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生技仿製藥規範與公費報銷政策對藥廠經營策略之影響 — 美國、歐洲與日本制度之比較分析

Biosimilar Regulations and Reimbursement Policies and Impact on Corporate Strategy: A Comparative Analysis of the US, EU, and Japan Pharmaceutical Markets

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Abstract

This thesis identifies major trends in biosimilar regulations and reimbursement policies, using the US, EU, and Japan pharmaceutical markets as the case subjects. Research is focused on a comparative analysis of regulatory policies with respect to market licensing of biosimilars and major reimbursement policies affecting market use of biosimilars. The information from this comparative analysis, as well as data reported by biologic manufacturers, is used to evaluate the corporate strategies that incumbent, patent holding biologic manufacturers are pursuing to respond to future biosimilar competition. Lastly, recommendations are provided to domestic biosimilar manufacturers planning to enter their home market of Taiwan.

Regulatory agencies in the US, EU, and Japan have established abbreviated review processes to allow biosimilars to come to market faster than if they were to be reviewed as completely new molecular entities. Key differences between the agencies are in granting 'interchangeable/substitutable' labels and in the timing of the first biosimilar submission. For instance, the US FDA's option for biosimilars to be licensed as 'interchangeable,' a shorter time in which biosimlars have to wait to submit applications, and an exclusivity period for the first-to-market biosimilar will theoretically encourage wider biosimilar adoption in the market.

The US is expected to have wide variation in biosimilar reimbursement policies as policies will vary on the size of the insurance market and the level of competition between plan administrators. On the other hand, the EU member states analysed for reimbursement policies - Germany, France, and the UK - and Japan have national-level policies that influence the type of pharmaceuticals covered as benefits and their

reimbursement prices. European countries were found to use pricing tools, such as negotiated discounts, reference pricing, and tendering, that should provide an opportunity for biosimilars to gain market share.

Differences in major regulations and reimbursement policies in the studied markets were found to lead to differences in the degree of potential competition between biologics and biosimilars. In response to greater potential biosimilar competition in the US, biologics marketed for the US were more likely to take legal action to defend patent rights. In Japan, the market determined to have the lowest degree of potential biosimilar competition, the incumbent biologic manufacturers were more likely to apply for additional indications, which can be revenue increasing only without biosimilar competition. Lastly, the EU, which is the more mature system in terms of regulation and reimbursement policies for dealing with biosimilars, also sees incumbents applying for new indications, as well as developing new biologics to cannibalise sales of the existing biologic.

Finally, advice for Taiwan domestic biosimilar manufacturers are to work with the government in developing regulations and health insurance policies more favorable for biosimilars, and to gain first-mover advantage as preferred suppliers for large hospitals and medical centers, focussing on additional incentives manufacturers can offer providers for biosimilars requiring infusions.

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Chapter 1: Introduction

This thesis analyzes the current environment for an emergent class of medicines known as biosimilars. Biosimilars are the competitor "copies" of biologic medicines which have been the main drivers of pharmaceutical spending growth in recent years. Biosimilars present an opportunity for healthcare systems worldwide to realize more competitive pricing and wider access to beneficial biologic treatments. However, there is still much uncertainty regarding the safety and efficacy of biosimilars. These trade-offs have led government regulators and health insurance administrators to develop complex regulations and reimbursement policies through which biosimilar manufacturers must navigate to have their products sold on the market. These regulations and reimbursement policies, in addition to patents on originator biologic products, create both entry barriers and incentives for competition that will shape the future of this important market for pharmaceuticals.

The goal of this thesis is to examine major trends in biosimilar regulations and reimbursement policies, within the context of the implications they have on market competition. This information will be valuable for biosimilar manufacturers, such as those based in Taiwan that must not only prepare products for regulatory review; they must also face challenges from incumbents.

Focusing on the US, EU, and Japanese markets for pharmaceuticals, the research results have wider implications for other markets which are influenced by the largest three. This thesis addresses the following research questions:

1) *What barriers to entry and incentives for competition have regulators and policy makers created in the market for biologic and biosimilar pharmaceuticals?*

2) *How have these barriers to entry and incentives for competition influenced incumbent, patent-holding biologic manufacturer corporate strategies?*

Finally, after addressing these research questions with specific case studies from the three largest markets, attention is focussed on the smaller market of Taiwan, where domestic biosimilar companies are seeking to develop biosimilars for the domestic market. Recommendations for these companies are provided, based on research collected in this study.

1.1 Research Methodology

This thesis presents a qualitative analysis of primary sources: government regulations and policy guidance; and secondary sources: academic journal articles and industry reports. A comparative framework is developed, which identifies key similarities and differences between the jurisdictions chosen for this study (US, EU, and Japan). Attention is placed on regulations and reimbursement policies that create entry barriers protecting biologics from biosimilar competition, or create incentives for entry of biosimilars. This study is motivated by other comparative studies that analyze biosimilar regulations across the globe.[1,2,3] Other studies were found to be helpful in comparing national drug reimbursement agencies and policies across major developed economies.[4,5,6] However, these studies did not cover specific drug classes such as biologics or biosimilars. Two studies were identified for linking biosimilar regulations and reimbursement policies in comparisons of European Union member states.[7,8] This study appears to be the first that links biosimilar regulations and reimbursement policies

for the largest potential markets for biosimilars - US, EU, and Japan - with a focus on impacts to the competitiveness of the markets for these drugs.

The final section of research in this thesis analyzes the corporate strategy adopted by incumbent biologic manufacturers faced with patent expiration of biologic products and potential biosimilar competition. Six high worldwide sales volume biologics – Avastin, Enbrel, Humira, Lucentis, Remicade, and Rituxan – first introduced in Chapter 2 will be used as case examples to evaluate corporate actions in response to biosimilar competition. Similar to the comparative analysis of regulations and reimbursement policies, the analysis of corporate strategies is descriptive and qualitative in nature.

1.2 Structure of Thesis

The body of this thesis is divided into four main sections. First, the background section provides working definitions of biologics and biosimilars, as well as a literature review of major works cited in this paper. In this section, the concept of the "biologic patent cliff" is introduced, which is driving current interest in biosimilars. The second section analyzes regulations for marketing approval of biosimilars in the US, EU, and Japan. The third section analyzes these jurisdictions' major reimbursement policies related to coverage of biosimilars on national healthcare plans. In the US, the Medicare drug plans are the central focus. For the EU, country specific policies of Germany, France, and the UK are discussed. The fourth section analyzes the corporate strategies adopted by incumbent biologic manufacturers focusing on manufacturers of the six case biologics in the US, EU, and Japan markets. Finally, in the conclusion of the thesis, recommendations are provided for domestic biosimilar companies in Taiwan.

Figure 1.1 below illustrates the main points of comparison in this thesis from the perspective of the market pathway for biosimilars. The comparative analysis of regulatory and reimbursement policies identifies critical stages of review for biosimilars entering the US, EU, and Japanese markets.

Figure 1.1: Summary of Main Points of Comparison in Chapters 3 and 4

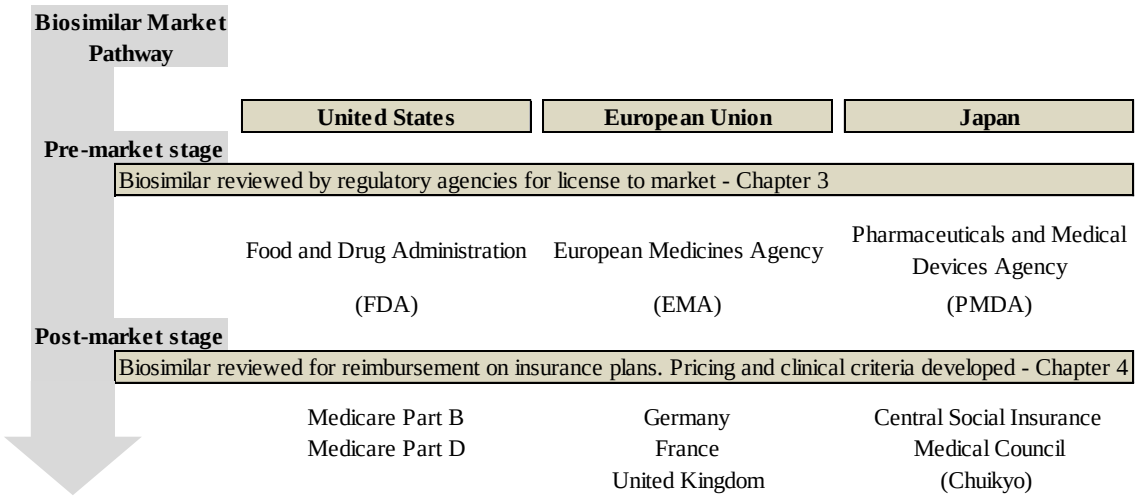
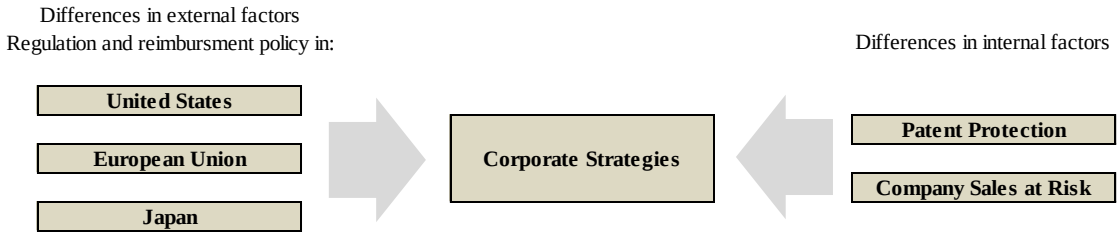


Figure 1.2 illustrates the framework used for understanding incumbent strategies in response to future biosimilar competition. This analysis compares differences in the factors influencing corporate strategies for biologics sold in the US, EU, and Japan.

Figure 1.2: Summary of Framework for Evaluating Biologic Incumbent Strategies in Chapters 5



Chapter 2: Background on Biologics and Biosimilars

2.1 Introduction

Total spending for pharmaceuticals in the developed world dropped for the first time in 2012.[9] The combination of government austerity measures and the "patent cliff" where former blockbuster drugs' patents expired at around the same time (e.g. Lipitor, Plavix, Crestor), opening markets for generic competition, caused this dramatic slowdown in spending. The new source of spending growth in pharmaceuticals are biologic type drugs which are expected to take up to 20 percent of the total pharmaceutical market by 2017.[9] These drugs are typically more expensive in per treatment costs and target smaller populations than traditional medicine. For example, patients in the US with moderate to severe rheumatoid arthritis may receive biologics costing $1,300 to $5,300 per month of treatment.[10] The most popular biologics treat rheumatoid arthritis along with other inflammatory diseases and various types of cancer.

As with the best-selling prescription drugs of the past, new biologic blockbusters are protected by a patent system in developed countries designed to reward innovation without over-extending monopoly profits to the patent holders. By 2020, most current biologic blockbusters will lose patent protection, leading to a phenomenon termed by analysts as the *biologic patent cliff*.[11] Whether the coming biologic patent cliff results a new wave of generic competition depends on a number of factors including regulations, reimbursement policies, and prescribing practices as they related to *biosimilar* versions of biologics. The body of this paper will explore these factors in further detail. Before proceeding to the body of this paper, the terms *biologic* and *biosimilar* will be clarified in further detail in the next two sections.

2.2 Definition of Biologic

The terms biologic(s), biologic drug(s), biologic product(s) are used interchangeably throughout this paper to refer to a class of medicine containing or manufactured by living organisms.[12] Examples of biologics include:

- vaccines;
- blood products used for transfusion and/or manufacturing into other products;
- allergenic extracts used for both diagnosis and treatment;
- human cells and tissues used for transplantation;
- gene and cellular therapies.[13]

Other information sources, including academic research, industry reports, and government regulations may use terms such as “biological products”, “biological drugs”, or “biopharmaceuticals” to generally refer to the same forms of medicine. Differences in the makeup of some products may exclude them from some sources’ classification of biologics (note the difference between US FDA and EU definitions of biologics for regulatory purposes in Radar, 2008).[12]

The following table lists six significant biologic products in terms of worldwide sales. The majority are monoclonal antibody types of biologics (mAb) indicated for treatment of autoimmune diseases. These biologics will be discussed regarding their manufacturers’ corporate strategies in Chapter 5.

