will have five global biosimilar product launches (Sandoz Company website, 2016). And in 2017, the active biosimilar trend continues as there has been multiple biosimilar filings and as well as a few market approvals in Europe and U.S.

To provide context, a timeline of the nascent U.S. biosimilar market is presented below and adopted from Amgen's 2017 Trends in Biosimilars Report (Trends in Biosimilars Report, 2017):

2014: July – FDA accepts the first biosimilar application
Dec – Three active filings for biosimilars pending FDA review

2015: March – FDA approves the first biosimilar in the U.S.

Sept – Launch of the first biosimilar in the U.S.

Dec – Six active filings for biosimilars in pending review

2016: April – FDA approves second biosimilar, first monoclonal antibody

July – U.S. Court of Appeals for the Federal Circuit rules 180-day notice must be given to reference product (innovator) sponsor before commercial marketing of biosimilar may begin

Sept – fourth biosimilar approved by the FDA

2017: January – U.S. Supreme Court agrees to hear lawsuits on information exchange ("Patent Dance")

January – FDA releases draft guidance on Considerations in Demonstrating Interchangability with Reference Product

The current approved biosimilars in the U.S. are listed below in Table 1 from the FDA Purple Book June 23, 2017 CDER listing (FDA Purple Book, 2017).

Table #1: June 2017 FDA Approved Biosimilars

Proprietary Drug Name	**Proprietary Company**	**Biosimilar Drug Name**	**Biosimilar Company**
Humira	AbbVie	Amjevita	Amgen
Enbel	Amgen	Erelzi	Novartis
Neupogen	Amgen	Zarixo	Novartis
Remicade	Johnson & Johnson	Renflexis	Samsung-Merck
Remicade	Johnson & Johnson	Inflectra	Pfizer

Using a basic definition, a biosimilar is a follow-on biologic pharmaceutical drug which is similar (but not identical) to the original innovator biologic product (Mora, 2015). The regulatory pathway for biosimilars created does not permit *product* innovation since the technical aspects of the product such as the amino acid sequence of the product, the product's post-translational modifications, and the formulation of the product must be identical to the originator product; however, this regulatory pathway does create an opportunity to advance the knowledge around *process* innovation (how the product is

made, which is firm-specific) and its impact on competitive dynamics in the pharmaceutical industry.

For the biosimilar to be competitive with pricing against the innovator product and since the end product must remain the "highly similar or nearly exact" to the original product, the biosimilar company must be innovative with the manufacturing process to achieve the lower cost of goods to support the estimated 15 – 30% pricing discount as compared to the innovator product.

Biologics "are much more difficult to produce than traditional chemical molecules: they are larger, more complex, less stable molecules, which require challenging R&D and production processes" (Niosi, 2017). Please refer to Table #2 below for a concise summary table of the major differences between biologics and chemically-manufactured drugs.

Table #2: Biologics and Chemically Manufactured Drugs Comparison

	Biologics	**Chemically-manufactured drugs**
Type of molecule	Large Polypeptide chains	Small chemical molecules
Production process	Organism/Cell based biotechnology	Chemical synthesis
Physio-chemical characteristics	Complex heterogenous structures	Well-defined structures
Immunogenicity (patient adverse immune response)	Potentially immunogenic risk	Very rare
Dosage form	Usually Parenteral (e.g. i.v.)	Usually oral (e.g. pills)

*Adapted from Daubenfeld et al, 2016

Due to the unique legislation restrictions, the biosimilar company will not have access to the innovator's specific manufacturing process, including the product's specific cell line

and the innovator's specific process details, creating an opportunity to study process innovation distinct from product innovation. The biosimilar firm can only match the publicly available information such as the final drug product's formulation, the final product specifications and the patient delivery. Due to these restrictions, the biosimilar company will need to "re-discover the research and production processes, and conduct clinical trials" (Niosi, 2017). This limited information and the need to control cost of goods will drive process innovation into the manufacturing by the biosimilar company since the entire manufacturing process for the biosimilar is different for the biosimilar product as compared to the innovative drug process. Please refer to the Table #3 below for a general comparison between generics (chemical entities) and biosimilars (biologics).

Table #3: Generics and Biosimilars' Comparison Chart

	Generics	**Biosimilars**
Product	Active molecules are identical; inactive ingredients may be different	Molecules have the same primary amino acid sequence but are not identical
Production & Analytics	Analytical proof of quality & pharmacokinetics (drug interaction)	Limited access to originator's data & methods
Clinical	No substantial clinical data required	Comparative analytical, non-clinical and clinical data required
Regulatory Pathway	1984 Hatch-Waxman Act (U.S.)	2009 Biologics Price Competition and Innovation Act (U.S.)

*Adapted from Ryan, 2015

However, there are some possible competitive advantages that the biosimilar company has over the innovator such as the ability to use a more modern and efficient manufacturing process as compared to the originator process since the biosimilar is filed

years later. In addition, the abbreviated clinical development to commercial launch requirements will aid with cost control for the biosimilar manufacturer.

From a healthcare market view, it is estimated healthcare expenditures worldwide for biologics will reach an estimated $210 billion USD by 2016 (Kudrin, 2012) and the top five biologics generate approximately $50 billion USD annually (PRNewswire, 2015). This financial estimate illustrates the tremendous market for these specialized medicines. Although biosimilars have been approved in the EU since 2006, the first biosimilar was just approved in the U.S. in 2015 by FDA regulatory pathway and the impact on the industry and the healthcare market still very early in its evolution (Dalgaard, 2013).

In total, the biosimilar potential market in 2020 has been estimated to be $11 billion USD per annum (PRNewswire, 2015). For the U.S. and EU market, the impact of biosimilars and in particular for monoclonal antibodies (a type of biologic drug that has the majority of the blockbuster pharmaceutical product sales) is currently developing since the approval pathway is still novel. Due to the novelty, there is a motivation to study this biosimilar phenomenon from both a practical and theoretical viewpoint through a competitive dynamic lens.

From a practical viewpoint since biosimilars are still a relatively new product, questions arise concerning the impact of biosimilars. For example, how many competitors are there and how will biosimilars impact the market for the off patent or soon-to-be off patent products like Remicade and Humira, which account for billions of dollars per year for the innovator companies?

The new regulatory pathway of biosimilars permits new competitors like generic firms, existing pharmaceutical companies and/or completely new firms to enter biopharmaceutical development with known successful and clinically active products. Also, the biosimilar pathway may permit a firm to strengthen an existing therapeutic area portfolio in a specific disease area (e.g. rheumatology or oncology) by allowing the biosimilar to be marketed against the innovative drug where before the biosimilar regulatory pathway approval, there was no direct competition of the innovator product for the lifetime of the product as was established for chemical or small molecules like generics. Further, it is envisioned that biosimilars will have a different impact on the competitive dynamics for the healthcare industry, depending upon the location of the major market with those markets being the U.S., Europe, Japan, and the global emerging markets due to the different healthcare policies and regulations.

Entry into the biosimilar market by a company must be made under strong consideration as estimates for the development prior to commercialization of a single biosimilar product dossier is estimated to be approximately $130M to $250M for a monoclonal antibody in the oncology field, which is approximately two to five times greater development cost than a generic small molecule (McKinsey Report, 2013). The barriers to market entry are significant which include manufacturing, marketing, cold storage, delivery devices, patient immunogenicity, and post-market pharmacovigilance (Blackstone, 2013). The benefit of a lower cost option to the greater population, however, by the introduction of biosimilars into market has the potential to save an accumulated savings of $250 billion for the U.S. healthcare system alone over the next ten years (McKinsey report, 2013).

From a theoretical or academic viewpoint, it is anticipated that the study of biosimilars' impact on the competitive dynamics of market entry will allow biosimilar construct and metrics to be created and the antecedents and consequences explored, which fills a current gap in the academic research, and will expand the knowledge around process innovation's impact on competitive dynamics. This study will also contribute to the field of competitive dynamics by introducing the study of an emerging product introduction with a complex market of payers, payees, and patients in the different marketing regions (U.S., EU, Japan, and emerging markets) as well as the innovation aspects of the regulatory pathway and the strategic thinking pertaining the individual firm's entry into the biosimilar market. Currently, this distinct opportunity exists to conduct an academic study of the competitive dynamic impact on the pharmaceutical and biopharmaceutical industry by the innovative paradigm shift of biosimilars as a type of process innovation.

Biotechnology Industry's Background

The general background of modern biotechnology in the biopharmaceutical industry as well as the history leading up to where the biopharmaceutical industry exists today and the relationship to biosimilars is important to review to understand the challenges as the industry begins a new regulatory journey into biosimilars building upon its' past.

To differentiate biopharmaceuticals from traditional chemical synthesis, biomanufacturing is used to produce biologics and biosimilars, which can be defined as "a type of manufacturing that utilizes biological systems to produce biomolecules for agricultural, food, energy, material and pharmaceutical industries" (Zhang, 2017). It is these biological systems (e.g. cells or microorganisms) that act as miniature individual

cell factories producing the complex target product (protein) of interest that makes biopharmaceuticals unique from chemical synthesis as well as technically challenging.

Biological processing itself has been in existence for thousands of years producing natural products such as beer, cheese, vinegar, acetone, etc.; however, modern biotechnology is relatively new (Zhang, 2017). In the late 1930s and 1940s, it has been stated that modern biotechnology was founded when the Rockfeller Foundation funded the basic research into molecular biology (Dano, 2002). It was the scientific spin-off from this basic molecular biology research from the Rockfeller Foundation that ultimately determined the structure of DNA in 1953 by Watson and Crick and further building from this scientific base, in 1973, researchers Cohen and Boyer developed the gene splicing techniques or also known as recombinant DNA technology, which is critical to biopharmaceutical production and thus modern biopharmaceuticals (Dano, 2002).

The recombinant DNA technology (genetic engineering) developed by Cohen and Boyer permits the taking of DNA from one organism and inserting it into the DNA of another organism to produce the product (recombinant protein) of interest (Marks, 2015). This technology allows production scale manufacturing to occur by inserting the typically inefficient native product "DNA blueprint" into an organism that can now be scaled-up for mass production. This permits large-complex molecules that cannot be produced economically by chemical synthesis and too expensive to be isolated from natural organisms to be commercialized (Zhang, 2017.) In 1976, Genentech spearheaded the commercialization of this technology into the pharmaceutical world with the production of human growth hormone and human insulin (Marks, 2015).

As outlined by Dano in his research, biotechnology is used for three main purposes in the pharmaceutical industry with these being: (1) products that diagnose human disease through a testing kit (2) products that treat human disease (3) products that prevent human disease (Dano, 2002). Most biosimilars currently all fall into the category of products that treat disease, which are the most commercially attractive currently.

Many pharmaceutical blockbuster biotech products (for example, Abbvie's Humira and Johnson & Johnson's Remicade) and new biosimilars like Celltrion's Remsima are a type of protein naturally formed by the immune system called monoclonal antibodies or mabs as known in the biopharmaceutical industry. In her book "The Lock and Key of Medicine", Marks states that "Mabs did not transform healthcare overnight or with major fanfare. Unnoticed at the time, mabs brought with them new treatment possibilities often taken for granted and considered mundane today" (Marks, 2015). Perhaps biosimilars may do the same?

It was not until 1975 that Kohler and Milstein at Cambridge University first developed the technique for the selection and reproduction of monoclonal antibodies building upon the previous genetic engineering knowledge (Marks, 2009). Adapted from Mark's research, listed below in Table 4: "Historical Monoclonal Antibody Approvals" are the first 20 monoclonal antibody drugs to the U.S. or E.U. market and their associated approval dates. It is noteworthy that the first mab was not approved until 1986 a decade after Kohler and Milstein's ground-breaking research (Marks, 2009).

Table #4: Historical Monoclonal Antibody Approvals

Company	Trade Name	Date of First Approval
Ortho Biotec	Orthoclone OKT3	1986
Centocor	Centoxin	1991
Centocor/Eli Lilly	ReoPro	1994
Centocor/GSK	Panorex	1995
Idec/Genentech	Rituxan	1997
Roche	Zenapax	1997
Novartis	Simulect	1998
MedImmune	Synagis	1998
Centocor	Remicade	1998
Genentech	Herceptin	1998
Immunex/Wyeth-Ayerst	Enbrel	1998
Wyeth-Ayerst/Pfizer	Mylotarg	2000
Genzyme/Ilex Oncology	Campath	2001
Idec	Zevalin	2002
CAT/Abbott	Humira	2002
Biogen Idec	Amevive	2003
Corixa	Bexxar	2003
Tanox/Genentech	Xolair	2003

Throughout the development of the modern biotechnology, collaboration has played and continues to play a key role in the establishment of the current biopharmaceutical industry and it is an important competitive dynamic of the operating environment. For example, Centocor, which was one of the first pioneer companies in the modern biotech industry, demonstrated the role of collaboration with both academics and the industry for an early biotechnology commercialization.

Centocor was founded in 1979 (three years after another biotechnology pioneer company, Genentech) and by 1984, Centocor was a profitable diagnostics company, which based their products upon monoclonal antibodies (Marks, 2009). Centocor's very name derived from the words (1) "cento" which is Latin for an old garment made of many patches and (2) "cor" which means center, demonstrates the collaborative intent (Marks, 2009). In

1979, Centocor signed an academic collaboration deal with the Wistar Institute for product targets and in 1980, Centocor established industrial alliances with FMC Corporation and F. Hoffman-La Roche pharmaceuticals (Marks, 2009).

Although Centocor attempted to move ahead independently in 1986, the company, due to a major product failure and the need for immediate cash, established partnerships with SmithKline Beecham (now GlaxoSmithKline) and Eli Lilly (Marks, 2009). In 1999 despite bringing 10 biotech products to the market including the now mab blockbuster Remicade, Centocor management realized that a takeover of the company was needed to be fully successful and it was at this time Johnson & Johnson, who was the first company to commercialize a monoclonal antibody in the industry, acquired Centocor for $5.2 billion dollars making Centocor, a fully owned Johnson & Johnson subsidiary.

The Centocor is just one example of biotech collaboration and there are many other examples some successful and others unfortunately not so much. Biosimilar's high cost of market entry and the associated risks with biosimilar development makes collaboration and partnering likely (Blackstone, 2013). In the future as in its' past, collaboration and alliances in biotechnology and the sharing of risks/rewards will continue to play a critical role on competitive dynamics in the industry including the establishment of biosimilars as companies like Merck partner with Samsung and Teva with Celltrion to develop biosimilar products and share the risk and the benefit of future profits.

Modern biotechnology took decades to establish with major scientific breakthroughs, and the competitive dynamics of numerous academic, government, and industrial collaborations and competition. Today, biopharmaceuticals including mabs (as well as marketed biosimilars) account for billions and billions of dollars per annum in

pharmaceutical sales and treat thousands of patients, who were often without any other treatment options without this biotechnology therapy, each year.

Literature Review

After conducting an extensive search of the academic literature, there is a general gap in the business knowledge / journals pertaining biosimilars and the impact on the pharmaceutical industry as well as on healthcare and process innovation. The published research of biosimilars appears to be mainly limited to medicine, regulatory, immunology, and other clinical type journals. Little academic research appears to have been conducted regarding the impact of biosimilars on the pharmaceutical industry and the healthcare economics / markets with a broad business or competitive dynamic perspective including market entry. However, there is one recent article by Niosi published in 2017 discusses the imitation and innovation that biosimilars and biobetters may bring to the biopharmaceutical industry and ultimately the market, which complements this research.

Biosimilar Definitions

First, it is important to define the construct of biosimilars, which are defined a few different ways from the multiple disciplines. From the Regulatory viewpoint, biosimilars are defined and viewed slightly differently across the globe from each independent regulatory body and this difference is due to the fact that exact bioequivalence for a biosimilar product cannot be easily established (Kumar et al, 2015). In particular for the EU, biosimilars are defined as the following: "the biosimilar must be sufficiently similar to the reference product (already licensed in the EU) to be used in the same clinical indication at the same dose; requiring additional clinical trials but likely

more abbreviated where the risk of failure is less, as the target and mechanism of action are well demonstrated" (Strand & Cronstein, 2014).

In the U.S., biosimilars are defined by the FDA as "biologic product highly similar to the reference product with no clinically meaningful differences… in terms of the safety, purity and potency of product" (Strand & Cronstein, 2014). A key point to note is that the EU and U.S. definitions are in close alignment which will aid with the pharmaceutical industry's approach to this regulatory pathway and both definitions permit the study of process innovation in the isolation from product innovation since the product at the genetic level and the biosimilar regulatory pathway are equivalent.

In addition, over the years, there has been a number of terms from the biopharmaceutical and other disciplines that defined a biosimilar which included me-too biologic, non-innovator biologic, second-generation biologic, biobetter, follow-on biologicals, subsequent-entry biologics, similar biopharmaceuticals, and biogenerics (Weise, 2011). Currently, the term of biosimilar appears to be the WHO, EU, and U.S. regulatory associated definition with a much narrower scope than the terms above. For the purposes of this research, biosimilar will use the definition from the U.S. regulatory agency.

For biosimilar definitions, please refer to Appendix A for a more comprehensive list from the different disciplines.

Competitive Dynamic Perspectives

The biosimilar construct is studied specifically using the competitive dynamics perspective, which is defined as "the study of interfirm rivalry based upon specific competitive actions and reactions, their strategic and organizational contexts", and their

drivers and consequences, which resides within competitive strategy purview (Chen & Miller, 2012). It has been researched that competitive dynamics mostly concerns the following: "gaining advantage over competitors, who are rival companies; that victories can be achieved by taking a limited range of actions, and be measured in market share or profit; and that rewards are pursued mainly for the short-term advantage of firm owners, who are key players and main focus of analysis;" however, Chen argues that this viewpoint may be too simplistic (Chen & Miller, 2015). Chen & Miller proposed the following viewpoint that gaining advantage is not always the most sensible objective that non-competitors like governmental agencies are critical to competitive outcomes and that outcomes may extend past economic gain (Chen & Miller, 2015). Certainly, in the case of biosimilars, the effects of governmental and regulatory policy have a tremendous impact on the pharmaceutical and healthcare industry. The government agencies have created and govern this new regulatory paradigm of biosimilars themselves, which has an interesting competitive dynamic and innovation impact themselves and should likely be researched further in the future.

This specific research on biosimilars studies, using empirical observation and analysis, the fundamental questions that drive competitive dynamic research such as the interaction of the firms when they compete and how does the competitive behaviors influence organizational performance (Chen & Miller, 2012). Chen &Miller noted "firms act and rivals respond, and these actions and reactions determine survival and long-term performance" (Chen & Miller, 2012). This research, which has not been conducted thus far on biosimilars, will be evaluated from the perspective of process innovation's impact on competitive dynamics of the firm and in particular on the firm's entry into biosimilars.

In 1994, Chen and Miller stated with their competitive dynamic research that it is "essential to understand how a competitive action affects the internal behavior of the defending organization" (Chen & Miller, 2012). In the case of biosimilars, the defending organization is the innovator company. Markman, Gianiodis, and Buchholtz noted that "key initiatives often come from players outside a given industry and from non-competitors or non-governmental organizations at home and aboard, thereby transforming the nature of competition" (Chen & Miller, 2015). Due to the external competitive environment generated by the governmental agencies in creating the regulatory pathway for the industry, biosimilars are certainly opening up the competitive landscape permitting new competition from new players like Samsung (in partnership with Merck), who has recently received their first biosimilar product marketing approval in April of 2017 for the U.S. market (Merck website, 2016) (Big Molecule Watch website, 2017).

Using the competitive dynamics research approach, the biosimilar phenomenon, which is representative of the broader construct of process innovation, may be modeled by using the Awareness-Motivation-Capability (AMC) structure that affects the firm's competitive activity including market entry (Chen & Miller, 2012). Thus far, no such competitive analysis of biosimilars in the pharmaceutical industry has been presented in the academic literature. The AMC model is explained by the following statement: a competitor will not be able to respond to an action unless it is **aware** of the action, **motivated** to react, and **capable** of responding (Chen & Miller, 2012).

The AMC model permits a wide variety of methodical approaches to conduct the analysis. This approach includes archival record search, questionnaires from managers

and industry subject-matter-experts, and analytical approaches such as simulation and quantitative methodologies (Chen & Miller, 2012). This latitude in methodical approach greatly aids in the study of the biosimilar process innovation where currently limited studies and industry experience exist.

Traditionally, studies in competitive dynamics have generally been focused on product innovations (Piening & Salge, 2015). Research of product innovation included automobiles, electronic calculators, airlines, laser printers, etc. Biosimilars create a very unique and novel opportunity to study a product under the precise lens of process innovation due to the regulatory requirements without the impact of product innovation.

Process Innovation

Process innovation is defined as "the introduction of new or significantly improved production, supply chain, and administrative processes" and this is an important source of competitiveness and organizational renewal (Piening & Salge, 2015). The biosimilar pathway may be viewed as type of process innovation from an administrative or a regulatory view point. Prior to the biosimilar regulatory pathway, there was not a procedure in place to permit a non-innovative biological on the U.S. or EU market. Due to the strict regulatory definition of biosimilars from the regulatory agencies, this creates and permits an opportunity to study process innovation separately from product innovation in a competitive dynamic landscape. This regulatory requirement for biosimilars to be "as similar as possible" to the innovator biologic modifies the traditional Utterback & Abernathy's innovation model of mutual relationships between the product and process innovation by separating the product innovation from the process innovation (Adner & Levinthal, 2001). Please refer to Figure #1 and Figure #2 respectively.

Figure #1: Utterback & Abernathy's Model of Innovation

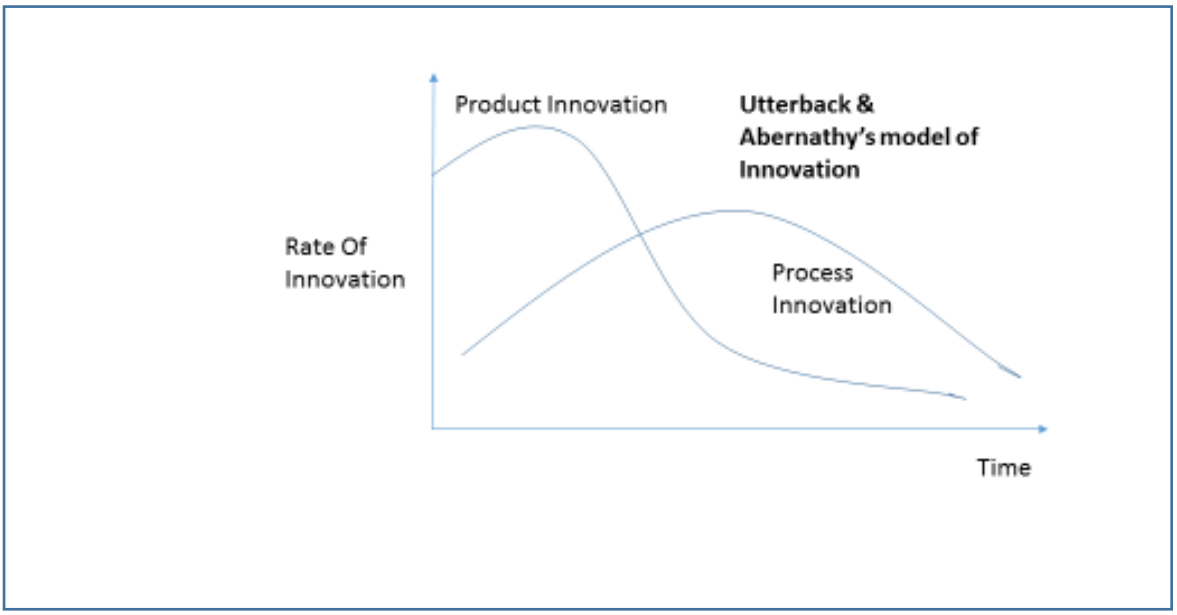
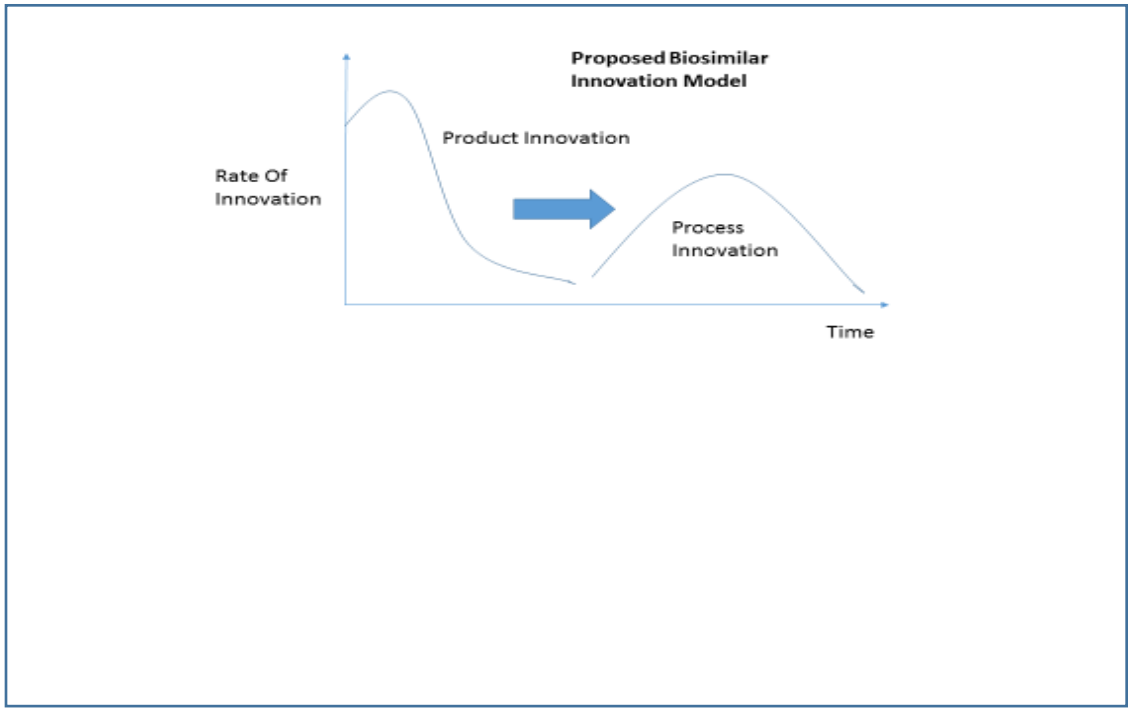


Figure #2: Proposed Biosimilar Model of Innovation



In general, Piening and Salge note that our understanding of process innovation's antecedents, contingencies, and effects remains limited but process innovation can be studied using the dynamic capabilities model, which is defined as "a firm's ability to integrate, build, and reconfigure internal and external competences to address rapidly changing environments" and is an extension of the resource-based view of the firm (Piening & Salge, 2015).

There have been many research studies on innovation's impact as well as theories. Below is a summary table of the relevant literature reviewed on process and production innovation and its related findings.

TABLE #5: Relevant Process Innovation Literature Review

Reference	Related Findings
Adner & Levinthal, 2001	The dynamics of process and product innovation throughout the technology lifecycle
Dunlap-Hinkler et al, 2010	Breakthrough versus incremental innovation in the pharmaceutical industry
Kuratko & Welsch, 2001	Incremental process innovation impact
Niosi, 2017	Imitation and innovation with biologics, biobetters, & biosimilars; generic manufacturers entering biologics via biosimilars
Piening & Salge, 2015	The impact of process innovation understanding remains limited
Tushman & Nadler, 1986	Definitions of process & product innovation
Utterback & Abernathy, 1975	Description of product and process lifecycle

The biosimilar research on the process innovation may addressed using the competitive dynamic AMC model providing information to fill the current managerial and academic research gaps.