Table 2.1: Summary of Select Biologics with Patents Expiring 2012 - 2019

US Marketing Company	Brand Name (Molecule Name)	Indications	Class of Biologic	Global Sales 2011 (billion USD)	Patent Expiration Year
AbbVie	Humira (adalimumab)	RA, JIA, PsA, AS, plaque psoriasis, ulcerative colitis (UC), Crohn's disease	monoclonal antibody (mAb)	8.2	2016
Amgen	Enbrel (etanercept)	rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis	dimeric fusion protein	7.9	2019
Janssen (J&J)	Remicade (infliximab)	RA, PsA, AS, plaque psoriasis, UC, Crohn's disease	mAb	7.2	2018
Biogen Idec	Rituxan (rituximab)	certain types of non-Hodgkin's lymphoma, leukemia, RA	mAb	6.8	2015
Genentech (Roche)	Avastin (bevacizumab)	certain types of colorectal, lung, kidney, brain cancers	mAb	6.0	2019
Genentech (Roche)	Lucentis (ranibizumab)	wet macular degeneration, diabetic macular edema, macular edema following retinal vein occlusion	mAb	3.8	2019

Sources: Calo-Fernandez & Martinez-Hurtado, 2012;[11] Indications from products' US webpages. Patent expiration dates provided by Calo-Fernandez & Martinez-Hurtado validated by dates provided in company 2013 annual reports. After validation, dates for Enbrel[14] and Rituxan[15] were updated.

For traditional medicines, the patent expiration dates indicate roughly the time when the brand name product's exclusivity for sales ends and when generic manufacturers can start to sell same versions of the brand name product. Much of the sales for the brand product would be a risk as a result of heavy price competition and market share displacement of generic pharmaceuticals.

However, unlike for traditional medicines, the upcoming patent expiration dates for these biologic products will not see the introduction of identical generic copies and an immediate displacement of brand name versions' market shares. Instead, the market will be open to similar, but not identical, "biosimilar" products (defined in the next section). The timing and level of market adoption of biosimilars is not certain and will

depend on regulations, reimbursement policies, and prescribing practices that are still works in progress. The body of this paper will explore these factors in further detail.

2.3 Definition of Biosimilar

Biosimilars can be thought of as generic versions of biologics. Unlike generic versions of traditional medicines, which can be shown to be chemically identical to brand versions in chemical structure, generic versions of biologics can never be shown to be as identical to brand versions of the same biologic. This is due to the complexity of biologics' molecular structures, proprietary manufacturing processes including originating cell cultures, and uncertain responses in real life use. Regulatory agencies developed terms to describe these generic versions of biologics as being very similar, but not exactly the same as the brand version.

The US Food and Drug Administration (FDA) define biosimilarity as: "a biological product highly similar to the reference product notwithstanding minor differences in clinically inactive components;" and with "no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product."[16] Other regulatory agencies use the terms "follow-on biologics" or "subsequent entry biologics" to generally refer to the same "biosimilar" products, emphasizing the common characteristic of these products as imitators of the originator product.

For the remainder of this paper, the terms biosimilar(s), biosimilar drug(s), biosimilar product(s) will be used interchangeably to refer to imitator versions of originator biologic products.

2.4 Literature Review

This study is motivated by other comparative studies that analyze biosimilar regulations across the globe.[1,2,3] Ricardo Ibarra-Cabrera et. al., 2013 conducts a world-wide comparison on biosimilar regulations highlighting European Medicines Agency (EMA) product-specific guidelines and special focus on laws in Mexico forming the basis of the country's "biocomparables' regulations.[1] While Abreu et. al., 2014 also describe global biosimilar regulations, special focus in their study is on the information requirements of regulators to address uncertainty in outcomes from biosimilars in comparison to the originator biologic.[2] Knezevic and Griffiths, 2011 highlight WHO's role in developing recommendations for biosimilar regulations and the opportunity for global and regional cooperation in setting standards for licensing biosimilars.[3]

Other studies were found to be helpful in comparing national drug reimbursement agencies and policies across major developed economies.[4,5,6] Cohen, Malins, and Shahpurwala, 2013 describe how national health insurer's reviews of comparative-effectiveness and cost-effectiveness evidence can lead to lower drug prices in comparison to the US which does not conduct such reviews at a national level.[4] O'Donnell et. al., 2009 also describes in detail national bodies conducting health technology assessments (HTA) and some challenges they face such as arguments on rationing health care.[5] Barnieh et. al., 2014 similarly describes national bodies (in OECD countries) that administer restrictive formularies as an approach to manage drug expenditures.[6] This thesis applies many of results from these three studies to the biologics or biosimilars drug classes. A similar approach was taken by Rovira et. al., 2011 and Declerck and Simoens, 2012 which were identified for linking biosimilar regulations and reimbursement policies in comparisons of European Union member states.[7,8]

In the analysis of corporate strategies of pharmaceutical companies, Wilkie, Johnson, and White, 2012 was cited for empirically testing relationships between brand name defense strategies against generic competition in traditional, small-molecule pharmaceuticals.[17] Rothaermel, 2001 describes strategic alliances between large pharmaceutical companies and smaller biotech companies in the early development of biologics.[18]

In developing hypothesis for incumbent biologic manufacturer's corporate strategy, in response to potential biosimilar competition, Porter, 1979 motivates the view that corporate strategy can be viewed in part as a response to competitive forces in the market.[19] An important addition to this view of competition comes from Ellison and Snyder, 2010 who propose a theory of countervailing power where the effectiveness of reimbursement policy in obtaining pricing concessions from suppliers depends on the size and market power of payers, as well as the degree of competition between suppliers.[20] Lastly, the time dimension of corporate strategy is viewed by Ramaprasad and Stone, 1992 as event-based, where time is measured relative to a series of important events that may pose a threat or opportunity for the company.[21] Applying this event-based view of strategy to patent-holding biologic pharmaceutical companies, the short- or long-term time horizon of their strategy can be measured by the time required to prepare new pharmaceuticals for market and the temporary lifetime of their patents.

Chapter 3: Regulation of Biosimilars. *Comparison of FDA, EMA, and PDMA*

3.1 Introduction

This section discusses the regulation of biosimilar drugs in the US, Europe, and Japan. The primary focus is the market licensing process established by these markets' main pharmaceutical regulatory agencies: the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Japan's Pharmaceutical and Medical Devices Agency (PMDA). These agencies directly influence the US$590 billion pharmaceutical markets over which they have jurisdiction;[9] the regulations from these agencies are also closely followed by regulatory agencies of other countries around the world.

This section will first introduce the three regulatory agencies. The approaches these agencies take with respect to generic drugs is briefly described, along with the challenges posed by the new class of biologic drugs. Each regulatory agency's approach to biosimilars is then discussed in further detail. This section concludes with the main observations found in comparing the three agencies.

3.2 Regulatory Mandate of FDA, EMA, and PDMA

The FDA is responsible for ensuring that drugs, vaccines and other biological products and medical devices are safe and effective.[22] The FDA also has a goal of advancing public health by supporting product innovations. The formal step in which the FDA is asked to consider approving new drugs is called the New Drug Application (NDA). The NDA includes all animal and human data, and information about how the drug behaves in the body and its manufacturing process.[23] The Prescription Drug User Fee Act (PDUFA) gives the FDA the authority to collect user fees for NDA submitted to the FDA's drug review agency, the Center for Drug Evaluation and Research

(CDER), and the biological product review agency, the Center for Biologics Evaluation and Research (CBER). With this fee-collecting authority, the CDER and CBER are required to meet certain performance metrics related to the review of new drug applications.[24]

The EMA's main responsibility is the protection and promotion of public health through evaluation and supervision of medicines.[25] The EMA acts as the centralised review body, responsible for providing an opinion to the European Commission on whether the medicine should be marketed or not. The European Commission then provides the centralised marketing authorisation for European Union (EU) states. EMA reviews and European Commission marketing authorisations are compulsory for the following categories of medicines:

- human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases;
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- officially designated 'orphan medicines' (medicines used for rare human diseases).[26]

The PMDA is responsible for protecting public health by assuring safety, efficacy and quality of pharmaceuticals and medical devices.[27] Similar to the EMA, the PMDA provides a review report to Japan's Ministry of Health, Labour and Welfare which has final authority for whether the applicant drug can be marketed in Japan. The

PMDA's drug reviews encompass all new drugs, generic drugs, over-the-counter drugs, and quasi-drugs.[28]

All three agencies have a role in providing pre-submission guidance and consultations (when the drugs may be in various stages of clinical trials), as well as post-market pharmacovigilance, where drugs are monitored in the community setting for adverse events.[28,29,30]

3.3 Regulation of Traditional Generic Drugs and the Challenge of Biosimilars

Generic drugs, in principle, contain the same amount of the same active ingredient and have the same indications, dosage, and administration, and the same route of administration as those of its brand-name reference drug.[28] Recognizing the potential welfare gains from having price competition in the generics market, the US government passed the Hatch-Waxman Act in 1984, establishing the Abbreviated New Drug Application (ANDA) which expedited the FDA approval process of generic drugs.[31] After the establishment of ANDA, applicants no longer needed to conduct clinical trials of the generic drug to demonstrate safety and efficacy. The main evidence required from applicants is proof of bioequivalence to the brand-name reference drug; that is, the generic version delivers the same amount of active ingredients into a patient's bloodstream in the same amount of time as the brand-name drug.

Currently the FDA, EMA, and PDMA share a similar abbreviated approval process for generic drugs, in which the main evidence requirements are bioequivalence studies.[28,32,33] The safety and efficacy studies conducted for the brand-name drug can be used to demonstrate safety and efficacy of bioequivalent generic drugs. The agencies still regulate quality and manufacturing processes to the same standards as brand-name

drugs; also, the applications are only to be submitted after the brand-name drug loses patent protection.

The emergence of complex, large-molecule, biologic drugs in the 1990s and 2000s presents a challenge to the relatively straightforward regulatory treatment of traditional generic drugs. Biologics are made in living organisms to produce proteins to treat diseases, often by genetically modifying cell constructs or cell lines.[34] The manufacturing process for biologics is highly complex, involving several factors that make it difficult for competing firms to produce copies of the brand-name biologic drug, even after the drug's patent has expired:

- Biologic manufacturers have their own master cell bank producing unique cell lines replicated for manufacturing, often under a proprietary process;
- The physical and clinical properties of the medicine are sensitive to small variations during the manufacturing process. Small changes to the properties of biologic medicines can cause serious harm to a patient by way of unwanted immune responses;
- Production requires a high level of monitoring and quality testing: typically around 250 in-process tests for biologics compared to around 50 tests for traditional small-molecule medicines.[35]

Due to the nature of the manufacturing process of biologic drugs, copies of biologic drugs produced by unrelated manufacturers will not be bioequivalent to the reference product. Regulatory agencies needed to develop special regulations for these biosimilar drugs, as the minimum standard of bioequivalence used for traditional generic drugs could not be used to evaluate marketing approvals for this class of medicine. At the same time, the safety and efficacy of biosimilars are still a high

concern for regulators because small variations in the biologic product can have a significant impact on the safety and efficacy profile of the drug.

The next three subsections describe the biosimilar regulations developed specifically for the US FDA, EMA, and Japan PDMA.

3.4 Regulation of Biosimilars by the US FDA

The US FDA's regulatory pathway for biosimilar approvals are the result of amendments to the Public Health Service Act (PHS Act) introduced by the Patient Protection and Affordable Care Act, signed into law in 2010. The amendments as part of the Biologics Price Competition and Innovation Act (BPCI Act) create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (section 351(k) in PHS Act).[36] To date, no biosimilars have been approved for market under this abbreviated pathway; however, numerous biosimilars are in various stages of investigation prior to final submission of the 351(k) application for FDA's right-to-market decision.[37]

The 351(k) application includes information demonstrating that the applicant product is:

- Biosimilar to a reference product that is licensed for sales in the US;
- Utilizes the same mechanism of action for the proposed conditions of use, only to the extent known for the reference product;
- Conditions of use proposed in labeling have been approved for the reference product;
- Has the same route of administration, dosage form, and strength as the reference product.[36]

The main criteria for approval under the abbreviated pathway - ***biosimilarity*** - is defined to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product".[36] The sponsor must include information demonstrating biosimilarity including data from analytical studies, animal studies, and one or more clinical studies. The FDA can determine at its discretion whether certain studies are not necessary for demonstrating biosimilarity.

Market approval with the higher standard of comparability to the reference product - ***interchangeability*** - allows the biosimilar to be substituted for the reference product without the intervention of the prescribing healthcare provider. In order to meet the standard of interchangeability, the applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the product can be expected to produce the same clinical result as the reference product in any given patient. Furthermore, if the product is switched with the reference product, the risk in terms of safety or diminished efficacy is no greater than the risk of using the reference product without such switch.[36] The higher evidence requirements for a biosimilar to be approved as an interchangeable product underscore the greater uncertainty inherent in using biosimilars for the same line of treatment. However, the interchangeable label is necessary for biosimilars greater acceptance in the market vis-à-vis the brand-name reference biologic.