Innovation & Organizational Design

Further, this research study begins to explore the firm's strategic innovation decisions to have science-driven or process driven innovation or have ambidexterity as related to conducting both process and product innovation. O' Reilly and Tushman,'s 2004 research on the ambidextrous organization describes the company's need for breakthrough (product innovation) as well as the incremental product improvements (process innovation) to existing commercial areas as one of the most difficult managerial decisions to make (O'Reilly & Tushman, 2004).

What is the strategic group theory in the industry of those in biosimilars & generics in comparison to those who are focused on solely on product innovation? Porter defined a strategic group as "the group of firms in an industry following the same or a similar strategy along the strategic dimensions" (Porter, 1980).

For the ambidextrous firm, the management keeps the alignment and balance between the competing needs of process innovation with drivers of cost, operational efficiency, and operational competences versus a model of innovation, growth, adaptability and entrepreneurial approach (O'Reilly & Tushman, 2004). Andriopoulos and Lewis' research further studied the firm's paradoxical challenges and balance between exploitation and exploration using the dimensions of strategic intent, customer orientation, and personal drivers (Andriopoulos & Lewis, 2009). Dunlap-Hinkler's

research also references that "contemporary Schumpeterian scholars have given closer attention to the theoretical and empirical complexities associated with integrating both break-through innovations or exploration activities and incremental innovations or exploration activities inside the firm" (Dunlap-Hinkler et al, 2010).

Pharmaceutical Regulatory and Legal Perspectives

The biosimilar market is emerging and is very much different from the small molecule (chemical) generics market. One of the regulatory differences is that biosimilars are not considered to be interchangeable to the innovator product at the pharmacy since biosimilars are assumed to be not perfectly identical to the original product (but highly similar to the originator product) (Nickisch & Bode-Greuel, 2012) (Grabowski, 2014). This difference is due mainly the current inability to test and definitely provide prove that the product is exactly the same as the innovative product due to the molecular and physical structure complexity of biologics.

The Biologics Price Competition and Innovation Act created the abbreviated licensure pathway within section 351(k). Unlike the Hatch-Waxman Act for generics, the biologics pathway permits the FDA to determine what type of data the biosimilar manufacturers must provide for licensure including analytical, animal or clinical data and the FDA is the agency that will approve or deny commercialization of the product in the U.S. (Falit et al, 2015). This creates a high level of uncertainty for the biosimilar manufacturer regarding what information or studies and resources will be required for licensure as the FDA has the governance by law to determine the "rules of entry."

The Act also mandates that the biosimilar company submits to the innovator company their biosimilar product's dossier that includes the FDA application and a description of the process used to manufacture the biosimilar prior to approval allowing a full review by the innovator company (Falit et al, 2015). With this regulatory requirement, the biosimilar applicant and the innovator company exchange patent-related information, called a "Patent Dance", before the biosimilar can enter the market (Fazzolare & Brougher, 2014). This permits the innovator company to challenge, delay and / or potentially prevent the biosimilar from commercially making or selling the biosimilar until the court determines patent validity (Fazzolare & Brougher, 2014). This "Patent Dance" requirement in 2017 has been challenged up to the U.S. Supreme Court and debates on the legitimacy continues in the U.S. courts (Big Molecule Watch website, 2017).

Market Entry

The barrier for entry for biosimilars is also formidable beyond the regulatory and legal challenges. In one study, it has been assumed that biosimilar development will take between 7-9 years in development with a $50-$200M USD in investment costs including a 50-75% probability of success and 17-43% cost of goods as it is assumed biosimilars will be priced ~30% lower compared to the innovative drug (Nickisch & Bode-Greuel, 2012). These development and market challenges will drive process innovation to be aggressive on cost of goods and healthcare market pricing, for example, since the product innovation is not permitted under the regulatory pathway.

Also, there is an advantage of taking the risk of being the first biosimilar to the market as this permits up to 18 months of market exclusivity for that specific biosimilar product

(Fazzolare & Brougher, 2014). Overall with such risks, the entry into a specific biosimilar should include: a competitive dynamic evaluation of being first or second to market (*an Awareness*), determination of the threat of alternative products (*an Awareness and Motivation*), estimation of production costs *(an Awareness and Motivation*), and having effective sales force (*Capability*) (Nickisch & Bode-Greuel, 2012). Due to these challenges, it is assumed that biosimilar competition in the US will be limited to a small number of companies offering modest price concessions (Falit et al, 2015). This 2012 prediction by Niskisch and Greuel is already coming true with the Pfizer pricing announcement in November 2016 of only 15% discount for the Remicade biosimilar (Fortune, 2016).

CHAPTER 2.0
BIOSIMILAR DEPENDENT VARIABLE STUDY

Biosimilar Study Abstract

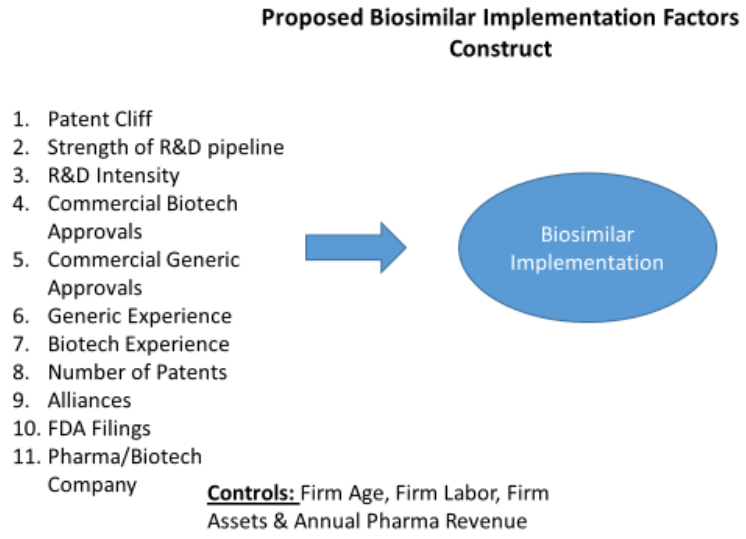
The purpose of this study is to demonstrate the impact of process innovation via the biosimilar phenomenon on the pharmaceutical industry evaluating the Top 31 pharmaceutical firm's decision making centered around innovative strategic implementation (process, product, or ambidexterity) and the impact on competitive dynamics using an Awareness-Motivation-Capacity (AMC) model approach creating a biosimilar construct and associated metrics. From the findings, this study determines which metrics may be significant to guide the thinking towards a future research.

Conceptual Model & Hypotheses

To assist in addressing the research gap in the literature, the proposed research pertains to biosimilars and the impact of this new biologic process innovation paradigm on the competitive dynamics within the pharmaceutical biological industry using the AMC model. This new research will expand create the construct independent variables and conducts an investigation into the scientific innovation drivers of the firm and those decisions of the firm to be a science-driven innovator (product innovation), a biosimilar/generic innovator (process innovation) or have the challenges of innovation ambidexterity by being both a science-based innovation company and a biosimilar/generic company.

The following conceptual model in Figure #3 below is proposed for the biosimilar construct with the identified antecedents/metrics.

Figure #3: Proposed Biosimilar Construct



The definitions of the construct's variables (antecedents) are as follows:

- Patent Cliff: the firm's key products that are impacted by patent expiry in key markets usually either U.S. and/or E.U. markets
- R&D Intensity: percentage of R&D investment to overall sales per annum
- Generic Experience Product Total: a firm's non-branded or branded generics market experience (Japan, EU, or U.S.). Authorized generics, which are defined as "which are drugs made by or under license from the innovator company and sold without a brand name" are excluded in the definition due to differences in the firm's individual strategy on generics (Lamb, 2008).
- Biotech Experience Product Total: a firm that has biotechnology products in development or commercialized in the market (Japan, EU, U.S.).

- Number of Patents: the number of U.S. patents filed under the firm
- Alliances: the parent firm's alliances with other partners as self-reported on new FDA applications
- FDA filings: the number of U.S. regulatory filings for clinical trial start or marketing applications
- Drug Approvals: the number of New Drug Applications (NDAs) approved by the FDA per annum per firm
- Generic Approvals: the number of generic drug approvals by the FDA per annum per firm
- Biologic Approvals: the number of Biologic License Applications (BLAs) approved by the FDA per annum per firm
- Pharma/Biotech Company: categorical variable coded whether the company is considered a "traditional" pharmaceutical company or biotechnology company.

From a McKinsey & Company report on biosimilars, some strategic questions were identified, which in turn can be further developed into specific questions for a qualitative or quantitative study. From a biologic's originators/innovators perspective using the competitive dynamics strategic view, potential questions may include: do we develop biosimilars, how should our operating model adapt to the changing market, how should we respond to the increased competition (Dalgaard, 2012)? From a biosimilar manufacturer viewpoint, potential questions that may be considered may be: are biosimilars the main portfolio driver or are innovative medicines, or what is the market

size for a particular biosimilar, and/or how many indications should be pursued (Dalgaard, 2012)? The analysis of these strategic questions fit well into the competitive dynamic AMC model.

From a generic research study in 1991 by the Brookings Institute titled "Patent Expiration, Entry, and Competition in the US Pharmaceutical Industry, the researchers evaluated competition related to patent expiration and generic drug entry (Cave, 1991.) This study although focused on drug pricing and other marketing factors is a related study to this current biosimilar research. And, another study titled "A Story of Breakthrough Versus Incremental Innovation: Corporate Entrepreneurship in the Global Pharmaceutical Industry" complements this biosimilar process innovation research as well.

This biosimilar research will address and develop understanding in the following four hypotheses from a competitive dynamic market entry perspective on process innovation using the AMC model. It should be noted that this proposed research is likely only be the beginning of future studies into biosimilars as more biosimilars enter the market, the legislative/regulatory clarity develops, and the business landscape evolves.

Using the AMC model, the patent cliff (or patent risk) aligns with the firm's Awareness (as the firm's risk drives external search and competitive scanning) and Motivation (the firm's risk of revenue loss and need for product replacement). It is hypothesized that firms that are at patent risk for the firm's key marketed products will be more aggressive into entering the biosimilar market to create an on-going profit stream. By the firm entering into the biosimilar development, it permits the firm to build a "late stage" R&D biologics" portfolio quickly by providing potential products to replace the company's marketed products at risk for patent expiry or to create a new market opportunity. From a

2012 article from the Journal of Commercial Biotechnology, Nickisch and Bode-Greuel list the generic companies, pharmaceutical, and Asian companies that have publicly announced their plans to develop biosimilars, which could then be evaluated for their patent risk and the overall R&D pipeline strength. The table is recreated below as Table #6.

Table #6: Biosimilar Companies*

Generic Companies	Pharmaceutical Companies	Asian Companies
Sandoz	Abbott	Fuji Pharmaceuticals
Teva	Astra Zeneca	Samsung / Biogen Idec
Hospira	Novo Nordisk	Biocon
Mylan	Sanofi Aventis	Celltrion
Ranbaxy / Daiichi Sankyo	Baxter	Intas/Apotex
	Eli Lilly	Ranbaxy/Phenex
	Merck	Dr. Reddy's
	Pfizer	
	Roche	
	Boehringer Ingelheim	

*****adapted from (Nickisch and Bode-Greuel, 2012)

Changes in some of the companies' biosimilar strategy or mergers (e.g. Pfizer-Hospira) have occurred since the 2012 article but the table as first published in 2012 provides insight into the variety of companies pursuing biosimilars at the time and the table still remains fairly accurate with a few of the companies now having launched biosimilars in the U.S. market like Pfizer.

Hypothesis 1a: Firms with more patent risk will enter into biosimilar market more frequently than firms with strong patent protection.

R&D Pipeline

Further and related to the patent cliff hypothesis in terms of end-to-end portfolio / revenue management, it is hypothesized that a firm with a less robust internal R&D pipeline will be more apt to enter into the biosimilar development than a firm with a strong internal R&D pipeline and this aligns with the AMC model that the firm's Motivation (e.g. the firm's risk of revenue loss and need for product replacement) will drive action. By entering into biosimilars, this will permit the firm to quickly build up a strong late stage R& D pipeline using the scientific and medical knowledge that the indication and the molecule will likely be successful through clinical development as well as the approval process allowing the development risk to be minimized.

However as a counter to this hypothesis, this action will also draw resources from product innovation into process innovation (incremental innovation) and since the firm has only limited resources, this could constrain the firm from truly achieving novel innovative products (Dunlap-Hinkler, 2010). Typically, the innovative product revenue and profits (in particular biologic blockbusters like Remicade or Humira) will overshadow any potential biosimilar drug profits based upon the latest sales forecasts of biosimilars.

Hypothesis 1b: Firms with less robust R&D portfolios will enter into the biosimilar market more frequently than firms with a robust R&D pipeline

Generic Experience

Experience aligns with the Capabilities of the firm using the AMC model. Since the biosimilar pathway is still relatively new in the United States and even though generics

have a different regulatory legislation and pathway to approval, one may hypothesize that firms with generic drug experience may be more willing to enter into the biosimilar market than firms without previous generic experience. This is driven from the competitive dynamic experience of Capabilities that companies that produce generics have business knowledge or corporate DNA of how to compete in a lower margin product landscape, in the developing markets, and in a dynamic cost competitive generic market. Generic companies also have a commercial strategy of pursuing products that are already marketed. As noted by Table #2 above, several known generic companies have already a stated strategic interest in biosimilars for example, Teva and Sandoz. (Nickisch and Bode-Greuel, 2012) Niosi's research supports this observation and also states that "the most advanced generic pharmaceutical producers are trying to enter the industry through biosimilars and biobetters" (Niosi, 2017).

Previous research has also shown that a firm that conducts process innovation will focus on that business model rather than strategically shift to product innovation. (Dunlap, 2016) For example, previous generic experience will drive further generic-like business efforts by the firm aligning with the Capabilities from the AMC model.

Hypothesis 2a: Firms with previous generic drug experience will enter into biosimilars more frequently than those that do not have generic experience.