FDA's biosimilar regulation also specifies the exclusivity period for the first-to-be licensed reference biologic product (12 years) during which biosimilars referencing the product may not be approved for market. The reference biologic also has a initial 4-year exclusivity period during which biosimilars may not submit the 351(k)

application.[35] Similar to the FDA's first-to-market generic exclusivity period, there will be an exclusivity period for the first interchangeable biologic, during which subsequent biosimilars may not be determined to be interchangeable. The length of this exclusivity period may vary depending on the date of first marketing and patent litigation milestones.[37]

The following diagram shows the main features of FDA's biosimilar regulation under the BPCI Act's abbreviated licensing process:

Figure 3.1: Main Features of US FDA Biosimilars Regulation

Exclusivity for reference biologic		Exclusivity for first interchangeable biologic
0 First biologic licensed	**4 years** Biosimilar sponsor may submit 351(k) for FDA review	**12 years** **time: case by case** First biosimilar may be licensed
Licensing threshold	Biosimilarity	Interchangeability
Evidence requirement	data from analytical studies, animal studies, and one or more clinical studies	biosimilarity, plus evidence demonstrating same clinical results as reference biologic for any patient, and same risks of switching from reference to biosimilar as remaining on reference biologic

3.5 Regulation of Biosimilars by the EMA

The European agency has the longest history of biosimilar regulation, with the current overarching guidelines for biosimilar reviews being in effect since October 2005. As the early leader of biosimilar regulations, the EMA's guidelines are influential for other non-European countries' adoption of biosimilar market license regulations. The EMA's overarching guidelines set the basic principles for evaluating 'similar biological medicinal products' based on comparability studies with a licensed reference product, as opposed to bioavailability studies used for traditional generic drugs. The biosimilar

must have the same pharmaceutical form, strength, and route of administration as the reference product, with any differences justified by additional studies on a case-by-case basis.[38]

An important distinction between EMA's advice and the FDA is the EMA does not give advice on whether a biosimilar is interchangeable/substitutable with the reference product.[39] Individual member states must make the decision on interchangeability of the biosimilar because it touches on the regulations of professional practice among health care providers, which is the jurisdiction of the member states.

The EMA's guidelines recognize that that acceptance of a biosimilar product, as being a 'similar biological medicinal product,' will depend on technology of the analytical procedures, the manufacturing process, and clinical and regulatory experiences.[38] Each of these factors will evolve over time and vary across the spectrum of biologics. The EMA guidelines, therefore, specify product-class specific guidance which is made over time.

To date, the EMA has published product-class guidance for 9 classes of biologics. Overarching evidence requirements are also listed, while the specific requirements are published within the product-class guidance forms. Table 3.1 below shows classes of biologic drugs for which the EMA has published class specific guidelines:

Table 3.1: Biologic Product Classes Covered by EMA Guidelines for Biosimilars

Product Class	Effective Date	Topics Covered in Guidelines
Biosimilars containing recombinant follicle-stimulating hormone	September 2013	• Non-clinical studies (in vitro, in vivo, toxicological) • Clinical studies (pharmacokinetics, pharmacodynamics, clinical efficacy, clinical safety) • Extrapolation of indications • Pharmacovigilance plan
Biosimilars containing interferon beta	September 2013	
Biosimilars containing monoclonal antibodies	December 2012	
Biosimilars containing recombinant erythropoietins	September 2010	
Biosimilars containing low-molecular-weight heparins	October 2009 (effective revision date to be determined)	
Biosimilars containing recombinant interferon alpha	April 2009	
Biosimilars containing recombinant human insulin and insulin analogues	June 2006 (effective revision date to be determined)	
Biosimilars containing somatropin	June 2006	
Biosimilars containing recombinant granulocyte-colony stimulating factor	June 2006	

Documents can be downloaded at EMA's webpage for scientific guidelines on biosimilars.[40]

An example of different standards for evidence for different classes of biologics is the extrapolation of indications, which describes cases when studies on a biosimilar in use for one indication can be used to determine biosimilarity of the drug in use for a different indication. For example, in the Extrapolation of indications section in the guidelines for interferon beta, the EMA states that:

> *Extrapolation of clinical efficacy and safety in confirmed RRMS (relapsing-remitting multiple sclerosis) to the other indications of the reference medicinal product in MS is possible on the basis of the totality of the evidence provided from the comparability exercise.* (Ref# CHMP/BMWP/652000/20100, Pg 8)[40]

The EMA's guidance for interferon beta biosimilars does not require specific studies for proving biosimilarity with the reference product used in other indications of MS. On the other hand, in guidance for monoclonal antibodies (mAb) biosimilars, which have indications for wider array of diseases, EMA's guidance lists a number of cases where further studies are required to extrapolate to different indications, including challenges faced when the mAb is licensed both as an immunomodulator and as an anticancer antibody (Ref#EMA/CHMP/BMWP/403543/2010).[40] In such cases, the EMA may require separate studies demonstrating comparability for the different indications rather than an extrapolation of the data.

EMA's biosimilar review process allows submissions of applications at earliest 8 years after the reference biologic received its initial marketing authorisation through the centrally-licensed process (licensed by European Commission) or by any individual member state.[41] This period of 'data-exclusivity' is longer than the 4 year period specified by FDA regulation.

3.6 Regulation of Biosimilars by the Japan PDMA

Japan's Ministry of Health, Labour and Welfare issued guidelines for PMDA review of biosimilars in March 2009. Since this date, two biosimilar products have been approved in Japan: Somatropin BS s.c. and Epoetin alfa BS.[42] Although the two products were submitted to PDMA before 2009 in the same pathway as new biologics, they both experienced shorter review times as a result of the new biosimilar guidelines.

The PDMA guidelines refer to biosimilars as "follow-on" biologics, developed to be comparable in quality, safety, and efficacy to and existing biologic approved for sale in Japan. The PDMA approach to evaluating follow-on biologics is generally the same as the EMA, whereby the evidence that the applicant provides demonstrates

comparability with the reference product in terms of quality, safety and efficacy. Any differences in quality should be demonstrated with existing information to have no adverse impact on safety or efficacy.[43]

PDMA provides guidance on the following items making up the follow-on biologics review application:

- Manufacturing process and quality characterization of follow-on biologics (including drug formulation and stability testing);
- Evaluation studies of comparability of quality attributes;
- Specifications and test procedures;
- Non-clinical studies (including toxicity studies and pharmacological studies);
- Clinical studies (including pharmacokinetic and pharmacodynamic studies, comparison of clinical efficacy, and evaluation of clinical safety);
- Post-marketing surveillance.[43]

Similar to the unique requirements for different types of biologics set out in EMA's biologic class guidance, the PDMA will consider different types of evidence depending on the class of biologic being reviewed. The PDMA recommends manufacturers consult with the regulatory authority to determine the applicability of the guidelines on a product by product basis.[43]

Japan's regulatory authority prohibits automatic substitution and interchangeability of biosimilars.[44] In this regard, Japan's regulations for the adoption of biosimilars are more restrictive than the US and Europe, with the US FDA providing an opportunity for licensing with an 'interchangeable' label, and the European Commission handing this decision to individual member states.

In terms of timing for the follow-on biologic submission, the PDMA allows for submissions to occur typically 8 years after the date the original biologic was licensed.[45] This date begins the 'reexamination' period, when the follow-on biologic submission may include data from the original biologic submission.

3.7 Discussion

The regulation of biosimilars is still in its infancy: the US FDA, as the regulatory authority for the world's larget pharmaceutical market, has yet to make any rulings under its new biosimilar approval pathway; the EMA and Japan's PDMA, despite having a longer history with established biosimilar review processes, have only begun to review the largest classes of biologics which are starting to lose patent protection. Regulations of biosimilars will surely change as the agencies gain more experience reviewing this class of drugs.

The three agencies described in this section have established abbreviated review processes to allow biosimilars to come to market faster than if they were to be reviewed as completely new molecular entities. As a motivation for the creating the abbreviated review process, the FDA has stated that it aims to create regulations that help industry develop biosimilars to "enhance competition" and "lead to better patient access and lower cost to consumers."[46]

In general, these regulations have the same goal, to ensure that new biosimilar products are nearly the same as their referenced biologic product in terms of safety, efficacy, and quality. Generally, the same type of evidence will be required to demonstrate similarity (summarized in Table 3.2 below). Key differences between the agencies are in granting 'interchangeable/substitutable' labels and in the timing of the first biosimilar submission. The FDA's option for biosimilars to be licensed as

‘interchangeable,’ shorter time in which biosimlars have to wait to submit applications, and an exclusivity period for the first-to-market biosimilar will theoretically encourage wider biosimilar adoption in the market. It remains to be seen whether this will materialize in practice.

Table 3.2: Summary of Comparasion of Biosimilar Regulation for FDA, EMA, and PDMA

	FDA	EMA	PDMA
Goal	• ensure that new biosimilar products are nearly the same as their referenced biologic product in terms of safety, efficacy, and quality; • generally the referenced biologic must be licensed in the respective market		
Evidence considered	evaluation of manufacturing process, non-clinical & clinical studies, pharmacovigilance plan		
General approach	• consider 'totality' of evidence; • different requirements for different classes of biologics; • possible extrapolation of indications depending on class of biologic; • consultations with sponsors throughout the process		•
Interchangeability	Option for approved biosimilar with further evidence of interchangeability	Decision for individual member states	Prohibited
Earliest submission date	4 years after 1st biologic licensed to market	8 years after 1st biologic licensed to market	8 years after 1st biologic licensed to market
Other important differences	exclusivity period also available for first-to-market biosimilar	no special treatment for first-to-market biosimilar	no special treatment for first-to-market biosimilar

Chapter 4: Reimbursement Systems for Biosimilars. *Comparison of US, Europe, and Japan*

4.1 Introduction

The high cost of biologics (and likely high cost of biosimilars) leads to large payer organizations funding the majority of the drug costs for individual patients. The US, EU countries and Japan have different systems of pharmaceutical reimbursements that will be discussed in this section to explain different biosimilar pathways to market across developed economies.

The US healthcare system is highly fragmented with numerous sources of private and public financing to insure the costs of medical services. Out-of-pocket spending on healthcare is significant burden for many patients with out-of-pocket expenses of nearly $1,000 US per capita.[47] Major reforms to the US healthcare system were introduced in the 2010 Patient Protection and Affordable Care Act (ACA), with steps to expand healthcare coverage through the "individual mandate" and Medicaid expansion taking effect in 2014.[48]

Under the Medicare program (social insurance for US seniors 65 and older and people with disabilities), Medicare Part B provides a major source of funding for biologics administered in a clinical setting. Medicare Part B provides medical coverage for services administered in a non-acute care clinical setting, including treatments which require infusions in a clinic. Medicare Part B uses private contractors to process claims, using public funds to reimburse the treatment cost (pharmaceutical products) and services on behalf of the government.

However, within publicly financed care, the largest program for pharmaceutical funding is Medicare Part D which provides subsidies for private drug coverage to

beneficiaries eligible for Medicare. Medicare Part D is administered by private insurance organizations, primarily drug benefit management organizations which act as third part administrator of employer, patient, or public funded plans. In 2012, Medicare Part D subsidized drugs for 31.3 million beneficiaries at an expense to the government of $65.5 billion US.[49]

Although the EMA and European Commission are responsible for reviewing and granting licensing of drugs for sale in the EU, individual member states have jurisdiction over the healthcare systems provided to citizens of the state. Compared to the US, EU countries have relatively large public systems; however there are differences in the types of payers (public or private insurance) and providers of healthcare across member states.[47]

The pharmaceutical reimbursement systems of the three most populous EU member states, Germany, France, and the United Kingdom will be discussed in this section. Each country has a national review body that makes recommendations on whether a treatment should be covered by public insurance.[4] Germany's reimbursement of prescription drugs including biologics and biosimilars is primarily through compulsory insurance provided by a number of public and private healthcare funds. France, similarly, reimburses drug costs through compulsory health insurance administered by non-competing, occupation-based funds.[47] However, in the UK, reimbursement of prescription drugs is primarily through a single government payer (National Health Services); although in each country, there is a small market for supplementary private insurance.[50] Impacting reimbursements of biologics (and biosimilars in the future) are different pricing policies these countries take at the national level either through regulation or reimbursement policies.

Lastly, Japan, like most EU member states, has a universal healthcare system in which health insurance is compulsory for all Japanese citizens. Prescription drugs are reimbursed through the insurance system which is made up of roughly 3,500 private and public insurers. Japan's Central Social Insurance Medical Council makes coverage decisions and sets the price list for all pharmaceuticals which must be covered by all insurance plans in the country.[47] Therefore, despite having many different insurance organizations operating within the country, Japan's major healthcare reimbursement policies are set at a national level and apply universally for all insurance plans.

This section will introduce in further detail each country's drug reimbursement system and specific policies toward reimbursement of biologics and biosimilars. As biosimilars are emergent issue, many of the policies towards this class are under development and subject to change with more experience with this class.