Since the biosimilar pathway is relatively new in the United States and even though generics are different regulatory legislation, one may hypothesize that firms with generic drug experience may be more willing to enter into the biosimilar market than firms without previous generic experience. This is driven from the competitive dynamic experience of Capabilities that companies that produce generics have business knowledge

of how to compete in a lower margin product landscape, in the developing markets, and in a dynamic cost competitive generic market. Generic companies also have a commercial strategy of pursuing products that are already marketed. As noted earlier, several known generic companies have already a stated strategic interest in biosimilars (Nickisch & Bode-Greuel, 2012). For example, the major generic manufacturers of Teva and Sandoz (subsidiary of Novartis) are pursuing biosimilars. Niosi's research supports this observation and also states that "the most advanced generic pharmaceutical producers are trying to enter the industry through biosimilars and biobetters (Niosi, 2017)."

However, a counter discussion point to this is that companies that have experience with solely generic drugs may not have the deep biological technical understanding to develop biosimilars, which may lead to product launch delays, added expense, and in the extreme case, failure of the biosimilar product line as well as an appreciation of the development time and cost difference between generics and biosimilars. This lack of biologic knowledge may lead to alliances or partnerships with external firms that have the biologic capability.

Hypothesis 2b: Firms that have generic drug approval (ANDAs) will enter into biosimilar implementation with a greater frequency than firms that have less generic commercial experience.

Biologic Experience

These related hypotheses analyze both the biotech experience as well as the frequency (total number) of commercial biologic products (BLAs) approved for commercialization by the firm to elucidate if there is any statistically relevant information related to biosimilar implementation aligning with the Capabilities and Motivation from the AMC model.

The hypothesis proposes that companies with previous biologics expertise (i.e. Capabilities) will be more likely to enter the biosimilar market due to the technical knowledge and intrastructure of biological product and process development. A firm example of this is Amgen, which is a U.S.-based biotechnology company, which has publicly presented in October of 2015 that part of their strategy of entering into biosimilars was to "leverage existing biologics capabilities." Amgen further stated that the scientific difficulty is high for biosimilars as well as the manufacturing process is long and complex and that branded commercial capabilities is required which only increases the need for previous biologics expertise, which is a potential barrier-to-entry for new comers in the biotechnology field (Foraker, 2015). Amgen has created an entire division within the company named Amgen Biosimilars to address this new regulatory pathway to develop biosimilars and capture market share.

Due to the complexity of biologics in contrast to chemical pharmaceuticals, where end-product testing can prove equivalence, the production process is critical to the outcome of the product and slight variations can make dramatic differences. For the biosimilar developers, the innovator's manufacturing process and critical production materials (like the biological cell culture bank used to produce product) are not known to them so this

tacit knowledge held by innovator company on the manufacturing process is a tremendous advantage. Having previous expertise with biologic manufacturing, will aid with biosimilar development.

Hypothesis 3: Firms that have biotech experience will enter into biosimilar implementation with a greater frequency than firms that have less biosimilar commercial experience.

Scientific Strategic Innovation Drive

Hypothesis 4a – 4c are all related to the firm's scientific intensity via number of patents filed, alliances, and FDA filings. This analysis of the variables will allow the study of the impact of strategic group theory on science-driven firms in comparison to more generic driven firms as well as ambidextrous firms, who do both. The number of patents filed is a common variable to determine innovation between firms.

The number of FDA filings and alliances are similar to variables previously used in a study by Dunlap-Hinkler (2010) in the review of breakthrough versus incremental innovation and these variables align with Awareness and Capability from the AMC Model. The hypothesis is that firms that are generating new patents have more product innovation and less process innovation.

Hypothesis 4a: Firms that have a greater number of patents filed will enter into biosimilar implementation with a lesser frequency than firms with lesser patents filed.

Previous research has demonstrated that firms with more alliances have more breakthrough innovation (Dunlap-Hinkler, 2010). This research around learning organizations and alliances has previously been conducted by Cohen and Levinthal as

well as Lane and Lubatkin among many others. The question that arises is: are biosimilars (as a true type of process innovation) different from other types of incremental innovation due to the complexity of biosimilar development and the expense to the firm engaging in the effort. And if the firm has many alliances, then is the firm less likely to enter into biosimilar development or, could one hypothesize that the firm may need more alliances to develop a biosimilar due to the complexity? Using the AMC model, alliances would align with Awareness and Capability of the firm.

Hypothesis 4b: Firms that have more alliances will be less likely to enter into biosimilar implementation.

This hypothesis is also related to biotech technology and commercial approval. It is proposed that firms, who have frequent biological license approvals (BLA) or new drug application (NDA) approvals will not enter into biosimilars. The basis of the assumption is the following that the firm which is generating new revenue on innovative biologic and/or chemically-based products and has a R&D robust pipeline does not have the interest, resources, or corporate culture for biosimilars.

However, one may state that due to the frequent BLA approvals, the firm that is primed for biologic development and a biosimilar product would strategically fit ideally into the firm as a known Capability.

It is further hypothesized that firms which submit more new drug applications whether they are NDAs or BLAs filings that this has two consequences from a practical view. Firstly, the filings demonstrate internal R&D strength for innovation as well as depth of the R&D portfolio. Secondary, the number of filings also impacts resources both

positively and negatively. The positive impact is that NDAs and BLAs lead to product approvals which drives new product revenue. The negative impact is that the filings and associated work with them whether it be clinical trials or product launches places additional financial and resource pressure on the firm.

Hypothesis 4c: Firms that have more FDA filings will be less likely to enter into biosimilar implementation than firms with less FDA filings.

Pharmaceutical or Biotech Company

This variable is to define the possible impact of the strategic group theory as defined by Porter as "the group of firms in an industry following the same or a similar strategy along the strategic dimensions" (Porter, 1980).

The variable itself is categorical (biotech or pharma) and will be researched based upon traditional categories usually company defined whether they are biotech or traditional pharmaceuticals. It is hypothesized that the incremental management organizational structure (e.g. generic-like) will strategically drive more traditional pharmaceutical firms to biosimilars than biotechnology firms. The premise is that biotech firms are known to be more product innovation driven; however, there is a distinct possibility that the Capability of the biotech firms (e.g. having the biologics experience and infra-structure) will have a positive impact upon their entry into biosimilars. On-the-other-hand, would the Motivation of the biotech firm towards innovation drive the biotech firm away from biosimilars?

Hypothesis 5: More traditionally defined pharmaceutical companies will adopt biosimilars more frequently than "biotechnology" companies.

The controls for the proposed research are the firm's incorporation age, the firm's labor, the firm's assets and the firm's pharmaceutical revenue. This will allow for any correlations due to firm size to be identified and previous research has shown that these controls can have an effect on the firm's innovation. For example, the controls of revenue and firm age are chosen based upon prior research that firm size has an impact on innovation (Dunlap-Hinkler, 2010). Firm age is calculated at the corporate level using the year of incorporation and subtracted this from the study year and firm size is determined by revenue per annum. The proposed controls have been used in previous research and have shown to have an impact on innovation.

AMC Summary of Independent Variables

Table # 7: Independent Variables Selected Against AMC Criteria Table below summarizes the variables as well as the proposed AMC criteria for each variable.

Table #7: Independent Variables Selected Against AMC Criteria Table

Variable/Metric	AMC Criteria Selection
Patent Cliff	Motivation and Awareness
Biotech Experience	Motivation and Capability
Generic Experience	Motivation and Capability
Drug (NDA) Approval	Motivation
Generic (ANDA) Filing Approval	Awareness
Biotech (BLA) Filing Approval	Motivation and Capability
Patent Number	Awareness and Capability
Alliances	Awareness and Capability
Pharmaceutical or Biotech company	Capability and Motivation

Analytics and Description of Data

The formative construct of biosimilar implementation (Figure #3) and its independent variables (patent risk, strength of R&D pipeline, generic experience, biotech experience, R&D intensity, pharm/biotech company, generic approvals, drug approvals, biologic approvals, alliances, as well as the control variables of revenue, firm assets, employee number, and firm age) have been analyzed using the Cox model linear regression (hazard analysis) using SPSS software. The research data for the top 31 prescription sales biopharmaceutical and pharmaceutical firms are drawn from the years from 2010 through to and including 2015, which required the use of multiple public, government, and private databases as well as a review of over 150 annual company reports and thousands of pages.

Please refer to Table #8: Data Sources & Variables below for the measures and data source. The data for the control variables of pharmaceutical revenue and firm age were obtained from PharmaExec.com, annual reports and Mergent database respectfully. In addition in Appendix K Company & Biosimilar Implementation Chart, there is a listing of the top 31 companies and their biosimilar activity analyzed for this research.

Table #8: Data Sources & Variables

Variable/Metrics	Measure	Data Source
Patent Cliff	Calculated by (Expired Patent Drug Revenue/Rx Sales) per annum starting with the year of expiry until non-reporting based upon the company's annual filings	Company annual reports, SEC 10K or 20F filings
Biotech Experience	Firm's experience either in development or commercially with biologics; categorical variable (yes/no)	Company annual reports, SEC 10K or 20F filings
Generic Experience	Firm's experience with generics: categorical variable (yes/no)	Company annual reports, SEC 10K or 20F filings
Drug Approval	Number of drug product commercialized per annum	FDA.gov
Generic Approval	Number of generic products commercialized per annum	FDA.gov
Biotech Approval	Number of biotech products commercialized per annum	FDA.gov
Patent Number	Number of U.S. patents filed	Patft.uspto.gov (US governmental patent office) or ,Statiscia database
FDA Filings	Number of NDA/BLA or INDs filed	FDA.gov
Alliances	Parent firm's alliances as self reported on FDA drug filings	Cortellis Database, FDA.gov, 10K or 20F filings
R&D Intensity	R&D spend divided by Pharma Revenue	Company annual reports, PharmaExec.com
Pharmaceutical Revenue	Pharmaceutical sales per annum	Company annual reports, PharmaExec.com
Pharmaceutical or Biotech company	Categorical coding	Company annual reports and financial websites
Firm Age	Incorporation age subtracted from reporting year	Mergent database
Firm Assets	Assets of parent company	Mergent database
Firm Labor	Number of employees at the parent company	Mergent database

Please refer to Appendix B for the list of the top 50 pharmaceutical/biotech firms from 2014 as listed from PharmExec.com and Appendix C for the list of the 31 pharmaceutical companies analyzed for this research using publicly available information.

The secondary data gathered from the years of 2010 to 2015 (annual intervals) permits the evaluation of firms entering the biosimilar field over the study period. The dates were chosen as the first biosimilar approvals on the US market occurred in 2015 but the individual company's research and development into the biosimilar products started years earlier which permits the strategic thinking and the competitive landscape to evolve and mature.

Measures

Similar to other constructs, the measures of biosimilars varies depending upon the discipline's viewpoint. For example, biosimilars may be measured by: the number of clinical indications approved to treat patients (medicinal view point), or how similar is the molecular structure using detailed analytical testing (generic medicines' view), or to the pricing of the treatment (generics / health economics view). The current research thus far is very limited on the metrics and the measured outcomes for biosimilars and this is likely due to limited history in the industry and in the U.S. market.

For this research, the measures are, using the AMC model from a competitive dynamic perspective, to support the biosimilar construct from Figure #3 above. The biosimilar antecedent of patent risk is measured by conducting a product patent search of the selected biotech and pharmaceutical companies using key licensed product patents as identified by the firm that have expired and recorded until no longer reported annually by

the firm. Once the key expiring products are identified, this total risk is measured by the ratio of the percentage of key product expiring revenue divided by total revenue per annum. By taking this ratio, this normalizes the measurement across the variously sized companies.

The R&D portfolio strength independent variable is measured by the number of clinical trials per annum for the years 2010 through to 2015. The company's product pipeline information is typically available on the company's website or in the company's quarterly/annual report or at ClinicalTrials.gov for the selected pharmaceutical / biotech firms (please refer to Appendix A). The timeframe of 2010 through 2015 is proposed since the U.S. biosimilar regulations were approved in 2009 and the first biosimilar approved filing in the U.S. was in 2015. If a company had a "weaker" R&D pipeline in this time window, then the approval in 2009 may prompt the company to invest in the biosimilar development due to the new regulatory option. For this research, the U.S. Food and Drug Administration's clinicaltrials.gov was used to collect the number of trials per company per annum at an aggregate level demonstrating potential indications and R&D pipeline strength.

The previous generic and biopharmaceutical experience data is drawn from the selected companies' websites and annual reports, SEC filings (10K or 20F annual reports), or the FDA's Orange or Purple Books. Experience for the purposes of this research is defined as at least one non-branded generic or biopharmaceutical product in the portfolio respectively and is reported as a categorical variable (yes or no) either in the R&D pipeline and/or commercialized.

The NDA/BLA/ANDA drug approval data was recorded from the Food and Drug Administration's FDA.gov website. This information, however, does focus the data solely on the U.S. approvals and the U.S. market is the largest pharmaceutical market in the world. The data does not take into account Europe (EMA) or Japan, which are other major revenue markets.

The alliances and collaboration data was primarily secured from the Cortellis Deals Database (formerly known as ReCap). The Cortellis database pulls public information on deals that were executed in the pharmaceutical industry.

R&D intensity (R&D spend / revenue) is pulled from secondary data such as company annual reports and SEC filings which include 10K or 20F annual reports. A control variable of favorable reimbursement is assumed; however, the information may be drawn from government websites, government publications, and / or pharmaceutical and medical journal articles keeping in mind, that the reimbursement itself is a very complex and multi-facetted topic.

Biosimilar Testing Results

The data was gathered for the top 31 biopharmaceutical and pharmaceutical companies for each of the previously described variables (antecedents) and the Cox model regression analysis was run in the IBM statistical software program SPSS. The following results from the SPSS Cox model regression analysis are presented in Table #9: SPSS Case Processing Summary and Table #10: SPSS Independent Variable Results below. The raw data tables from the SPSS software are located in Appendix D: SPSS Summary Tables for further reference.