4.2 US Reimbursement of Biosimilars

4.2.1 Medicare Part B

Medicare Part B was established as part of the Medicare plan's coverage for medically necessary services for patients outside of the hospital, acute care setting. Medicare Part B covers lab tests, procedures, and doctor visits deemed medically necessary or preventative, as well as prescription drugs and vaccines which patients are unable to administer themselves.[51] In 2012, Medicare Part B's fee for service reimbursements benefited 32.8 individuals, costing $166.6 billion US (approximately 30% of the total Medicare budget).[49]

Some of the top spending items in Medicare Part B are biologics which require infusions at clinics. According to Government Accounting Office (GAO), the 8 highest expenditure pharmaceuticals in Medicare Part B in 2010 were biologics. These 8

products accounted for $8.3 billion US in spending and included monoclonal antibody products such as Rituxan, Lucentis, Avastin, and Remicade.[52]

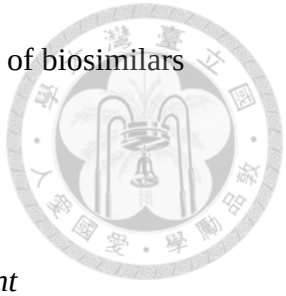
4.2.2 Medicare Part B Biosimilars Policy

Biosimilars will likely be introduced in reference to biologics that are existing benefits under Part B, including the high expenditure biologic products previously listed. The approval of biosimilars for benefits where the reference biologic is already a Medicare Part B benefit should not require extensive review by Part B plan administrators.[53]

The main mechanism Medicare Part B uses with respect to reimbursement of prescription drugs is setting a maximum price with which in reimburses providers of the prescription drug. For brand name drugs and biologics, the maximum reimbursement price is 106% of the lower of the Average Sales Price (ASP) and the Wholesale Acquisition Cost based on calculating ASP for all drugs belonging to the same billing code.[54]

The definition of biologic and biosimilar products included in the calculation is an important factor to determining the eventual weighted average price and prescribing practices that are incentivised by the price change. If lower cost biosimilars are included in the same billing code, thus decreasing the average price, prescribing would be incentivised toward lower cost biosimilars because they would offer higher margin for the prescriber based on the difference between the wholesale cost and reimbursement price. However, according to legal experts, the exact criteria for including biosimilars in the same billing code and ASP calculations has not yet been determined by regulation.[54] One issue limiting further clarification of the Medicare Part B pricing regulation is the

FDA has not given specific rulings on determining interchangeability of biosimilars with the reference biologic (discussed in Chapter 3 on regulations).



4.2.3 Medicare Part D and the Role of Pharmacy Benefit Management

Medicare Part D subsidizes private drug insurance for patients eligible for Medicare. The government role in this subsidized insurance system is to set regulation under which partnering insurance companies operate. For example, reimbursement policies were introduced in the 2010 Affordable Care Act with the aim of reducing the Medicare Part D coverage gap between initial insurance coverage and catastrophic drug costs coverage (known as the "donut hole"). Beginning in 2013, drug companies must provide discounts to patients within the coverage gap, with the discounts also counting towards the accumulated costs needed to qualify for catastrophic coverage.[55]

Medicare Part D is a large funder of biologics that may be administered by patients at home (in contrast to infusion products funded by Medicare Part B). The biologics, Humira and Enbrel which are self-injectable treatments for Rheumatoid Arthritis, are covered by Medicare Part D. These biologics were expected to take significant market share from the Part B covered biologic, Remicade, when Medicare Part D began coverage in 2006. However, research found mixed results, with Remicade maintaining its share of use when coverage under Part B was more generous. More low-income individuals were likely to initiate biologic treatment on Humira and Enbrel because they received more assistance from Medicare to cover the otherwise high out-of-pocket costs for these treatments.[56,57]

Pharmacy Benefit Management (PBM) organizations have an important role in administering drug insurance for much of the US market, including for patients under Medicare Part D. PBM began by providing pharmacy claims processing services to

employee benefit health plans in the 1990s. PBM have since expanded into managing networks of pharmacies that accept negotiated discounts on drug prices and dispensing fees for plan members. An estimated 71% of the US population are on private insurance with PBM.[58]

Medicare Part D was not found to have any specific policies or regulations directed to the reimbursement of biosimilars. However, PBM have an important role in determining the reimbursement policies for Medicare Part D patients, and PBM have a range of policies directed toward specific drugs or classes of drugs including biologics and biosimilars. The following policy tools PBM use can be applied to many classes of drugs:

- Formulary development and management;
- Generic substitution;
- Therapeutic interchange;
- Rebates and discounts.[58]

PBM manage a formulary which includes all treatments it determines to be "worth" covering as insurance benefits for patients. Benefit managers may use clinical and pharmacoeconomic evaluations to determine which treatments should be coverage and under which type clinical criteria (for pre-authorized coverage). In this role, PBM act similar to national review agencies in countries with forms of public health insurance (see sections on EU countries and Japan).

Generic substitution and therapeutic interchange policies can shift utilization to lower cost pharmaceuticals deemed bio- or therapeutic- equivalence. PBM's main tool to shift behavior is setting different co-pay rates, with lower rates for treatment that save the drug plan more money. Sometimes the costs of these treatments are kept

confidential with hidden discounts and rebates so that manufacturers can maintain higher published prices.

PBM have been aggressive in lowering costs with generic substitution.[58] With biosimilars entering the market, they will make use of similar substitution policies to shift utilization from higher cost originator biologics to biosimilars.[59]

4.3 Europe Reimbursement of Biosimilars. *Comparison of Germany, France, and the UK*

4.3.1 Introduction

Germany, France, and the UK are the three most populous countries in the EU.[47] These countries differ from the US in that they have high, direct government support for pharmaceutical care for nearly all of the population. Germany provides most of its prescription drug reimbursements through non-governmental, not-for-profit health insurance funds, or substitutive private insurance. France, similarly, provides drug reimbursements through multiple occupation-based funds, while most reimbursements in the UK go through a single, public payer system, the National Health Services (NHS).[47]

Biologics make up a significant share of public funding compared to other drug classes because of the high-cost of individual treatment on biologics and features of insurance that limit total private expenses for health care. These large markets are also influential for guiding policies in other countries with national-level policies for pharmaceutical reimbursements. For example, the UK's National Institute for Health and Clinical Excellence (NICE) which makes recommendations to NHS on whether it should cover new medical technologies has far reaching impacts beyond the UK.[5]

The following table summarizes each country's biologic market size, representing the total potential size for biosimilar penetration and health care cost savings. Also included in the summary table are each country's national review body for new pharmaceuticals, such as UK's NICE, and other key points of comparison with respect to the reimbursement of biosimilars.

Table 4.1: Comparason of Reimbursment Policies for Germany, France, and the UK

	Germany	France	UK
Market value of biologics (% of total medicines spend)	7.0 billion € (24%)	6.2 billion € (21%)	2.4 billion € (17.1%)
National Health Technology Assessment Agency	Institute for Quality and Efficiency in Healthcare (IQWiG)	National Authority for Health (HAS)	National Institute for Health and Clinical Excellence (NICE)
Type of recommendations	Reimbursement decisions, pricing, prescribing information	Reimbursement decisions, pricing, prescribing information	Reimbursement decisions, clinical practice guidelines
Pricing policies	Mandatory discount for social insurance, negotiated rebates for providers, reference pricing	Mandatory discounts for insurance	Negotiated rebates, competitive tender by purchasers
Substitution of biosimilars by pharmacy	Prohibited	Permitted	Prohibited

Sources: Cohen et. al., 2013;[4] Rovira et. al., 2011;[7] Declerck and Simoens, 2012.[8]

4.3.2 National Health Technology Assessment Agencies

Germany, France, and the UK have national agencies responsible for making recommendations on whether new treatments should be covered by public funded healthcare plans. These Health Technology Assessment (HTA) agencies make recommendations that are based on evidence reviews that take into account clinical benefits of new treatments in comparison to existing treatments (comparative

effectiveness) as well as economic considerations such as cost-effectiveness and budget impact. In this respect, HTA agencies differ from the EU level EMA reviews which are focused solely on safety and clinical efficacy. Reviews must take place at a national level because of each country's unique healthcare system and financial situation. Research has shown that the presence of these agencies improves affordability for payers and increases access for patients to the new health technologies that receive positive recommendations from the review agency.[4]

HTA are expected to use different types of evidence to review biosimilars depending on how they are shown to be equivalent to the reference biologic in clinical trials. Biosimilars that are approved for sale in the EU by showing equal safety and efficacy to the reference product in head-to-head trials may go through a shortened review process at the national level. In these cases, the biosimilar may be evaluated on the basis of cost-minimization, where the recommended treatment provides equal benefit at the lowest cost. When the biosimilar shows differences in clinical outcomes to the reference biologic, the national review agency may still require a full evaluation in which the lower cost of the biosimilar will be weighed against the clinical and economic impacts from the difference in efficacy or safety.[8]

Besides recommendations for whether there should be public funding of new treatments, HTA are also responsible for developing guidelines on how best to prescribe new treatments. These guidelines are designed to ensure that prescribing takes into account the cost-effectiveness of the new treatment for different severities of illness. NICE clinical practice guidelines detail the clinical criteria that must be present before a patient can receive coverage NHS coverage for the new treatment. Clinical practice guidelines are especially important for prescribing of biologics because of their high cost and the range of treatment options depending on severity of illness and response to

alternative treatments (e.g. NHS commissioning guide for biologics[60] and NICE guidance on biologic drugs for treatment of rheumatoid arthritis,[61] see Appendix 1). Biosimilars will play a larger role in the development of NICE clinical guidance because they are lower cost treatment options that may be prescribed earlier than higher cost originator biologics.

4.3.3 National and Sub-National Insurance Pricing Policies

In most EU countries including the largest three, national insurance agencies are active in seeking discounts on the price pharmaceuticals. This was most evident during 2010 to 2012 EU debt crisis and period fiscal deleveraging.[62] Germany and France both mandate manufacturer discounts on pharmaceuticals covered on social insurance plans. The UK does not mandate discounts at the national level; however, if NICE issues a negative recommendation because of cost, drug sponsors may agree to provide rebates to the NHS in exchange for giving patients access to the drug.[4]

Germany's reference price system will play an important role in influencing future prices and adoption of biosimilars in the German market. Reference pricing in Germany occurs when the IQWiG finds a new drug does not offer additional benefit over existing treatment, it will be clustered and priced with similar drugs treating the same medical condition (therapeutic class).[4] Insurers will reimburse costs up to an average price for the therapeutic class, or possibly up to the lowest price drug in the class. Reference pricing may lead to price competition as lower priced drugs gain market share because prescribers will want to avoid drugs that may unnecessarily entail patients paying out-of-pocket costs. Germany has already included early biosimilar products, erythropoietins and human growth hormones in its reference price system.[8] Reference-pricing will allow biosimilars to be included in a competitive pricing

program even as small differences are found between biosimilar products treating the same medical condition.

Lastly, negotiations between manufacturers and sub-national level payers in Germany and the UK will influence the pricing and adoption of biosimilars in the future. In Germany, a 2007 law allows manufacturers to negotiate rebates with individual health insurance funds. These negotiations can secure savings for the insurance funds in exchange for preferential coverage of certain rebated products. It has been suggested that these negotiations have led to Germany having relatively high market shares for the earliest types of biosimilar products.[7] In the UK, hospitals may engage in competitive tendering of biosimilars as a means to secure the lower costs for biosimilars which the hospital agrees to use as its primary treatment, given availability of other treatment options.[8] As mentioned in policy tools taken by pharmacy benefit managers in the US, these negotiated or tendered prices are kept confidential so that manufacturers can maintain higher published prices.

4.3.4 Biosimilar Substitutions in EU Member States

EU level regulations do not dictate whether biosimilars are permitted to be substitutable/interchangeable with the reference biologic. Individual member states must make the decision on biosimilar substitution at the point of dispensing at the pharmacy because it touches on the regulations of professional practice among health care providers, which is the jurisdiction of the member states. An important note to this section is that of the three countries discussed, only France permits biosimilar substitutions at the pharmacy.[7,63] France's law on biosimilar substitution takes effect in 2014 and only allows for pharmacy substitutions when patients are initiating treatment on a biologic.[64] France's law may set a precedent for other EU countries to follow if it

proves successful in leading to wider biosimilar adoption without the perceived risks associated with differences in bioequivalence between biosimilars.