Table #9: SPSS Case Processing Summary

	Events (N)	Percent
Case Event (Biosimilar)	72	38.9
Censored	113	61.1
Total	185	100
Cases Dropped	0	0

There were no missing data from the analysis of the Top 31 pharmaceutical companies from 2010 through 2015. Over the time period studied, there was seventy-two (72) biosimilar events and a summary total of one hundred eighty-five events analyzed.

Below is Table #7 containing the summary statistics from the data set analyzed of the Top 31 pharmaceutical / biotechnology companies, which provides a snap shot of the "average company" in the analysis. Based upon the summary statistics, the "average company" is a mid-to-large pharmaceutical company around the size of Teva, Amgen, or Boehringer Ingelheim.

Table #10: Company Summary Statistics

Covariate	Mean
R&D Intensity (%)	19.4%
Patent Risk (%)	15.4%
Generic Experience (1); else (0)	0.324
Biotech Experience (1); else (0)	0.962
Number of Clinical Trials/Annum	114.6
Revenue ($MM)	$17,633 MM
Incorporation Years	62.7
Total Assets ($MM)	$47,017 MM
Pharma (1) or Biotech Company (0)	0.708
Patent Filing Number	340.8
Generic (ANDA) Approval Number	2.25
Drug (NDA) Approval Number	1.02
Biologic (BLA) Approval Number	0.141
Employee Number	46,473
Collaboration Number	3.25

The results from the analysis of biosimilar implementation are listed below in Table #11: SPSS Cox Regression Independent Variable Results.

Table #11: SPSS Cox Regression Independent Variable Results

Variable	Significance	Exp (B): Hazard Ratio
R&D Intensity	0.055	1.065
Patent Risk	0.0003	0.951
Generic Experience	8.129x10e-8	6.903
Biotech Experience	0.664	1.599
Number of Clinical Trials	0.722	0.999
Revenue	0.525	1.000
Incorporation Year	0.203	0.995
Total Assets	0.411	1.000
Pharma or Biotech	0.313	1.578
Number of Patent Filings	0.214	1.000
Number of Generic (ANDA) Approvals	0.395	1.013
Number of Drug (NDA) Approvals	0.229	0.902
Number of Biologic (BLA) Approvals	0.569	0.823
Employee Number	0.670	1.000
Number of Collaborations/Alliances	0.008	1.157
-2 Log Likelihood Value (model fit)	**641.960**	**N/A**

Based upon the results, only hypothesis #1b, previous generic experience, of the five hypotheses has significance and is strongly supported by the hazard ratio (Exp (B)). The data analysis supports the hypothesis that a firm with previous generic experience will be

more than 6x more likely to be developing biosimilars as compared to a firm that does not have previous generic experience.

The other hypothesis that is very weakly supported is the number of collaborations or alliances, which has statistical significance and a hazard ratio of 1.2, which just slightly above one. This variable then may lend itself to further investigation either with additional years analyzed or with an increased number of companies to determine if it becomes strongly statistically supported.

The remaining hypotheses either do not have significance and/or Exp (B) hazard ratio lacks statistical support based upon the sample data including no statistical impact from the control variables related to firm size or age.

The correlation result table of the variables is attached in Appendix E: Biosimilar Implementation Variable Correlation Matrix. It is interesting to note that generic experience and generic approvals have a slight negative correlation. One may expect that the correlation would be positive; however, this result may be caused by the limited timeframe of the sample set as compared to the generally long development and approval cycle times for drug approvals and / or the fact that the generic approval is not a global metric for this study. Generic experience is based upon previous and cumulative approvals as well as general company policy of developing generics as compared to generic approval for this data set, which is solely based upon FDA annual approval.

A summary of the results for each of the five hypothesis is listed below and the results against the hypotheses will be discussed further:

- *Hypothesis 1a: Firms with more patent risk will enter into biosimilars more frequently than firms with strong patent protection**: not supported***
- *Hypothesis 1b: Firms with less robust R&D portfolios will enter into biosimilars more frequently than firms with a robust R&D pipeline: **not supported***
- *Hypothesis 2a: Firms with previous generic drug experience will enter into biosimilars more frequently than those that do not have generic experience: **supported***
- *Hypothesis 2b: Firms that have generic drug approval (ANDAs) will enter into biosimilar implementation with a greater frequency than firms that have less generic commercial experience: **not supported***
- *Hypothesis 3: Firms with previous biotechnology experience will enter more frequently than firms without biotech experience: **not supported***
- *Hypothesis 4a: Firms that have a greater number of patents filed will enter into biosimilar implementation with less frequency than firms with less patents filed: **not supported***
- *Hypothesis 4b: Firms that have more alliances will be less likely to enter into biosimilar implementation: **weakly supported***
- *Hypothesis 4c: Firms that have more FDA filings will be less likely to enter into biosimilar implementation than firms with less FDA filings**: not supported***
- *Hypothesis 5: More traditionally defined pharmaceutical companies will adopt biosimilars more frequency than "biotechnology" companies: **not supported***

Discussion of Biosimilar Testing Results

Of the hypothesis, only prior generic experience was statistically supported from the data set analyzed. It may be hypothesized that the limited and analyzed data of the top 31 pharmaceutical / biotech companies has some impact on the results and whether the data is generalizable to the entire pharmaceutical industry. Of the top 31 pharmaceutical firms studied, this data set, however, captured the vast majority of the pharmaceutical industry sales of the top 100 pharmaceutical companies globally and thus has considerable influence on the direction and representation of the pharmaceutical industry.

Specifically, Hypotheses #1a and 1b, which relate to the firm's portfolio health as well as Hypotheses #2a, 2b, 4a and 4c, which are regulatory approvals and patent filings, from a commercial and an R&D investment, were not statistically supported. The results from Hypotheses #1a and Hypotheses #1b are somewhat surprising as one may expect that a patent cliff for a firm or a firm with a less robust portfolio would invest into a potential area of significant growth from a biosimilar and develop a known commercial product, especially in a scientific field where R&D failures occur frequency. Upon reflection, this result may be due to the variety of firms that have entered into biosimilars for several reasons from strategic intent, idle capacity, to new markets. Further, the result of patent risk, although not statistically supported by the hazard ratio, is statistically significant (p-value) so further research on patent risk may be merited using other variables of an orthogonal nature or an expanded study. R&D Intensity, however, did not show statistical significance for the hazard ratio or the associated p-value. This result does continue to support previous research findings that firms "learn by doing" and firms practice what is naturally occurring already within the firm (Cohen & Levinthal, 1989).

Regarding Hypothesis 3, which is the firm's prior biotechnology experience, the finding was neither supported by the hazard ratio nor by the p-value; thus based upon the data set, the hypothesis appears to be not relevant to biosimilar implementation. From a practical or managerial viewpoint, one would assume that firms that have prior biotechnological experience and existing infrastructure would be more apt to enter into biosimilars development. For example, Amgen has publicly stated that their biotech experience allows them to develop biosimilars using their prior knowledge. However, it has been stated that firms who are in the generic business (with or without biotech experience) are entering heavily into biosimilars (Niosi, 2017). This again supports previous research findings that "firms may be expected to behave in the future according to routines they have employed in the past" (Nelson & Winter, 1982). Since hypothesis #3 was not proven statistically, the finding supports the practical view and supports that the decision to enter into biosimilars is not driven by existing experience in technical area but by other factors like generic experience (Capability) but more likely by either Awareness and/or Motivation by leadership.

Hypothesis 4b, which theorized that "firms that have more alliances will be more likely to enter into biosimilar implementation", was weakly supported from analysis. Previous research has demonstrated that firms with more alliances have more breakthrough innovation (Dunlap-Hinkler, 2010). The analysis of the data, however, shows a weak support of biosimilar implementation and number of alliances from the Hazard Ratio of 1.02 and the p-value significance of 0.008. Although not a strong indicator from the current data set, this hypothesis certainly merits further future research as it may demonstrate alliances and biosimilar implementation as a means of process innovation

have a positive relationship. This could be due to the fact that biosimilars are technologically challenging and expensive thus in some ways similar to breakthrough innovation.

For Hypothesis 5, the analysis of whether the relationship of biosimilar implementation between traditional pharmaceutical companies and biotechnology companies differed was not supported from the data analyzed. From the analysis, it appears that biosimilar implementation is not dependent upon the traditional definition of pharmaceutical versus biotech company definition. This is not a complete surprise as the blurring between the top biotech and pharma companies has been occurring in the industry making it more difficult to use the traditional definitions.

The statistical finding of prior generic experience (Hypothesis 2a) supports the thinking and results from previous academic studies that the firm's strategy and prior history to compete in the generic and generic-type business like biosimilars drives the firm's decision to enter into the biosimilars market, rather than prior technical expertise or capability in biologics. As stated earlier, the other presumed factors of patent risk, prior biopharmaceutical experience, and R&D portfolio strength did not demonstrate statistical hazard rate significance with the sample set regarding the strategic and competitive movement of the firm for biosimilar implementation. The findings were not expected that these other forces would not influence the decision since the variables are strongly related to firm performance and financial impact; however, this provides a solid example that the leadership and vision of the firm is what drives decisions to enter into novel competitive markets like generics and biosimilars. The impact of the CEO/company's management to

set the long term strategic vision and invest into a process innovation like biosimilars does appear to fit with the known role of the CEO and upper management.

From a competitive dynamic perspective, both the generic and the biosimilar market share will be driven by cost to compete in the healthcare market (an Awareness); therefore, the process innovation by the firm for the biosimilar product will be important to achieve and maintain the cost of goods targets and sales targets by having cost competitive manufacturing processes.

The result of prior generic experience impacting the decision to enter into biosimilars also complements a previous study on breakthrough innovation versus incremental innovation regarding generic and innovative pharmaceuticals. The study's conclusion that "prior experience in generics significantly reduces the likelihood that the current innovation will be breakthrough and increases the likelihood that it will be incremental (Dunlap-Hinkler, 2010).

Incremental innovation for this biosimilar phenomenon may be considered as a type of process innovation such as the biosimilars' unique production processes to achieve lower cost of goods in comparison to the innovator drug. The 2010 Dunlap-Hinkler research further states that "it may be the case that an increase in cumulative generic knowledge significantly reduces the knowledge complexity and diversity within the firm, which dampens the need for effective communication and coordination, which is necessary for new learning and technological change" (Dunlap-Hinkler, 2010). Thus, supporting the statistical results from this research that a firm that has been working on generics or biosimilars may be set-up organizationally/managerially to optimize this for this type of product rather than truly innovative products.

From a practical or managerial viewpoint, the hypotheses of R&D portfolio strength, the key product patent cliff, and previous experience are considered important factors to the firm's management due to the overall fiscal impact and health of the firm. For example, the patent cliff concern/risk for key products that bring significant value to the firm's profitability often drives key decisions and mergers with pharmaceutical firms. And further regarding previous experience of biopharmaceuticals as it relates to the firm's resources to develop, launch and produce a challenging product, this may require hiring new key technical talent and building significant infrastructure.

The statistical results from the data analysis of the top 31 pharmaceutical firms are therefore surprising at first glance that these factors were not significant in the decision to pursue biosimilars; however, upon further reflection, the outcome that only the previous generic experience is a significant factor may not be so surprising and aligns with previous academic research. In addition, O' Reilly and Tushman,'s 2004 research on the ambidextrous organization describes the company's need for breakthrough (product innovation) as well as the incremental product improvements (process innovation) to existing commercial areas as one of the most difficult managerial decisions to make (O'Reilly & Tushman, 2004). From a competitive dynamic perspective, the construct variables may be considered more operational and tactical to achieve competitiveness immediately and the significant factor of previous generic experience demonstrates a previous and long term strategic approach of the firm's leadership (such as the CEO) to set the visionary tone and strategy of the competitive dynamics of the firm for key market entry like biosimilars.

Conclusion & Future Research

In conclusion, this initial research begins to close a gap in the literature on biosimilars from both a practical and academic viewpoint contributing to greater understanding of process innovation and regulations on competitive dynamics, the role of the CEO/firm management, and the impact on the growing healthcare industry.

This research creates an opportunity to further explore the other variables that may impact biosimilar implementation, opening the discussion to strategic group theory in the industry of those in biosimilars and generics (ambidextrous firm), and those who are focused on solely on product innovation as Porter defined a strategic group as "the group of firms in an industry following the same or a similar strategy along the strategic dimensions" (Porter, 1980).

For the ambidextrous firm, the management keeps the alignment and balance between the competing needs of process innovation with drivers of cost, operational efficiency, and operational competences versus a model of innovation, growth, adaptability and entrepreneurial approach (O'Reilly & Tushman, 2004). Andriopoulos and Lewis' research further studied the firm's paradoxical challenges and balance between exploitation and exploration using the dimensions of strategic intent, customer orientation, and personal drivers (Andriopoulos & Lewis, 2009). Dunlap-Hinkler's research also references that "Contemporary Schumpeterian scholars have given closer attention to the theoretical and empirical complexities associated with integrating both break-through innovations or exploration activities and incremental innovations or exploration activities inside the firm" (Dunlap-Hinkler et al, 2010). This is certainly an area to explore for further research.

Based upon this research of the Top 31 biopharmaceutical and pharmaceutical firms, the data supports the theory that the firm's overarching strategy/principles and the Capabilities of business knowledge and generic strategy from the AMC model trumps the other studied variables of the firm's patent risk/patent cliff and the firm's specific biopharmaceutical experience with influencing the strategic direction and implementation of biosimilar strategy.

CHAPTER 3.0
BIOSIMILAR'S IMPACT ON ALLIANCES

Alliance Abstract

The proposed quantitative research will expand upon the previous study of biosimilars as a "true" type of process innovation and independent of product innovation. This research evaluates the association between alliances / collaborations and a number of specific independent variables that underpin competitive dynamics in the pharmaceutical industry. These include biosimilars, firm size, and product approvals; however, this study does not address the question of causality. This may be the first quantitative study to use biosimilars as an independent variable for research in the pharmaceutical industry and likely the first to evaluate the impact of process innovation on alliances.

Introduction & Motivation

The research motivation for this study is to build upon the previous study's biosimilar research and findings regarding biosimilar process innovation and the impact on competitive dynamics. The previous research demonstrated that from the factors analyzed that generic experience was the significant factor for pharmaceutical firms to enter into biosimilar implementation. The research findings also noted that a relationship with alliances as an independent variable was weakly statistically supported.

Throughout the development of the modern biotechnology, collaboration and alliances have played and continue to play a key role in the establishment of the current biopharmaceutical industry and it is an important competitive dynamic of the operating environment. For example, Centocor, which was one of the first pioneer companies in the modern biotech industry, demonstrated the role of collaboration with both academics and the industry for an early biotechnology commercialization.

Centocor was founded in 1979 (three years after another biotechnology pioneer company, Genentech) and by 1984, Centocor was a profitable diagnostics company, which based their products upon monoclonal antibodies (Marks, 2009). Centocor's very name derived from the words (1) "cento" which is Latin for an old garment made of many patches and (2) "cor" which means center, demonstrates the collaborative intent (Marks, 2009). In 1979, Centocor signed an academic collaboration deal with the Wistar Institute for product targets and in 1980, Centocor established industrial alliances with FMC Corporation and F. Hoffman-La Roche pharmaceuticals (Marks, 2009).

Although Centocor attempted to move ahead independently in 1986, the company, due to a major product failure and the need for immediate cash, established partnerships with SmithKline Beecham (now GlaxoSmithKline) and Eli Lilly (Marks, 2009). In 1999 despite bringing 10 biotech products to the market including the now mab blockbuster Remicade, Centocor management realized that a takeover of the company was needed to be fully successful and it was at this time Johnson & Johnson, who was the first company to commercialize a monoclonal antibody in the industry, acquired Centocor for $5.2 billion dollars making Centocor, a fully owned Johnson & Johnson subsidiary.

The Centocor is just one example of biotech collaboration and there are many other examples some successful and others unfortunately not so much. Biosimilar's high cost of market entry and the associated risks with biosimilar development makes collaboration and partnering likely (Blackstone, 2013). In the future as in its' past, collaboration and alliances in biotechnology and the sharing of risks/rewards will continue to play a critical role on competitive dynamics in the industry including the establishment of biosimilars as companies like Merck partner with Samsung and Teva with Celltrion to develop biosimilar products and share the risk as well as the benefit of future profits.

Modern biotechnology took decades to establish with major scientific breakthroughs, and the competitive dynamics of numerous academic, government, and industrial collaborations and competition. Today, biopharmaceuticals including mabs (as well as marketed biosimilars) account for billions and billions of dollars per annum in pharmaceutical sales and treat thousands of patients, who were often without any other treatment options without this biotechnology therapy, each year.

This new research will evaluate alliances quantitively using linear regression for the Top 31 pharmaceutical and biotechnology companies as listed in Appendix C to determine which independent variables are significant to alliances in the pharmaceutical industry.

Literature Review

This new research study will expand upon the previous construct and will explore the firm's strategic decisions to have alliances using biosimilars as well as generic and biotech experience as an independent variable. From the literature search, this may be the first quantitative study to evaluate the possible effect of the independent variable of biosimilars on alliances in the pharmaceutical industry.

This research also opens the discussion to strategic group theory in the pharmaceutical industry of those in biosimilars & generics and those who are focused on solely on product innovation. Porter defined a strategic group as "the group of firms in an industry following the same or a similar strategy along the strategic dimensions" (Porter, 1980). This research will evaluate if there is a relationship between the process innovators as compared to the product innovators using the construct of alliances. Also in a previous alliance study, Rothaermel and Boeker determined that pharmaceutical and biotechnology firms created alliances when the biotechnology firm was usually younger (Dunlap-Hinkler, 2010).

For the ambidextrous firm, the management keeps the alignment and balance between the competing needs of process innovation with drivers of cost, operational efficiency, and operational competences versus a model of innovation, growth, adaptability and entrepreneurial approach (O'Reilly & Tushman, 2004). Andriopoulos and Lewis'

research further studied the firm's paradoxical challenges and balance between exploitation and exploration using the dimensions of strategic intent, customer orientation, and personal drivers (Andriopoulos & Lewis, 2009). Dunlap-Hinkler's research also references that "Contemporary Schumpeterian scholars have given closer attention to the theoretical and empirical complexities associated with integrating both break-through innovations or exploration activities and incremental innovations or exploration activities inside the firm" (Dunlap-Hinkler et al, 2010). Is this strategic choice of innovation (e.g. generic, biosimilars or both) have an impact on alliances?

Cohen and Levinthal's research identified R&D generating innovation as well as developing the firm's ability to identify, absorb, and gain knowledge from the environment (known as absorptive capacity) through such means as alliances (Cohen, 1989). It has been previously recognized from Lane & Lubatkin and Yang, Mudambi and Meyer that interorganizational and intraorganizational learning processes have been positively impacted when student-teacher relationships shared similar basic knowledge bases and research communities (Dunlap-Hinkler, 2010).

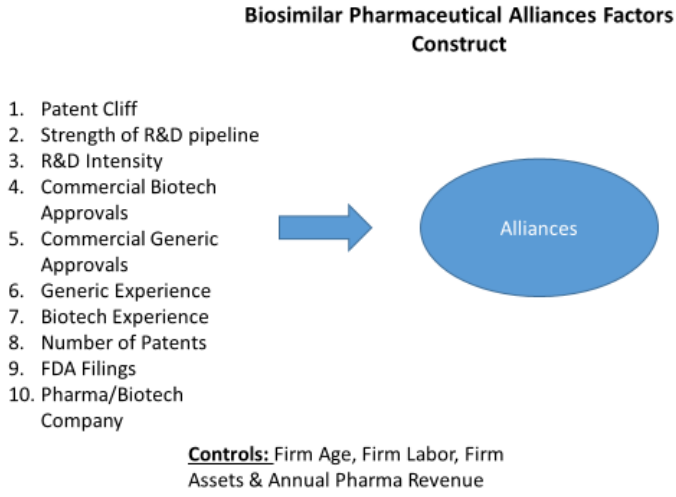
Based upon the literature search and the previous research, the biosimilar phenomenon representing a "pure-type" of process innovation merits further exploration into the competitive dynamics of the firm's innovation decision making via external alliances and collaborations.

Conceptual Model & Hypothesis

To assist in addressing the research gap in the academic literature, the proposed research pertains to biosimilars and the impact of this new biologic process innovation paradigm

on alliances within the pharmaceutical's industry. The following conceptual model is proposed for the alliance construct for the pharmaceutical industry with the identified antecedents/metrics. This new model will further elucidate the impact of the firm's competitive dynamics via alliances and scientific innovation by evaluating the proposed new variable of biosimilar implementation. The controls of revenue and firm incorporation will be in the study in addition to the firm's labor number and the firm's assets have been added as controls. The proposed model is in Figure 4: Biosimilar Pharmaceutical Alliances' Factors Construct below.

FIGURE # 4: Biosimilar Pharmaceutical Alliances' Factors Construct



Independent Variables Definitions

The independent variables and the definitions of the construct's variables (antecedents) are as follows:

- Patent Cliff / Risk: the firm's key products that are impacted by patent expiry in key markets usually either U.S. and/or E.U. markets
- R&D Intensity: percentage of R&D investment to overall sales per annum
- Generic Experience Product Total: a firm's non-branded or branded generics market experience (Japan, EU, or U.S.). Authorized generics, which are defined as "which are drugs made by or under license from the innovator company and sold without a brand name" are excluded in the definition due to differences in the firm's individual strategy on generics (Lamb, 2008).
- Biotech Experience Product Total: a firm that has biotechnology products in development or commercialized in the market (Japan, EU, U.S.).
- Number of Patents: the number of U.S. patents filed under the firm
- FDA filings: the number of U.S. regulatory filings for clinical trial start or marketing applications
- Drug Approvals: the number of New Drug Applications (NDAs) approved by the FDA per annum per firm
- Generic Approvals: the number of generic drug approvals by the FDA per annum per firm
- Biologic Approvals: the number of Biologic License Applications (BLAs) approved by the FDA per annum per firm
- Pharma/Biotech Company: categorical variable coded whether the company is considered a "traditional" pharmaceutical company or biotechnology company.

The firm controls for the proposed research are the firm's incorporation age, the firm's labor number, the firm's assets and the firm's pharmaceutical revenue. This will allow for any correlations due to firm size to be identified.

Neither the proposed alliance model/construct in Figure #4 nor the subsequent analysis addresses the issue causality. The study assesses the association between alliances / collaborations and variables that underpin competitive dynamics in the pharmaceutical industry.

Construct Hypotheses

One would expect that firms with large R&D efforts or an increased patent filing strategy would have more alliances due to the incremental innovation or breakthrough nature of this work. Dunlap-Hinkler found that "innovations originating from joint ventures and strategic alliances are significantly more likely to be breakthrough" (Dunlap-Hinkler, 2010). In a similar vein, patent risk of the firm may drive the firm to develop more external alliances to create value via breakthrough technologies and product innovations.

However, on-the-other-hand, one may assume that large R&D efforts and patent filings may indicate that the firm is more internally focused and strategic alliances are not as important.

Hypothesis 1: Patent risk, R&D intensity and / or number of patents filed will be significantly associated to the number of alliances formed.

Previous research has known that organizations have "DNA" and they will maintain their current business practices and strategic intent (Nelson, 1982). This means that firms practicing product innovation will more than likely continue to practice product

innovation and firms executing incremental innovation will continue to do so as well (Dunlap-Hinkler, 2010). Generics and bioimilars may be considered types of process innovation or incremental innovation. Incremental innovation usually does not require breakthrough discovery, which requires new ideas and alliances to achieve a novel result; thus, it is hypothesized that firms which are practicing experiences like biosimilars and generics related to incremental innovation will not require as many alliances. However, it could be argued that biosimilars are not a "typical" process innovation due to the cost and the technology and firms will want or need to partner to balance risk or achieve scientific awareness. It has been stated that biosimilars' high cost of market entry and the associated risks with biosimilar development makes collaboration and partnering likely (Blackstone, 2013).

Hypothesis 2: Generic experience / approval and biosimilar experience will be significantly associated to the number of alliances formed.

Typically, through the lens of the media and industry viewpoints, biotechnology firms are viewed as "tech savvy" and product innovators. In stark comparison, traditional pharmaceutical firms are viewed as slower moving and product adaptors rather than product innovators. Alliances as previously demonstrated through the history of biotechnology are key piece of new breakthrough technology and product innovation. It is thus hypothesized that biotech companies will have more alliances than traditional pharmaceuticals.

Hypothesis 3: Biotech firms will enter into alliances more frequently than pharmaceutical firms.

New product approvals either drug or biologics in the pharmaceutical industry leads to new revenue and market growth for the firm. Approval of drug New Drug Applications (NDA) or biological Biological License Agreements (BLA) often demonstrates product innovation and breakthrough technologies. Previous research has shown that alliances and breakthrough innovation are linked. Thus, it is hypothesized that NDA and BLAs will be significantly associated with the number of alliances formed.

Hypothesis 4: Product approvals (either drug or biotechnology) will be significantly associated to the number of alliances.

Previous research has stated that firm size is linked to breakthrough innovation and breakthrough innovation is linked to alliances (Dunlap-Hinkler, 2010). However, Rothaermel and Boeker's research found that smaller firms are more likely to search for and produce breakthrough innovation (Rothaermel, 2008). Does this mean that smaller firms will have more alliances if one assumes alliances and product innovation are linked?

Hypothesis 5: Firm size will be significantly associated with the number of alliances.

Data Collection & Data Analysis

The proposed data collection for the variables is listed below in Table 12: Alliance Data Sources and Variables. The data for the control variables of pharmaceutical revenue and firm age were obtained from PharmaExec.com, annual reports and Mergent database respectfully.

Table #12: Alliance Data Sources & Variables

Variable/Metrics	Measure	Data Source
Patent Cliff	Calculated by (Expired Patent Drug Revenue/Rx Sales) per annum starting with the year of expiry until non-reporting based upon the company's annual filings	Company annual reports, SEC 10K or 20F filings
Biotech Experience	Firm's experience either in development or commercially with biologics; categorical variable (yes/no)	Company annual reports, SEC 10K or 20F filings
Generic Experience	Firm's experience with generics: categorical variable (yes/no)	Company annual reports, SEC 10K or 20F filings
Biosimilar Experience	Firm's experience with biosimilars (either marketed or in development); categorical variable (yes/no)	Company annual reports, SEC 10K or 20F filings
Drug Approval	Number of drug product commercialized per annum	FDA.gov
Generic Approval	Number of generic products commercialized per annum	FDA.gov
Biotech Approval	Number of biotech products commercialized per annum	FDA.gov
Patent Number	Number of U.S. patents filed	Patft.uspto.gov (US governmental patent office) or, Statiscia database
FDA Filings	Number of NDA/BLA or INDs filed	FDA.gov
R&D Intensity	R&D spend divided by Pharma Revenue	Company annual reports, PharmaExec.com
Pharmaceutical Revenue	Pharmaceutical sales per annum	Company annual reports, PharmaExec.com
Pharmaceutical or Biotech company	Categorical coding	Company annual reports and financial websites
Firm Age	Incorporation age subtracted from reporting year	Mergent database
Firm Assets	Assets of parent company	Mergent database
Firm Labor	Number of employees at the parent company	Mergent database

Please refer to Appendix B for the list of the top 50 pharmaceutical/biotech firms from 2014 as listed from PharmExec.com and Appendix C for the list of the 31 pharmaceutical companies analyzed for this research using publicly available information.