4.4 Japan's Reimbursement of Biosimilars

4.4.1 Health Insurance in Japan

Japan's $116 billion US pharmaceutical market is influenced by regulations set at the national level that are intended to define the type of benefits and prices accessible to all citizens under the country's universal health care system.[9] The Central Social Insurance Medical Council (Chuikyo) is the national body responsible for these making coverage decisions and setting prices for all pharmaceutical products for sale in the country. Roughly 3,500 insurance organizations covering nearly the entire population must follow the central council's decision making and are not permitted to compete with one another over new enrollees to their plans. Insurers must offer the same benefits at the same prices; however plans vary greatly in the premiums charged and employer contribution rates.[65]

Nearly every pharmaceutical receiving market authorization in Japan is approved for health insurance reimbursement by the Ministry of Health, Labour and Welfare (MHLW). Pharmaceuticals do not require the additional clinical evidence that national review agencies in most other OECD countries require before being considered a benefit on national insurance schemes.[6]

Another unique feature of Japan's regulation of pharmaceuticals is the price setting process which occurs at the same time as market authorization. Patented pharmaceuticals are priced either according to prices of similar comparator drugs on the market, or using a cost-accounting method when there are no similar drugs on the market. A premium is added to the base price when the new drug is shown to offer

clinical benefits over existing treatment.[45,66] Generic drugs also follow a similar process of price setting; however they are priced at a set discount to the brand price. Prices are adjusted once every two years to capture savings from discounts to the official price often received by hospital or pharmacy purchasers of medications.[66]

4.4.2 Issues Facing Reimbursements of Biosimilars in Japan

Japan has a large, growing market for biologics – spending on biologics for rheumatoid arthritis reached $1 billion US in 2009 following growth of over 40% from 2008.[67] A challenge for Japan is that it currently does not many of the policy tools found in European countries to encourage more cost-effective use of biologics and obtain expenditure reductions from lower prices. Japan is still developing a national agency to take into account economic evaluations such as cost-effectiveness and budget impact. The government has targeted the formation of a HTA agency in 2014 -2016; however, there is pressure from industry groups to prevent such an agency from setting prices and restricting access to new medications, drawing on Germany and UK as negative examples.[68]

Whether the HTA agency developed for Japan will have the mandate to makes recommendations related to pricing and restrict access on the basis of unfavorable cost-effectiveness will be an important factor in guiding the future market for biosimilars. Biosimilar adoption will be helped by policies that promote prescribing of lower cost treatment options before higher cost biologics are chosen. Japan's current clinical guidelines for rheumatoid arthritis and psoriasis were not found to take into account the cost of treatment, which contrasts guidelines developed by NICE for UK prescribers.[66,69] It remains to be seen whether Japan's HTA agency will also develop clinical guidelines incorporating the cost-effectiveness of different treatment guidelines.

Japan's price regulations allows for a premium for biosimilars of up to 10% of the base price depending on data from clinical trials[45] This premium is intended to reward biosimilars that meet certain standards of safety and efficacy. Critics have noted that the criteria for determining this premium are subjective and may lack scientific basis.[66] The impact on biosimilar adoption from Japan's pricing regulations is also unclear. The premium may result in wider adoption of biosimilars if it makes biosimilars more profitable to market in Japan or gives prescribers an additional profit incentive to prescribe the biosimilar. However, the impact will likely be limited if insurance plans are restricted from making preferential coverage criteria that could be used to reduce insurance plans' expenditures. Furthermore, the national healthcare system which limits competition between insurance plans and defines benefits and prices for all plans, further limits the measures insurers may take to use biosimilar reimbursement policies to reduce plan expenditures.

4.5 Discussion

The US, the EU countries analyzed in this paper (Germany, France, UK), and Japan have unique health care systems that lead to different health insurance policies that will affect future reimbursements of biosimilars. Table 4.2 summarises the key points of comparison between the drug reimbursement systems in the five countries discussed in this paper.

The US system is mainly privately operated with government playing a role in subsidizing drug insurance for various populations, including drug insurance for the Medicare eligible population under Medicare Part B and D. Pharmacy Benefit Management organizations will play an important role in developing reimbursement policies for biosimilars, and will use various strategies such as formulary management,

therapeutic substitution, and price negotiations to lead to more biosimilar adoption, if biosimilar use the plan administrator's economic interest. In this respect, the US is expected to have wide variation in the reimbursement policies of biosimilars as policies will vary on the size of the market covered by insurance and the level of competition between plan administrators.

Germany, France, the UK, and Japan have national-level policies influencing the type of pharmaceuticals covered as benefits and the reimbursement prices for health insurance plans available to the entire population of the country. Compared to Japan, the European countries appear to have policy mechanisms in that are better suited to take advantage of the entry of cost-saving biosimilars to the market. These countries have national HTA agencies which make recommendations for determining whether new pharmaceuticals should be covered under universal healthcare, taking into account the cost implications of the new treatments. Japan is still developing such an agency, with its implementation scheduled between 2014 and 2016.

German healthcare funds and UK medical providers appear to use market forces in the competition between different drugs in the same therapeutic class to obtain cost-savings. These are obtained through negotiated price discounts, reference pricing, or in the case of UK hospitals, through tendering. These pricing tools should provide an opportunity for biosimilars to gain market share relative to the reference biologic, or other biologics treating the same medical condition. Japan's price regulations, set at the national level through a bureaucratic process, do not appear take advantage of competition between different drug manufacturers. It is uncertain whether Japan's reimbursement environment is as conducive to wide adoption of biosimilars. One advantage Japan has over European markets is that market approval and reimbursement

policy are set at the same time, by the same government ministry (MHLW). This feature of Japan's healthcare system could lead to faster market access for biosimilars.

Table 4.2: Summary of Comparasion of Reimbursement Policies Affecting Biosimilars for US, Germany, France, UK, and Japan

	US	EU (Germany, France, UK)	Japan
National healthcare system[i]	Universal mandate (ACA, starting 2014), privately operated with government subsidies	All: universal coverage; Germany and France: public and private insurance funds; UK: national health insurance	Universal coverage, public and private insurance funds
Main agencies setting national reimbursement policies	Centers for Medicare & Medicaid Services (only applies to Medicare and Medicaid; limited guidance on actual reimbursement policies)	Germany: Institute for Quality and Efficiency in Healthcare (IQWiG); France: National Authority for Health (HAS); UK: National Institute for Health and Clinical Excellence (NICE)	The Central Social Insurance Medical Council (Chuikyo); National Health Technology Assessment agency still in development
Main reimbursers of pharmaceuticals	Private health insurance companies, primarily operated by Pharmacy Benefit Management (PBM)	Germany and France: public and private insurance funds; UK: national health insurance	Public and private insurance funds
Use of clinical criteria	Varies by insurance plan; set by plan administrators	Germany and France: varies by fund, guided by national recommendations; UK: NICE develops guidelines for NHS coverage	Set by clinicians, does not incorporate information on cost of treatment
Pricing policies	Medicare Part B: maximum reimbursement prices; Medicare Part D: driven by market prices, with negotiated discounts varying by insurers	Germany and France: mandatory discounts for insured benefits; Germany: reference pricing and negotiated prices for insurance funds; UK: market prices with negotiated and tendered prices for purchasing providers	National regulated prices with allowance for premiums and periodic price cuts
Issues for future consideration	Defining Medicare Part B billing codes for biosimilars - whether same code groups are inclusive of a wider range of biosimilar products, or are restrictive	Biosimilar substitution regulations: France started to permit pharmacy substitutions in 2014; Germany and UK still prohibit substitutions	Development of national HTA agency - whether the new agency will influence reimbursement policies to incorporate economic considerations

[i]Universal mandate under ACA requires nearly the entire US population to acquire health insurance with a tax penalty for non-compliance. Insurance benefits will vary by plan. Universal coverage in other countries provides nearly identical health insurance benefits for the entire population.

Chapter 5: Corporate Strategy - Incumbent Response to Future Biosimilar Competition

5.1 Introduction

This section analyzes the corporate strategy adopted by incumbent biologic manufacturers faced with patent expiration of biologic products and potential biosimilar competition. Six high worldwide sales volume biologics – Avastin, Enbrel, Humira, Lucentis, Remicade, and Rituxan – originally introduced in Chapter 2 will be used as case examples to evaluate corporate actions in response to biosimilar competition. Similar to the comparative analysis of regulations and reimbursement policies in the previous two chapters, the analysis of corporate strategies in this section is descriptive and qualitative in nature. Other studies have empirically tested relationships between brand name defense strategies against generic competition in traditional, small-molecule pharmaceuticals[17] and in strategic alliances between large pharmaceutical companies and smaller biotech companies in the early development of biologics.[18] Due to the small, selective sample of case subjects (six high sales volume biologics), a descriptive analysis would be sufficient to provide insight on the development of strategies around biosimilar entry.

The thesis posits that incumbents' strategic directions are influenced by expectations of future biosimilar competition, which in turn is a function of the regulatory and policy environment created to control the entry and major financing of pharmaceuticals in the market. Another factor influencing the incumbent company's strategic direction, specifically in terms of actions taken on the biologic product facing competition, is the importance of the individual product to the company's overall

business. This factor is introduced in this section as the sales of the individual biologic product as a percent of the company's overall sales.

This section begins by formulating a hypothesis for explaining incumbent biologic manufacturers' strategies. Next, the sources for relevant data on the case biologics and corporate strategies are described, along with the data collection process. Lastly, the findings are discussed in terms of conforming to, or contradicting the original hypothesis.

5.2 Hypothesis Development

5.2.1 Identification of Factors Influencing Strategy

A relationship between market factors driven by the regulatory and policy environment and corporate strategy is proposed in this section. Corporate strategy can be viewed in part as a response to competitive forces in the market.[19] These forces may be limited by entry barriers created by governments such as patents and market licensing regulations (of competitor products). Indeed, the major catalyst for the analysis of biosimilars is the upcoming end of patent protection for major branded biologics. Incumbent biologic manufacturers' development of strategies depends on the time remaining with patent protection. Companies with longer effective patent life may better able to invest in longer term strategies to cope with the eventual loss of patent protection. A shorter remaining patent life may force the incumbent to develop more short-term defensive strategies.

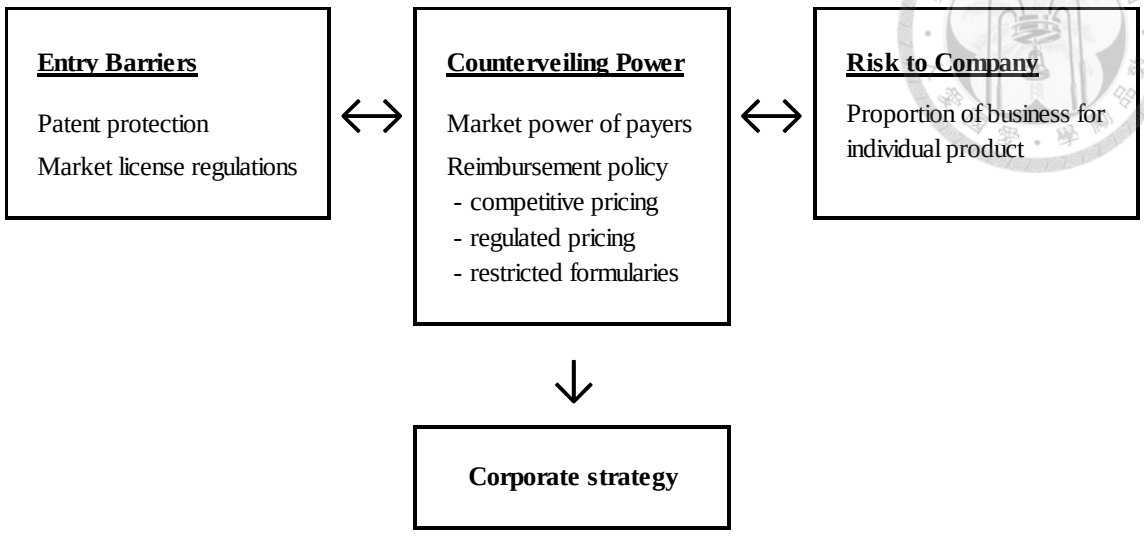
Even with the loss of patent protection, regulatory hurdles biosimilars must overcome may limit the degree of competition faced by the incumbent biologic manufacturer. The greater the regulatory hurdles for receiving market licensing approval, the more difficult it becomes for competitors to gain entry into the market,

and as a result, the less corporate action is needed by the incumbent to defend its position. Conversely, lower regulatory hurdles allow greater access for competitors, thus driving greater actions by the incumbent.

Reimbursement policies discussed in the previous chapter also shape the competiveness of the market in which biologics and biosimilars are to be sold. Certain policies may encourage greater competition in the market, such as tiered formularies, price discounts and tendering. In a more competitive market, the incumbent will be challenged by both loss of market share to competitors and lower selling prices. Based on the theory of countervailing power, the effectiveness of reimbursement policy in obtaining pricing concessions from suppliers depends on the size and market power of payers, as well as the degree of competition between suppliers.[20]

The importance of the individual biologic's sales to the company's overall business is also a determinant of the company strategy to make up for the potential loss in sales. The risk of losing a significant share of overall business due to biosimilar competition in one product class may push a company to take more significant action to find new sources of sales than a company with a lower share of business at risk.
The following diagram depicts the different factors influencing corporate strategy in response to biosimilar competition.

Figure 5.1: Factors Influencing Strategic Responses to Biosimilar Competition



5.2.2 Identification of Corporate Strategies

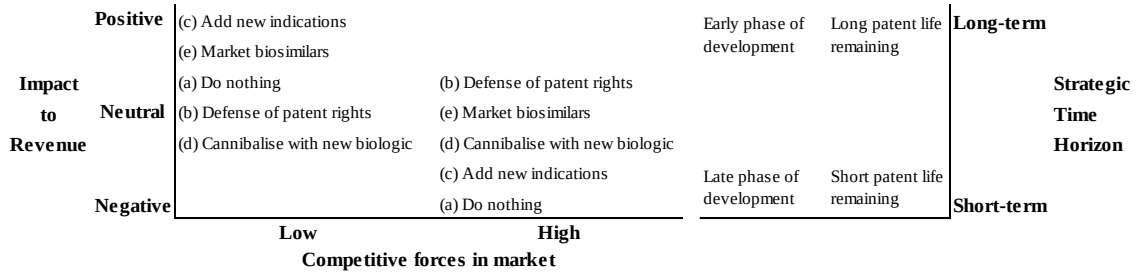
Corporate strategies in response to future biosimilar competition may range from minimal action such as maintaining the status quo to more significant mergers and acquisition types of actions. This section introduces individual biologic products as case subjects; as such, the focus of this analysis of corporate strategies will be on actions that can be directly attributed to biosimilar competition faced by the individual product. Strategies identified in this section can be viewed under two dimensions: (i) incremental impact to company revenue and (ii) short or long term time horizon of strategic planning. A strategy that has minimal incremental impact to company revenue is considered one that preserves the status quo revenue of the biologic. An example is launching patent infringement suits to prevent competitors from challenging the validity of the incumbent's patent.[70] Another example is launching a new patented product that competes in the same market as the original product. This action is considered product 'cannibalism' if the producer redirects sales from the original to the new product.[71]

The time dimension of corporate strategy can be viewed as event-based where time is measured relative to a series of important events that may pose a threat or

opportunity for the company.[21] For corporate strategy of pharmaceutical companies, the short- or long-term time horizon of a strategy can be measured by the time required to prepare new pharmaceuticals for market and the temporary lifetime of patents. To expand market share, or capture a segment that will be protected from competition, companies may apply for new indications on their existing product. New trials are required which may be in different stages of completion. The same holds true for launching a new product intended to replace the existing product. Originator biologic companies may also adopt the strategy of marketing biosimilars.[72] The time dimension of this strategy depends on the patent life of the biologic the company is targeting.

The figure below plots the corporate strategies identified for this study. A deciding factor on the impact to company revenue of each strategy is the degree of competition faced by the incumbent. The time horizon of the strategy depends on the patent expiration date and stage of application for new indications or new products. These determinations are then used to formulate the hypotheses in this section.

Figure 5.2: Dimensions of Corporate Strategies in Response to Biosimilar Competition



The five corporate strategies identified in this section are listed below:

(a) Do nothing;

(b) Defense of patent rights;

(c) Add new indications;

(d) Cannibalise with new biologic;

(e) Market biosimilars.

5.2.3 Assumptions about Corporate Strategies

The impacts to company revenue from each strategy are assumed based on the logic of the relative impact compared to other strategies. In a market without biosimilar competition, adding new indications (c) and marketing biosimilars for other markets (e) will lead to revenue growth for the company. The alternative strategies - do nothing (a), defense of patent rights (b), and launching a new biologic to cannibalise the existing biologic (d) - do not contribute positively to the company's revenue.

In a market with biosimilar competition, successfully defending patent rights (b) will prevent competition and have a neutral impact on company revenue. The impact of marketing other biosimilars (e) may make up for lost revenue from biosimilar competition. Lastly, cannibalising the existing biologic (d), adding new indications (c), and doing nothing (a) are ordered by the revenue that can be protected when faced with biosimilar competition.

5.2.4 Hypotheses

The following two hypotheses are formulated based on differences in the competitiveness of markets in which biologics are sold, given the different patent lives of biologics and the importance of the biologic sales to companies' overall business.

H1: Biologics sold in more competitive markets, with regulations and reimbursement policies more conducive for biosimilar competition, will cause companies to respond with strategies directed at protecting revenue.

H2: Biologics with shorter remaining time with patent life will cause companies to respond with short term strategies.

This case study does not provide statistical power to empirically test these hypotheses; however, evidence to the contrary indicates that the hypothesis may not accurately explain corporate strategy, or that the true underlying factors are not accurately depicted in the study. Despite the descriptive, qualitative approach, this examination still yields important information for understanding corporate strategies of the biologic incumbents.

5.3 Data Collection Process

5.3.1 Sources of Data

The primary sources for data on the case biologics are the information accumulated from Chapters 3 and 4 of this thesis and the annual reports released by the pharmaceutical companies marketing the case biologics in the US, EU, and Japan markets.[14,15,73,74,75,76,77,78,79,80,81]

5.3.2 Competitive Forces in Markets

The comparative analysis of regulations and reimbursement policies yield important results to determine the type of market in which biologics are sold and the constraints or incentives to biosimilar competition in those markets. From Chapters 3

and 4, key features of the US, EU, and Japan markets to determine the competitiveness of the market for biologics and biosimilars are summarized in the table below. Based on the comparison of these features, the relative degree of potential biosimilar competition between the three markets is then determined.

Table 5.1: Assessment of Relative Potential for Biosimilar Competition in the US, EU, and Japan

	US	EU	Japan
Biosimilar market licensing regulations	Earlier allowable submission date for biosimilars. Exclusivity period for first biosimilar.	No additional regulatory incentive vs. US, Japan	No additional regulatory incentive vs. US, EU
	US has competitive advantage for biosimilars		
Interchangeability labeling	Option for approved biosimilar with further evidence of interchangeability	France is only major EU with option for pharmacies	Prohibited
	US has competitive advantage for biosimilars		
Major payers	Private insurance. Government subsidy for Medicare	Public and private insurance funds. UK with National Health Insurance	Public and private insurance funds
	No clear advantage for biosimilars		
Pricing / Reimbursement of biosimilars	Market based pricing, with private insurers implementing own reimbursment policies	Government regulated- using competitive forces, market power to extract discounts	Government regulated pricing
	EU has competitive advantage for biosimilars (pricing, reimbursement environment more favorable for biosimilars). Japan has lowest competitive advantage for biosimilars		
Relative degree of potential biosimilar competition	Highest	Medium	Lowest

5.3.3 Patent Protection of Biologics

The primary source of information on the patent life of biologics is the expiration date provided in the US listed companies' annual report (10-K report).

Pharmaceuticals have multiple patents; it is a complicated process to determine the applicable patent actually providing market exclusivity for the product, and whether the expiration date is a reliable measure for when market exclusivity will end.[70,82] For biologics marketed by non-US listed companies, two industry analysis reports identified the relevant patent expiration dates.[83,84]

5.3.4 Risk to Company's Overall Business

The risk of the individual biologic product to the company's overall business is measured as the sales of the biologic as a percent of the company's overall sales. Sales for every case biologic are provided in company annual reports. Sales during the 2013 reporting year are used in this analysis.

5.3.5 Corporate Strategies

The sources for information on corporate strategies are the biologic companies' annual reports for the 2013 reporting year. The focus of this analysis of corporate strategies is on actions that can be directly attributed to biosimilar competition faced by the individual product.

Disclosures of any actions related to defense of patent rights, such as launching patent infringement suits or extending patent rights, and applications for new indications for the case biologic were identified.

For corporate strategy relating to the development of new biologics to cannibalise sales of the existing biologic or plans to market biosimilars, only disclosures of new biologics (or re-formulations of existing biologics) and biosimilar development for indications shared by the case biologic were identified.

The trial phases for development of new indications or new biologics were also identified to determine the time dimension of the strategy (short- verse long-term time horizon). New indications approved by the relevant regulatory agency during the reporting year were also identified; as well as any new biologics already on the market with labeling allowing it to compete with the original biologic.

5.4 Descriptive Analysis

5.4.1 Description of Data

Table 5.2 summarizes the data collected on the six case biologics. Included are the company with marketing rights in the US, EU, and Japan, the product sales as a percent of total company sales, year of patent expiration, and the major company actions in response to potential biosimilar competition. Appendix 2 contains the details about the company actions such as the specific indications and names of new biologics in development. Note that one of the strategies previously identified – do not take any action – was not taken by any company in this study. Every company marketing the case biologics have adopted some explicit action that relates to future patent expiration and potential biosimilar competition.

Table 5.2: Summary of Case Biologics and Company Actions in Response to Biosimilar Competition

Brand Name (molecule name)	Company	Percent of Company Sales	Market	Patent Expiration Year	Summary of Company Actions
Avastin (bevacizumab)	Roche	13.4%	US	2019	New indications in Phase III; New biologic in Phase I
			EU	2018	New indications in Phase III; New biologic in Phase I
	Chugai	17.8%	Japan	2020	New indications approved and in Phase III
Enbrel (etanercept)	Amgen	24.4%	US	2019	Defense of patent; Plans to launch biosimilars
	Pfizer	7.3%	EU	2015	New biologic in Phase III
			Japan	2015	New biologic approved
Humira (adalimumab)	AbbVie	56.7%	US	2016	Defense of patent; New indications in Phase III; New biologic in Phase II
			EU	2018	Defense of patent; New indications in Phase III; New biologic in Phase II
	Eisai	5.1%	Japan	2018	New indications approved
Lucentis (ranibizumab)	Roche	3.6%	US	2019	New biologic in Phase I
	Novartis	4.1%	EU	2018	New indications in Phase III; New biologic in Phase II; Plans to launch biosimilars
			Japan	2018	New indications in Phase III; New biologic in Phase II; Plans to launch biosimilars
Remicade (infliximab)	Johnson & Johnson	9.4%	US	2018	Defense of patent; New biologic approved
	Merck	5.2%	EU	2015	New biologic approved and in Phase II & III
	Mitsubishi Tanabe	18.5%	Japan	2015	New indications in Phase III; New biologics approved and in Phase I
Rituxan / MabThera in EU (rituximab)	Biogen Idec	16.2%	US	2015	Defense of patent; New biologic approved; Plans to launch biosimilars
	Roche	14.9%	EU	2013	Defense of patent; New indications approved; New biologic approved and in Phase III
	Chugai	6.2%	Japan	2013	New biologic approved and in Phase I

An important feature of the pharmaceutical industry identified in this study are the licensing agreements between companies to market the same biologic in different regions. Remicade and Rituxan (named MabThera in the EU) each have three different companies marketing the biologic in the US, EU, and Japan. However it must be noted that Roche has a 61.5% stake in Chugai.[74] Taking Roche's ownership of Chugai into account, the company appears to have the largest presence among the pharmaceutical companies in having marketing rights to 3 of the 6 blockbuster biologics identified in this study.

AbbVie, which attributes 56.7% of its total sales to Humira, was formed as a spin-off by Abbott in 2013. AbbiVie holds the patented pharmaceutical business formerly owned by Abbott. Other international pharmaceutical companies such as

Pfizer, Novartis, Johnson & Johnson, and Merck have less than 10% of company sales from one biologic product.

Rituxan/MabThera has lost patent protection in the EU and Japan, although it has yet to face biosimilar competition in the respective markets. Potential differences in the degree of biosimilar competition in the three markets could be observed when Rituximab's US patent expires in 2015. Biogen Idec and Roche have already received market approval in the US and EU for a competitor to Rituximab for its lymphocytic leukemia indication (Gazyva).

Amgen and Novartis have disclosed plans to develop biosimilars. Amgen's plans include a partnership with Actavis for oncology biosimilars and its own development of biosimilar versions of Humira and Remicade.[14] Novartis' strategy for biosimilar development appears to be solely under its generic pharmaceuticals subsidiary, Sandoz.[78] An important development to be seen in the biosimilar market will be differences between branded biosimilars, such as those marketed by Amgen, and generic biosimilars such as Sandoz's versions.

5.4.2 Hypothesis 1: Competitive Markets and Revenue Protecting Strategies

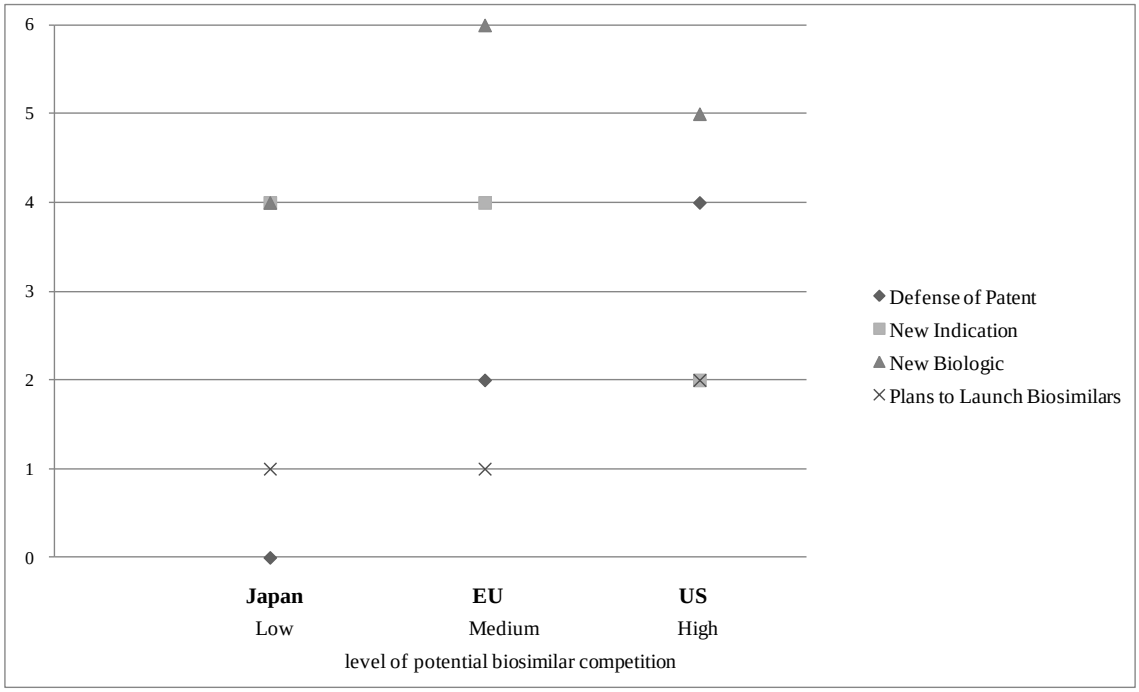
The first hypothesis proposed is that biologics sold in more competitive markets, with regulations and reimbursement policies more conducive for biosimilar competition, will cause companies to respond with strategies directed at protecting revenue. The US was determined to be the most competitive market for future biosimilar utilization, while Japan the least competitive. The EU ranked between the US and Japan in terms of likely degree of biosimilar competition.