The secondary data gathered from the years of 2010 to 2015 (annual intervals) permits the evaluation of firms entering the biosimilar field over the study period. The dates were chosen as the first biosimilar approvals on the US market occurred in 2015 but the individual company's research and development into the biosimilar products started years earlier which permits the strategic thinking and the competitive landscape to evolve and mature.

For this research, the measures are, using the AMC model from a competitive dynamic perspective, to support the alliance construct. The patent risk variable is measured by conducting a product patent search of the selected biotech and pharmaceutical companies using key licensed product patents as identified by the firm that have expired and recorded until no longer reported annually by the firm. Once the key expiring products are identified, this total risk is measured by the ratio of the percentage of key product expiring revenue divided by total revenue per annum. By taking this ratio, this normalizes the measurement across the variously sized companies.

The R&D portfolio strength independent variable is measured by the number of clinical trials per annum for the years 2010 through to 2015. The company's product pipeline information is typically available on the company's website or in the company's quarterly/annual report or at ClinicalTrials.gov for the selected pharmaceutical / biotech firms (please refer to Appendix A). The timeframe of 2010 through 2015 is proposed since the U.S. biosimilar regulations were approved in 2009 and the first biosimilar

approved filing in the U.S. was in 2015. If a company had a "weaker" R&D pipeline in this time window, then the approval in 2009 may prompt the company to invest in the biosimilar development due to the new regulatory option. For this research, the U.S. Food and Drug Administration's clinicaltrials.gov was used to collect the number of trials per company per annum at an aggregate level demonstrating potential indications and R&D pipeline strength.

The previous generic and biopharmaceutical experience data is drawn from the selected companies' websites and annual reports, SEC filings (10K or 20F annual reports), or the FDA's Orange or Purple Books. Experience for the purposes of this research is defined as at least one non-branded generic or biopharmaceutical product in the portfolio respectively and is reported as a categorical variable (yes or no) either in the R&D pipeline and/or commercialized.

The NDA/BLA/ANDA drug approval data was recorded from the Food and Drug Administration's FDA.gov website. This information, however, does focus the data solely on the U.S. approvals and the U.S. market is the largest pharmaceutical market in the world. The data does not take into account Europe (EMA) or Japan, which are other major revenue markets.

The alliances and collaboration data was primarily secured from the Cortellis Deals Database (formerly known as ReCap). The Cortellis database pulls public information on deals that were executed in the pharmaceutical industry.

R&D intensity (R&D spend / Revenue) is pulled from secondary data such as company annual reports and SEC filings which include 10K or 20F annual reports. A control

variable of favorable reimbursement is assumed; however, the information may be drawn from government websites, government publications, and / or pharmaceutical and medical journal articles keeping in mind, that the reimbursement itself is a very complex and multi-facetted topic.

Alliances Regression Testing Results

The formative construct of alliances (Figure #4) and its independent variables as well as its control variables was analyzed using linear regression using SPSS software. The research data for the top 31 prescription sales biopharmaceutical and pharmaceutical firms was drawn from the years from 2010 to 2015.

This research analyzes the data to determine if there are any significant associations that emerge from the quantitative variable analysis. Additionally, the biosimilar world is quickly changing and a refresh on the latest events, regulatory, and legal recommendations/rulings will add value to the research from both an academic and practical view.

The data was gathered for the top 31 biopharmaceutical and pharmaceutical companies for each of the previously described variables (antecedents) and the linear regression analysis was run in the IBM statistical software program SPSS. The raw data tables from the SPSS software are located in Appendix G: Summary Statistics for Alliance Regression, Appendix H: Alliance Regression Output, Appendix I: Alliance Regression Model Summary and Appendix J: Alliance Regression Correlation Matrix tables for further reference.

The R-square result from the model analysis resulted 0.501 fit to the data set with Firm Revenue and Number of Employees being significant from the analysis. The other variables were not significant to the overall model.

Discussion of Alliance Regression Results

A summary of the results for each of the five hypothesis is listed below:

Hypothesis 1: Patent risk, R&D intensity and / or number of patents filed will be significantly associated with the number of alliances formed: ***not significant***

Based upon the dataset, significant association was not proven despite previous literature supporting this hypothesis and this result is somewhat surprising. This may be due to the limited data set of companies and the number of years evaluated. Previous research has also demonstrated that R&D intensity can be related to patents since R&D is the firm's driver for patent filings (Dunlap-Hinkler, 2010). It is recommended that further follow-up occur with a broader data set with either additional companies or additional years.

Hypothesis 2: Generic experience / approval and biosimilar experience will be significantly associated to the number of alliances formed: ***not significant***

Generic experience and biosimilar experience was not proven to be significantly associated with the generic experience and biosimilars. This finding aligns some of the thinking in the industry and the previous literature findings that companies that focus on incremental innovation meaning that firms practicing product innovation will more than likely continue to practice product innovation and firms executing incremental innovation will continue to do so as well (Dunlap-Hinkler, 2010). It is recommended that a broader

data set be evaluated in the future as biosimilars become more established to determine impact.

Hypothesis 3: Biotech firms will enter into alliances more frequency than pharmaceutical firms: ***not significantly associated****.*

Based upon the results, the designation of biotech or pharmaceutical firm does not have an impact on alliances. One explanation is that this may be due to the "blending" of the biotech world and the pharmaceutical world over the past few years as the distinction between the two appears to be disappearing. Also, the data set itself may be biased against smaller biotech firms since the data set is solely comprised of the Top 31 pharmaceutical and biotech companies. If the data set was explained to smaller firms, the result may be different and more aligned with previous research.

Hypothesis 4: Product approvals (either drug or biotechnology) will be significantly associated to the number of alliances: ***not significant***

Product approvals were not proven to be significant with the analysis to the number of alliances. This result could be related to the companies analyzed since the data set only is compromised of the Top 31 pharmaceutical firms by prescription revenue. It is recommended that a broader data set be further evaluated. There is also a possibility that this result is predictive and that product approvals are not linked significantly to external alliances.

Hypothesis 5: Firm size is significantly associated and has an impact on the number of alliances: ***significantly associated***

This result of firm size is significantly associated on the number of alliances thus matching the hypothesis and supports previous literature findings. There are some interesting aspects of the data however. The Beta value for employee number is negative and the Beta value for revenue is a positive. This result would then predict a company with fewer employees but with more revenue will partner more often. Could this be due to lack of employee resources to execute or is this a corporate strategy to partner and keep the firm lean? Further, evaluation of this result is merited.

The overall model based upon the R-square result of 0.501, the model is 50% predictable of the alliances. It is anticipated that a broader data set would increase the predictability of the model.

Alliance Conclusion & Future Research

The analysis of the Top 31 pharmaceutical companies on alliances yielded results that were expected as well as surprising. From the analysis, "size matters" with regards to the number of alliances but revenue and employee number were opposite with the Beta value score. Other factors such as R&D intensity and patents were not significantly associated. And the new process innovation variable of biosimilars as well as generic experience were not significantly associated with alliances which aligns with previous research that alliances leads to break through innovation rather than incremental process innovation.

Overall, the analysis is intriguing and it is recommended that further follow-up occur with a broader data set and additional time points to further validate or challenge the current model.

CHAPTER 4.0
OVERALL EXPECTED RESEARCH CONTRIBUTIONS

Overall from both the biosimilar implementation and the alliance research, it is expected that this research will contribute to the pharmaceutical and biopharmaceutical industry by providing practical data and insight into the biosimilar pathway and alliances from a strategic viewpoint using the AMC model by providing an analysis of biosimilar entry and competitive dynamics. The companies working in the pharmaceutical and biopharmaceutical industry as well as potential "suitors" to the industry may use this information to aid in decision making regarding the biosimilar market and allow reflections on alliances. Thus far, no such study has been published on biosimilars in this comprehensive and practical fashion.

From an academic contribution, this research will contribute to the competitive dynamic field by providing a new construct, metrics, and a quantitative study on biosimilars as an example of "pure" process innovation from a strategic viewpoint by studying the behavior and decision making of the firms in the bio/pharmaceutical environment with this novel process innovation paradigm. The biosimilar construct by the definition from the regulatory agencies permits the academic study of process innovation while removing the possible interference of product innovation on competitive dynamics and demonstrates the ability of regulatory bodies to influence an industry's innovation. This research will expand our academic understanding of the impact of process innovation (in this case, the novel biosimilar pathway) using the perspective from the dynamic capabilities model, which is defined as "a firm's ability to integrate, build, and

reconfigure internal and external competences to address rapidly changing environments" and is an extension of the resource-based view of the firm (Piening & Salge, 2014).

The research proposal further contributes by addressing some of the questions that drive competitive dynamic research using the AMC model such as the interaction of the firms when they compete, form alliances, and the competitive behaviors that influence organizational performance (Chen, 2012). Contributing to the field of competitive dynamics, this study contributes by introducing the topic of an emerging product introduction with a complex market of payers, payees, and patients in the different marketing sectors as well as the innovation aspects of the regulatory pathway and the strategic thinking pertaining the individual firm's entry into the biosimilar market. Currently, such a construct on biosimilars has not been published from a competitive dynamic perspective.

In addition, future academic work in biosimilar research since this regulatory pathway is still novel and there are a very limited number of approved biosimilar filings in the U.S. currently, the consequences of the construct or the anticipated outcomes from entering into biosimilars in the U.S. or EU markets, have not been researched yet. This provides an excellent opportunity to expand the impact of "pure" process innovation on strategy and the firm. The consequences such as increased profitability due to favorable reimbursement or disease area market capture may be an opportunity as the market develops for a future longitudinal study on the effects of biosimilars implementation on the U.S. pharmaceutical market and the specific pharmaceutical companies and/or specific products as well as the global industry. Since the EU regulatory pathway has been established earlier than the U.S., there are some biosimilars on the EU market

currently but this is still a very limited set of information; however, this information may also be evaluated for future research.

Future research is also recommended to further study biosimilars (process innovation) as an independent variable impacting alliances as the dependent variable within the pharmaceutical industry. This future research could investigate the strategic group theory analyzing the upstream, downstream, and horizontal alliances created by biosimilars within the pharmaceutical sector from the large to small size firms.

Managerial Summary

Since biosimilars are still nascent in the pharmaceutical industry, this dissertation research has only started to investigate the impact of biosimilars on the pharmaceutical sector. From this research analysis of the Top 31 pharmaceutical firms, it can be stated that the culture and the strategy of the company as well as the managerial decisions which drive the implementation of biosimilars and the other factors like patent expiry and technology do not directly impact the biosimilar implementation decision. Although this result is surprising in some ways, it eludes to the fact that biosimilars are still new to the U.S. market and that management needs to understand and appreciate the impact of the company's innovation culture on the decisions being made by the corporation.

The biosimilar market will mature and the decisions around pricing and biosimilar interchangebility may promote competitive dynamic factors that are favorable to implement or not favorable to continue with biosimilar development; however, the management of each company will need to take into account the economics as well as the company culture when making a biosimilar or an innovation step-change decision.

Some pharmaceutical experts state that the current Remicade and Humira biosimilar implementation in the U.S. market will be quite telling as to the impact on healthcare costs and the industry response as to whether the biosimilar companies and biosimilar alliances will continue to mitigate the cost of biosimilar development, or whether the biosimilar launches are economically positive which will drive new entrants into the competitive fray, or whether these new biosimilar competitors are not successful, which may cause abandonment by some current companies in the industry as well as regulatory bodies to assess the current biosimilar regulatory guidance.

Further, some industry experts state that the uptake of biosimilars onto the U.S. market has been slow and that further changes are needed to the regulatory guidelines to increase the competition of off-patent biologics. This dynamic market will need to be reviewed with a regular frequency including pricing, which this analysis did not discuss.

In summary, a practical view continuing to monitor the changing landscape of the biosimilar regulatory/legal pathway and the market participants will provide an opportunity for future research into competitive dynamics using the AMC model and the impact of process innovation monitoring which firms will remain in the biosimilar market and who will drop or be pushed out due to competitive forces.

Conclusion

In conclusion, this research presents the phenomenon of biosimilars as a novel form of process innovation discreet from product innovation. The executed research begins to close a gap in the literature on biosimilars from both a practical and academic viewpoint contributing to greater understanding of process innovation, alliances, and regulations on competitive dynamics and the impact on the growing healthcare industry.