Corporate strategies such as adding new indications were proposed to more likely in less competitive markets, where additional indications could be revenue

expanding. Strategies such as legal actions to defend patent rights, or developing new biologics to cannibalise sales of the existing biologic were proposed to be more likely in more competitive markets where revenue protection is more pressing.

To examine this hypothesis, the strategies identified for the six case biologics are aggregated for each of the three markets, the US, EU, and Japan. The highest sum is six, if all six biologics in the market have companies adopting a specified strategy. The figure below shows the results of this simple analysis.

Figure 5.3: Number of Biologics with a Specified Strategy, Aggregated by Market



No companies marketing biologics in Japan were identified as taking legal action to defend patent rights, while two and four in the EU and US, respectively, took this form of defense action. Disclosure of this form of legal action may not be a perfect indicator of the competitiveness of a market, as it could reflect differences in the reporting requirements for public companies in the respective markets. Companies

marketing biologics in the US may indeed have competitive pressure to defend patent rights; however, reporting practices may also contribute to greater disclosure of legal actions.

Japan has two more cases of companies adding new indications than the US, which supports the original hypothesis. However, the EU also had the same number of cases of adding new indications and the highest number of cases of new biologics in development. The EU has more mature system in terms of regulation and reimbursement policies for dealing with biosimilars. Also, the more immediate patent expiration dates for certain case biologics (Enbrel, Remicade, and Rituxan/MabThera) may drive companies to develop more new biologics for EU markets relative to the US.

5.4.3 Hypothesis 2: Patent and Time Horizon of Strategic Response

The second hypothesis proposed that biologics with shorter remaining time with patent life will cause companies to respond with short term strategies. Strategies related to the development of new drugs or the application of new indications can be distinguished as being short- or long-term strategies based on how close the application (for a new drug or new indication) is to being approved. Shorter term strategies may be considered strategies in which the new drug or additional indication already has marketing approval. Longer term strategies have new drugs or indications under earlier stages of testing such as phase I or II trials. Added to the time required to complete each trial phase is the uncertainty that new drug or indication will meet some threshold of performance to proceed to the next stage of review.

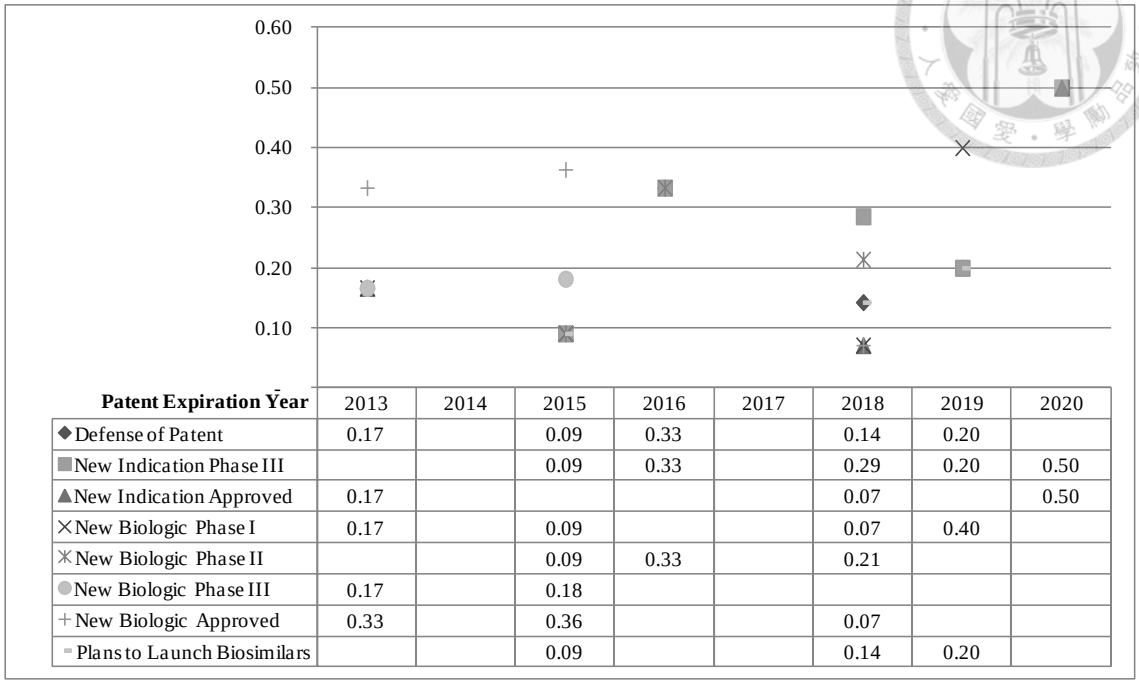
The other strategies to respond to biosimilar competition – defence of patent rights and the development of biosimilars – are not as clearly defined in terms of strategic time horizon. Actions to defend patent rights against infringement may occur

at any point during the effective life of a patent. Infringement lawsuits may occur at greater frequency toward the end of the patent life; however there may also be legal action leading to an extension of a patent, as occurred with Enbrel's US patent.[14]

The development of biosimilars, as reported by Amgen and Novartis in this study, does not have a definite time horizon. The development of biosimilars has a short-term dimension, if companies are preparing to launch biosimilars to compete with biologics with immanent loss of patent protection. If companies a developing biosimilars to compete with a wider range of biologics, including those with longer effective patent lives, the action could be considered more of a long-term strategy.

The following figure plots each of the competitive strategies (as a ratio of total strategies identified for each biologic) by year of patent expiration. The strategies for the application of new indications and new biologics have been separated by trial phase or approval stage in which the new indication or new biologic was reported during the 2013 reporting year.

Figure 5.4: Frequency of Strategies Reported Plotted Over Patent Expiration Year



Patent Expiration Year	2013	2014	2015	2016	2017	2018	2019	2020
Defense of Patent	0.17		0.09	0.33		0.14	0.20	
New Indication Phase III			0.09	0.33		0.29	0.20	0.50
New Indication Approved	0.17					0.07		0.50
New Biologic Phase I	0.17		0.09			0.07	0.40	
New Biologic Phase II			0.09	0.33		0.21		
New Biologic Phase III	0.17		0.18					
New Biologic Approved	0.33		0.36			0.07		
Plans to Launch Biosimilars			0.09			0.14	0.20	

Strategies to defend again patent infringement have been observed at a similar frequency for biologics with patent expiration in 2013, 2018, and 2019, indication the ambiguous relationship between effective patent life and legal action to defend/extend patent life.

Plans to launch biosimilars occur more often with biologics with longer remaining patent lives. However, with only two companies reporting these plans without great detail, it remains difficult to establish a clear relationship.

Cases of existing biologics having studies for new indications under Phase III increase with patents of later expiration dates. This pattern appears to support the hypothesis that adding new indications only has a positive impact on revenue if there is limited biosimilar competition, which can be supported under patent protection. Companies may be more likely to continue with trials for new indications if there is

sufficient time under patent protection to complete the trial, submit the marketing application for regulatory approval, and start sales for the new indication.

Launching new biologics to cannibalize sales of the existing biologic was originally proposed to be a strategy to protect revenues amid biosimilar competition. Biologics with early patent expiration dates have more cases where the new biologic is in a later trial stage (Phase III) or already approved for market. New biologics in earlier trial stages (Phases I and II) are being developed for nearly all cases, irrespective of patent expiration date. This finding suggests a long-term strategy that does not depend on the length of time free from biosimilar competition.

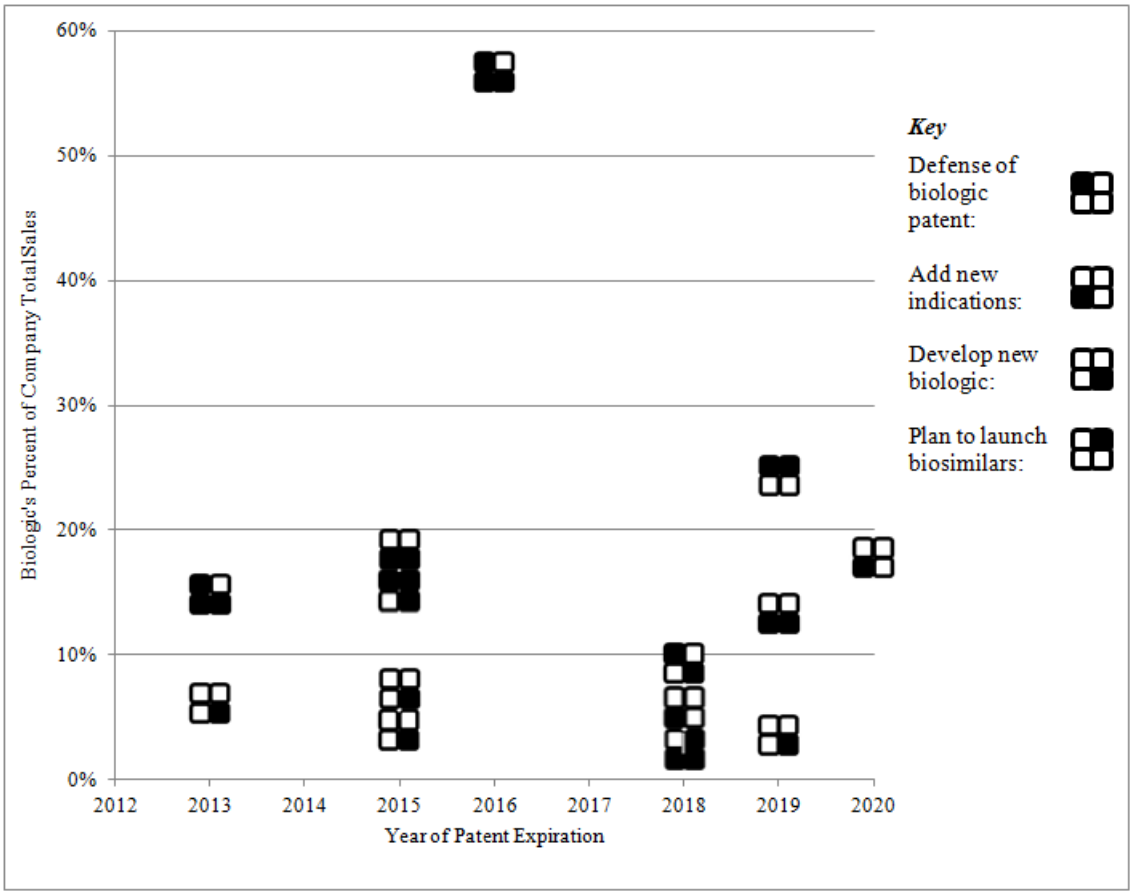
5.4.4 Importance of Biologic Sales to the Overall Business

The final section of analysis examines whether the proportion of a company's overall business derived from a single biologic product has any impact on the strategies the company in response to potential biosimilar competition. This relationship is not explicitly established in the hypothesis development section of this study; however, revenue generated by a single product is an important internal factor that also drives company's strategic decisions.[85] It is also of interest to examine any interaction between the sales at risk and the remaining patent life for a more complete measure of the company's risk from future competition. Further empirical research of the biologics / biosimilars market must take into account company internal factors such as individual product sales when attempting to model corporate strategy decisions.

The figure below plots the combination of corporate strategies (out of four) adopted the company by the year of patent expiration of the case biologic product (x-axis) and the percent of company total sales generated by the biologic (y-axis). The lowest percentage - 3.6% - are the sales from Lucentis for Roche, while the highest -

56.7% - are Humira sales for Abbvie. The earliest patent expiration year was in 2013 (for Rituxan/MabThera in EU and Japan) while the latest is in 2020 (for Avastin in Japan).