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APPENDICES

APPENDIX A

BIOSIMILAR DEFINITIONS

Biosimilar		
Discipline	**Definition**	**References**
FDA (USA)	**biologic product highly similar to the reference product with no clinically meaningful differences… in terms of the safety, purity and potency of product**	Strand & Cronstein, 2016
Pharmaceutical pathobiology	variety of administered proteins, including hormones, enzymes, immunoglobin-based monoclonal antibodies, blood products, and vaccines, which purposefully developed to be highly similar to another biologic product that has been approved for human administration	Ryan, 2015
Clinical pharmacology	high quality biological medicine shown to be in essence the same as an original product	de Mora, 2015
Biotechnology	copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based upon a comprehensive comparability exercise	Weise et al, 2011
Biotechnology	Me-too biologic: Biological medicinal product developed on its own and not directly compared and analyzed against a licensed reference biological. May or may not have been compared clinically.	Weise et al, 2011
Biotechnology	Second-generation biologic: biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance	Weise et al, 2011
Autoimmunity	a similar biologic at the molecular perspective and that potential small differences may be relevant to clinical outcomes	de Abreu et al, 2014
Internal medicine	non-proprietary biologics agents	Strand & Cronstein, 2014
World Health Organization (International Agency)	biotherapeutic product which is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product	Strand & Cronstein, 2014
European Commission (EMA)	the biosimilar must be sufficiently similar to the reference product (already licensed in the EU) to be used in the same clinical indication at the same dose; requiring additional clinical trials but likely more abbreviated where the risk of failure is less, as the target and mechanism of action are well demonstrated	Strand & Cronstein, 2015
Pharmacovigilance	non-innovator similar biologics	Kumar et al, 2015
Generic Medicines	1. product with primary structure identical to the reference biological product, 2. biosimilarity development pathway involving relevant orthogonal analytical comparabitility methods, non-clinical and clinical models has been utilized from the outset rather than in opportunistic fashion, 3. Quality, non-clinical and clinical attributes are sufficiently similar yet might not be identical between the biosimilar and the reference product, 4. products that are approved by national or regional authorities using the same product label as a reference product	Kudrin, 2012

APPENDIX B

TOP 50 PHARAMCEUTICAL COMPANIES (2014)

Ranking by Rx Sale	Company	2014 Rx Sales (000 USD
1	Novartis	$ 46,127
2	Pfizer	$ 44,514
3	Roche	$ 40,086
4	Sanofi	$ 38,223
5	Merck & Co	$ 36,607
6	Johnson & Johnson	$ 30,726
7	GlaxoSmithKline	$ 30,302
8	AstraZeneca	$ 25,694
9	Gilead Sciences	$ 24,474
10	AbbVie	$ 19,879
11	Amgen	$ 19,327
12	Teva Pharmaceutical Industries	$ 17,474
13	Bayer	$ 16,351
14	Eli Lilly	$ 16,349
15	Novo Nordisk	$ 15,825
16	Boehringer Ingelheim	$ 13,903
17	Takeda	$ 13,038
18	Bristol-Myers Squibb	$ 11,969
19	Actavis	$ 11,130
20	Astellas Pharma	$ 10,419
21	Baxter International	$ 8,694
22	Biogen Idec	$ 8,203
23	Merck KGaA	$ 7,683
24	Mylan	$ 7,585
25	Daiichi Sankyo	$ 7,575
26	Celgene	$ 7,476
27	Otsuka Holdings	$ 6,961
28	Allergan	$ 6,234
29	Les Laboratories Servier	$ 5,999
30	Shire	$ 5,830
31	Abbott Laboratories	$ 5,101
32	Sun Pharmaceutical Industries	$ 5,012
33	Valeant Pharmaceuticals International	$ 5,007
34	CSL	$ 4,743
35	Eisai	$ 4,422
36	UCB	$ 3,715
37	Fresenius	$ 3,707
38	Chugai Pharmaceutical	$ 3,576
39	Menarini	$ 3,442
40	Grifols	$ 3,255
41	Aspen Pharmacare	$ 3,066
42	Hospria	$ 3,035
43	Sumitomo Dainippon Pharma	$ 2,944
44	Mitsubishi Tanabe Pharma	$ 2,928
45	STADA Arzneimittel	$ 2,405
46	Mallinckrodt	$ 2,310
47	Endo International	$ 2,238
48	Alexion Pharmaceuticals	$ 2,234
49	Lundbeck	$ 2,223
50	Kyowa Hakko Kirin	$ 2,157

APPENDIX C

PHARMACEUTICAL COMPANIES ANALYZED FROM 2010 TO 2015

Novartis
Pfizer
Roche
Sanofi
Merck & Co
Johnson & Johnson
GlaxoSmithKline
AstraZeneca
Gilead Sciences
AbbVie/Abbott
Amgen
Teva Pharmaceutical Industries
Bayer
Eli Lilly
Novo Nordisk
Boehringer Ingelheim
Takeda
Bristol-Myers Squibb
Astellas Pharma
Baxter International
Biogen Idec
Merck KGaA
Mylan
Daiichi Sankyo
Celgene
Otsuka Holdings
Allergan
Shire
CSL
Eisai
UCB

APPENDIX D

SPSS CASE PROCESSING SUMMARY

Case Processing Summary

		N	Percent
Cases available in analysis	Event[a]	72	38.9%
	Censored	113	61.1%
	Total	185	100.0%
Cases dropped	Cases with missing values	0	0.0%
	Cases with negative time	0	0.0%
	Censored cases before the earliest event in a stratum	0	0.0%
	Total	0	0.0%
Total		185	100.0%

APPENDIX E

BIOSIMILAR IMPLEMENTATION RESULTS

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
R&D Intensity (%)	.043	.026	2.864	1	.091	1.044	.993	1.098
Patent Risk (%)	-.048	.013	14.646	1	.000	.953	.929	.977
Generic Experience	1.562	.281	30.884	1	.000	4.768	2.749	8.272
Biotech Experience	.854	1.030	.687	1	.407	2.348	.312	17.683
Number of Clinical Trials	.000	.001	.008	1	.929	1.000	.998	1.002
Revenue	.000	.000	3.830	1	.050	1.000	1.000	1.000
IncorporationYear	-.004	.003	1.369	1	.242	.996	.990	1.003

APPENDIX F

BIOSIMILAR IMPLEMENTATION VARIABLE CORRELATION MATRIX

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Patent Risk (%)	-0.451													
Generic Experience	0.175	-0.239												
Biotech Experience	-0.128	0.021	-0.024											
Number of Clinical Trials	-0.193	0.102	-0.041	-0.036										
Revenue	0.222	-0.141	0.106	0.212	-0.316									
IncorporationYear	-0.326	0.203	-0.198	-0.006	-0.127	-0.076								
Total Assets	-0.103	0.166	-0.312	-0.149	0.178	-0.718	0.274							
PharmBiotech	0.277	-0.118	-0.144	-0.083	-0.181	0.394	-0.05	-0.259						
PatentFilings	-0.171	0.172	0.288	-0.057	-0.024	-0.391	-0.047	0.29	-0.25					
Generic Approvals	0.512	0.009	-0.202	-0.14	0.094	-0.086	-0.143	0.248	-0.005	-0.059				
DrugApproval	-0.138	0.059	-0.024	0.099	-0.162	-0.049	-0.051	0.021	-0.054	0.14	-0.25			
BiologicApproval	0.05	-0.118	0.041	-0.015	0.121	0.07	-0.196	-0.014	0.056	-0.139	0.097	-0.219		
EmployeeNumber	0.005	-0.098	-0.05	-0.164	0.034	-0.517	-0.32	0.01	-0.308	-0.054	0.014	-0.045	-0.069	
Collaborations	-0.008	-0.087	0.306	-0.112	-0.011	-0.372	-0.07	0.013	-0.139	0.14	0.071	-0.177	0.015	0.241

1. R&D Intensity
2. Patent Risk
3. Generic Experience
4. Biotech Experience
5. Number of Clinical Trials
6. Revenue
7. Incorporation Year
8. Total Assets
9. Pharmaceutical or Biotechnology Based Company
10. Number of Patent Filings
11. Number of Generic Approvals
12. Number of Drug Approvals
13. Number of Biological Approvals
14. Employee Number

APPENDIX G

SUMMARY STATISTICS FOR ALLIANCES REGRESSION

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
R&D Intensity (%)	185	5.35	47.03	19.4356	6.89605
Patent Risk (%)	185	.00	89.11	15.4532	15.52190
Generic Experience	185	0	1	.32	.469
Biotech Experience	185	0	1	.96	.191
Biosimilar Experience	185	0	1	.39	.489
Revenue	185	3100	58500	17633.73	13288.743
IncorporationYear	185	0	152	62.69	44.965
Total Assets	185	4343.00	195014.00	47017.8541	43931.40270
PharmBiotech	185	.00	1.00	.7081	.45587
PatentFilings	185	3.00	3078.00	340.8108	635.23415
Generic Approvals	185	.00	55.00	2.2486	7.74757
DrugApproval	185	.00	7.00	1.0216	1.39859
BiologicApproval	185	.00	3.00	.1405	.41928
EmployeeNumber	185	4000.00	174000.00	46473.9027	39243.94577
Collaborations	185	.00	13.00	3.2541	3.00819
Valid N (listwise)	185				

APPENDIX H

ALLIANCE REGRESSION OUTPUT

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients		
		B	Std. Error	Beta	t	Sig.
1	(Constant)	-.145	1.026		-.141	.888
	R&D Intensity (%)	.016	.030	.036	.513	.609
	Patent Risk (%)	-.013	.013	-.066	-1.028	.306
	Generic Experience	-.676	.466	-.105	-1.451	.149
	Biotech Experience	.563	.937	.036	.600	.549
	Biosimilar Experience	-.178	.473	-.029	-.377	.706
	Number of Clinical Trials	.003	.002	.118	1.304	.194
	IncorporationYear	.005	.004	.081	1.229	.221
	Total Assets	6.244E-6	.000	.091	.671	.503
	PharmBiotech	.399	.440	.060	.907	.365
	PatentFilings	.000	.000	-.044	-.580	.563
	Generic Approvals	-.013	.027	-.033	-.477	.634
	DrugApproval	.052	.141	.024	.372	.711
	BiologicApproval	-.308	.432	-.043	-.712	.478
	EmployeeNumber	-2.183E-5	.000	-.285	-2.594	.010
	Revenue	.000	.000	.717	4.896	.000

a. Dependent Variable: Collaborations

APPENDIX I

ALLIANCE REGRESSION MODEL SUMMARY

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.708[a]	.501	.456	2.21773

a. Predictors: (Constant), Revenue, Generic Approvals, Biotech Experience, BiologicApproval, Patent Risk (%), IncorporationYear, Generic Experience, PharmBiotech, DrugApproval, R&D Intensity (%), Biosimilar Experience, PatentFilings, Number of Clinical Trials, EmployeeNumber, Total Assets

APPENDIX J

ALLIANCE REGRESSION PEARSON CORRELATION MATRIX

	Collaborations	R&D Intensity (%)	Patent Risk (%)	Generic Experience	Biotech Experience	Biosimilar Experience	Number of Clinical Trials	IncorporationYear	Total Assets	Pharm Biotech	Patent Filings	Generic Approvals	Drug Approval	Biologic Approval	Employee Number	Revenue
Collaborations	1.000	-.052	-.070	-.020	.036	.106	.568	.224	.558	.229	.365	-.076	.313	.092	.417	.665
R&D Intensity (%)	-.052	1.000	.374	-.262	.116	-.196	-.021	.144	-.153	-.154	-.033	-.420	-.115	.011	-.177	-.208
Patent Risk (%)	-.070	.374	1.000	-.043	.146	-.243	-.064	.046	-.033	-.019	-.127	-.199	-.079	.092	-.108	-.088
Generic Experience	-.020	-.262	-.043	1.000	.077	.560	.026	.050	.218	.242	-.053	.420	.113	-.122	.170	.161
Biotech Experience	.036	.116	.146	.077	1.000	.100	.091	.176	.098	.247	.084	.058	-.058	.067	.187	.043
Biosimilar Experience	.106	-.196	-.243	.560	.100	1.000	.075	.011	.344	.269	.080	.363	.162	-.030	.175	.257
Number of Clinical Trials	.568	-.021	-.064	.026	.091	.075	1.000	.344	.600	.339	.484	-.078	.428	.138	.607	.742
IncorporationYear	.224	.144	.046	.050	.176	.011	.344	1.000	.288	.273	.392	.017	.259	.235	.438	.282
Total Assets	.558	-.153	-.033	.218	.098	.344	.600	.288	1.000	.370	.511	-.001	.421	.208	.785	.875
PharmBiotech	.229	-.154	-.019	.242	.247	.269	.339	.273	.370	1.000	.275	.187	.257	.017	.469	.345
PatentFilings	.365	-.033	-.127	-.053	.084	.080	.484	.392	.511	.275	1.000	-.048	.250	.309	.593	.583
Generic Approvals	-.076	-.420	-.199	.420	.058	.363	-.078	.017	-.001	.187	-.048	1.000	.199	-.074	.028	.009
DrugApproval	.313	-.115	-.079	.113	-.058	.162	.428	.259	.421	.257	.250	.199	1.000	.078	.398	.439
BiologicApproval	.092	.011	.092	-.122	.067	-.030	.138	.235	.208	.017	.309	-.074	.078	1.000	.280	.221
EmployeeNumber	.417	-.177	-.108	.170	.187	.175	.607	.438	.785	.469	.593	.028	.398	.280	1.000	.752
Revenue	.665	-.208	-.088	.161	.043	.257	.742	.282	.875	.345	.583	.009	.439	.221	.752	1.000

APPENDIX K

COMPANY & BIOSIMILAR IMPLEMENTATION CHART

Biosimilar Implementation Year	2010	2011	2012	2013	2014	2015
Company Name						
Novartis	Yes	Yes	Yes	Yes	Yes	Yes
Pfizer	Yes	Yes	Yes	Yes	Yes	Yes
Roche	No	No	No	No	No	No
Sanofi	Yes	Yes	Yes	Yes	Yes	Yes
Merck & Co	Yes	Yes	Yes	Yes	Yes	Yes
Johnson & Johnson	No	No	No	No	No	No
GlaxoSmithKline	No	No	No	No	No	No
AstraZeneca	No	No	No	No	No	No
Gilead Sciences	No	No	No	No	No	No
AbbVie/Abbott	No	No	No	No	No	No
Amgen	No	Yes	Yes	Yes	Yes	Yes
Teva Pharmaceutical Industries	Yes	Yes	Yes	Yes	Yes	Yes
Bayer	No	No	No	No	No	No
Eli Lilly	No	No	Yes	Yes	Yes	Yes
Novo Nordisk	No	No	No	No	No	No
Boehringer Ingelheim	Yes	Yes	Yes	Yes	Yes	Yes
Takeda	No	No	No	No	No	No
Bristol-Myers Squibb	No	No	No	No	No	No
Astellas Pharma	No	No	No	No	No	No
Baxter International	No	Yes	Yes	Yes	Yes	N/A
Biogen Idec	No	Yes	Yes	Yes	Yes	Yes
Merck KGaA	No	No	Yes	Yes	Yes	Yes
Mylan	Yes	Yes	Yes	Yes	Yes	Yes
Daiichi Sankyo	No	No	No	No	No	No
Celgene	No	No	No	No	No	No
Otsuka Holdings	No	No	No	No	No	No
Allergan	Yes	Yes	Yes	Yes	Yes	Yes
Shire	No	No	No	No	No	No
CSL	No	No	No	No	No	No
Eisai	No	No	No	No	No	No
UCB	No	No	No	No	No	No

*Baxter is N/A for Year 2015 due to spin-off biologics to a separate company