Figure 5.5: Incumbent Strategy Combinations - Plotted Over Patent Expiry Year and Sales for the Biologic as Percent of Total Company Sales



Companies with higher proportions of sales from the single biologic product appear to have adopted more of the strategies identified as responses to biosimilar competition. At below the 9% sales figure, five out of six cases adopted only one strategy; four of those five adopted the strategy of developing new biologics. Above 9%, one out of eight cases adopted only one strategy for responding to biosimilar competition; the remaining seven have two or three strategies. There does not appear to

be a clear relationship between the patent expiration date, company sales at risk, and number of strategies adopted. Biologics with patent expiration dates between 2013 and 2016 had cases with lower sales at risk (less than 9%) and single strategies, as well as cases with higher sales at risk (at least 15%) and three competitive strategies.

The specific case which appears to indicate a company taking serious measures to protect revenue when faced with large share of sales at risk and a patent that has *already* expired is Roche adopting three of four competitive strategies for MabThera in Europe. In contrast, Roche has only adopted one strategy for Lucentis, which makes up a lower share of total sales and has patent protection until 2019.

The measure for sales of a biologic as a percent of total company sales may not be a stable measure for a company's internal risk due to reliance on sales of a single product. A company's reliance on single product can change based on selling the marketing rights to another company, or acquiring marketing rights of other products from other companies. As the case with Abbvie, the entire business units can be spun-off into a different company, or similarly acquired by other companies.

5.5 Discussion

This section examined the corporate strategies developed by incumbent biologic manufacturers in response to future biosimilar competition. Strategies that could be attributed directly to potential biosimilar competition against a company's biologic product were identified as: (i) legal defense of patent rights; (ii) seeking new indications for use of the original biologic; (iii) develop a new biologic to 'cannibalise' sales of the original biologic; (iv) planned launch of biosimilars.

Strategies vary based on the potential for competition in the market; length of patent protection, and the importance of individual product to the company's overall

business. Examining company disclosures for six high sales volume biologics, all with patents expiring by 2020 (Avastin, Enbrel, Humira, Lucentis, Remicade, and Rituxan), the study finds some evidence that strategies to respond to biosimilar competition have been developed in context of the markets in which the biologic is sold (US, EU, or Japan). Biologics marketed for the US were more likely to have defensive patent infringement suits or patent extensions. In Japan, the market determined to have the lowest degree of biosimilar competition, the incumbent biologic manufacturers were more likely to apply for additional indications, which can be revenue increasing only without biosimilar competition. The EU, which is the more mature system in terms of regulation and reimbursement policies for dealing with biosimilars, had the same number of instances of adding new indications and the highest number of cases of new biologics in development.

The timing of patent expiration may have an influence on the type of strategy adopted for a biologic incumbent. Cases of incumbent biologics having plans to add new indications under Phase III were more likely with patents of later expiration dates. This supports the view that adding new indications only has a positive impact on revenue if there is limited biosimilar competition, which can be supported under patent protection. Companies may be more likely to continue with trials for new indications if there is sufficient time under patent protection to complete the trial, submit the marketing application for regulatory approval, and start sales for the new indication. Biologics with earlier patent expiration dates had more cases where the new biologic is in a later trial stage (Phase III) or already approved for market. This finding underscores the more immediate necessity to have new biologics ready for market to replace sales at risk from biosimilar competition.

The simple, descriptive analysis presented in this section has many limitations. The sample size of cases is too small to statistically validate any of the hypotheses proposed in this section. The sample is also very selective- the biologics examined are the highest selling biologics, omitting many other biologics available in the market. These biologics may drive a certain strategic response from the license holder; while other biologics used to treat smaller patient populations may drive different strategies that were not examined in this study.

There may be other factors omitted in this section that also play a role in shaping the incumbent's strategy. Strategic interaction between the incumbent and other actors in the market, including future biosimilar competitors, plays a role in developing the incumbent's strategic focus. Also the ability for the incumbent firm to shape the regulatory and reimbursement environment through lobbying is not included in the study. Strategies such as mergers and acquisitions and further intercompany licensing agreements are not examined because of the difficulty in attributing them to a single biologic. This information may also not be found in the company annual reports, which this study relies on as its primary source of data.

Despite these limitations, this analysis does present both the key factors in determining the incumbent strategy, and the main types of strategies the incumbent will adopt. This can serve as an initial guide on the type of information that will be critical for any potential biosimilar entrants to collect to understand the competition they will face from the incumbent.

Chapter 6: Conclusion

6.1 Summary of Research Findings

This thesis identified major trends in biosimilar regulations and reimbursement policies, using the US, EU, and Japan pharmaceutical markets as the case subjects. The body of research from this thesis focused on comparative analyses of regulatory policies with respect to market licensing of biosimilars and major reimbursement policies affecting market use of biosimilars. The information from this comparative analysis, as well as data reported by biologic manufacturers, was used to evaluate the corporate strategies that incumbents are pursuing in response to future biosimilar competition.

The main findings from the comparison of the US, EU, and Japanese regulatory approach to biosimilars (Chapter 3) are as follows:

- Regulatory agencies in these markets have established abbreviated review processes to allow biosimilars to come to market faster than if they were to be reviewed as completely new molecular entities.
- In general, these agencies have the same goal, to ensure that new biosimilar products are nearly the same as their referenced biologic product in terms of safety, efficacy, and quality.
- Key differences between the agencies are in granting 'interchangeable/substitutable' labels and in the timing of the first biosimilar submission.
- The US FDA's option for biosimilars to be licensed as 'interchangeable,' shorter time in which biosimlars have to wait to submit applications, and an exclusivity period for the first-to-market biosimilar will theoretically encourage wider biosimilar adoption in the market.

The main findings from the comparison of the three markets' reimbursement policies (Chapter 4) are as follows:

- The US is expected to have wide variation in biosimilar reimbursement policies as policies will vary on the size of the insurance market and the level of competition between plan administrators.
- The EU member states analysed in Chapter 4 (Germany, France, and the UK) and Japan have national-level policies that influence the type of pharmaceuticals covered as benefits and their reimbursement prices.
- European countries were found to use pricing tools, such as negotiated discounts, reference pricing, and tendering, that should provide an opportunity for biosimilars to gain market share.
- Japan's price regulations, set at the national level, do not appear take advantage of potential competition between different biosimilar manufacturers.

The main findings from the analysis of corporate strategies of incumbent biologic manufacturers (Chapter 5) are as follows:

- Biologics marketed for the US were more likely to have defensive patent infringement suits or patent extensions.
- In Japan, the market determined to have the lowest degree of biosimilar competition, the incumbent biologic manufacturers were more likely to apply for additional indications, which can be revenue increasing only without biosimilar competition.

- The EU, which is the more mature system in terms of regulation and reimbursement policies for dealing with biosimilars, also sees incumbents applying for new indications, as well as developing new biologics to cannibalise sales of the existing biologic.
- The timing of patent expiration has an influence on the type of strategy adopted for a biologic incumbent. Companies may be more likely to continue with trials for new indications if there is sufficient time under patent protection to complete the trial, submit the marketing application for regulatory approval, and start sales for the new indication.
- Companies marketing biologics with earlier patent expiration dates also had plans to launch new biologics late trial stages (Phase III) or already approved for market. This finding underscores the more immediate necessity to have new biologics ready for market to replace sales at risk from biosimilar competition.

6.2 Recommendations for Biosimilar Manufacturers in Taiwan

With an aging population, a pharmaceutical industry worth US$4.6 billion, and a domestic biotech industry looking to play a larger role in the economy, Taiwan may provide opportunities for domestic manufacturers to enter the biosimilar market.[86] Taiwan's universal healthcare system involves heavy government involvement in paying for healthcare, including many high-cost prescription medicines.

Firstly, Taiwan's regulations of biosimilars are modeled after EU, which is an abbreviated process; however, these regulations were not found to provide additional incentives to first entry biosimilars unlike the US.[87] The pricing and healthcare coverage of drugs is determined in a similar process as Japan, where approval for sale equates

coverage on national health insurance plans, and prices are also determined at this stage.[88] However, Taiwan has gone further than Japan to review new drugs based on evidence and cost, relying on a health technology assessment agency similar to NICE in the UK, which provides guidance to the national insurer and develop clinical criteria for drugs. Taiwan's National Health Insurance (NHI) is more similar to the UK in being a large single payer able to extract savings from the health care system.[89] NHI relies on global budgeting, price volume adjustments, and drug expenditure targeting to control costs in the system.[90]

Based on similarities between Taiwan's healthcare system and certain aspects of Japan's and Europe member states' health care systems, the simple analysis of incumbent strategies (from the previous chapter) suggests that Taiwan's future biosimilar market will see the same type of incumbent response to competition. Biosimilar manufacturers should be prepared to compete against new biologics introduced by brand manufacturers as intended substitutes for biologics losing patent protection, as well as large generic manufacturers like Sandoz whose parent company Novartis will give it an advantage in bringing biosimilars to market.

The recommendations below are divided into recommendations directed toward competing with biologic incumbents (6.2.1) and recommendations directed toward competing with multinational generic manufacturers, which will also be the main competitors in the biosimilar market (6.2.2).

6.2.1 Recommendations for Competing Against Biologic Incumbents

1) Manufacturers may be developing biosimilars of a biologic in which the original manufacturer is still applying for new indications (for example, Roche applying for additional cancer indications in Avastin). The

manufacturer should be prepared to apply for all indications in the event that the original biologic is approved for more in the future. The manufacturer may find it beneficial to convince the market regulator (Taiwan FDA) to relax requirements for additional indications, such as automatic approval for new indications if the biosimilar already meets requirements for existing indications.

2) To respond to incumbents developing new biologics as substitutes for biologics losing patent protection, an assessment should be made whether regulators are expected to treat the new biologic as a major innovation, or if they will view the new biologic as more of a 'me-too' version of the current biologic. Biosimilars may not be able to compete against new biologics that regulators view as significant innovations over current treatment. Manufacturers may wish to discontinue development in these cases, or postpone development until more evidence comes out of the new biologic in development.

However, in competing against new biologics that regulators view as offering little or no improvement, manufacturers can claim that their biosimilar products will offer significant cost advantages to payers. Biosimilar manufacturers should ensure that health insurance policy reflects this advantage when determining reimbursement prices for these drugs. Similar to references pricing found in Germany (see section 4.3.3), Taiwan's NHI should also adopt pricing policies that include biosimilar product prices as references for new biologics not found to provide clinical benefit over

existing biologics. Manufacturers should also advocate preferential listing criteria in which lower cost biosimilars are prescribed before higher cost biologics. By creating incentives for prescribers to chose biosimilars over higher cost patented biologics, these policies will ensure that biosimilars will gain market share even when new biologics come to market.

6.2.2 Recommendations for Competing Against Multinational Generic Companies

1) In competition between domestic biosimilars and biosimilars developed by large, multinational companies, domestic companies cannot rely on the government to develop preferential policies for the domestic producers. Any difference in policy between domestic and international manufacturers of the same type of products (biosimilars) may be viewed as anti-competitive and protectionist.[91] For this reason, domestic companies must be prepared to compete with multinational generic companies at an even playing field.

2) Domestic manufacturers should secure market share by becoming preferential suppliers at Taiwan's larger public hospitals and medical centers which were found to be the leading prescribers of biologics in Taiwan.[92] Because prescribers are unlikely to switch patients between different biosimilars of the same drug class, there is a clear first-mover advantage for manufacturers entering the supply channel of major health care providers. Manufacturers must be willing to offer significant price concessions to secure this channel.

3) Biosimilar manufacturers may offer additional incentives to hospital providers through services such as administering the infusion of the drug (3

of 6 case study biologics require intravenous infusion). Under NHI global budgeting, although drugs are subsidized on a fee for service basis, other hospital services such as administering IVs are reimbursed at the end of the budget year, after the relative use of the service is calculated within the global budget. Researchers have found that hospitals substitute fee for service type items such as drugs for non-fee for service items.[93] This feature of global budgeting may lead to underuse of drugs requiring in-hospital administration, unless manufacturers can directly cover the administrative costs.

Taiwan biosimilar manufacturers may find an opportunity to share costs by cooperating on the establishment of jointly owned infusion clinics. Manufacturers of different biosimilars may cooperate in funding infusion clinics, which will avoid appearance of collusion to competition regulators. This cooperation may also be necessary in order to compete against international companies with much larger funds to afford additional services/incentives for their products.

6.3 Limitations and Directions for Future Research

The applicability of the results in this thesis is limited by the scope of evidence found in this study – that is, evidence limited to review of the three largest markets for pharmaceuticals and an analysis of corporate strategy around six blockbuster biologic drugs. Furthermore, biosimilars represent an emerging market which will be subject to change as the market matures. The results from this thesis are valid at the time of this writing; however, the results may not hold in the future if there are major, disruptive changes in the market. Despite these limitations, the findings from this thesis serve as an

initial guide on the type of information that will be critical for any potential biosimilar entrants in navigating the competitive market for their product.

Future directions of research related to this thesis may cover other countries' markets for pharmaceuticals and a wider range of candidate biologics to analyze corporate strategies. Comparability studies between biosimilars and the originator biologics will increase as more biosimilars enter the market; the impact of more and more comparability studies on development of biosimilar regulations and reimbursement policies will also be a future area of research. More opportunities may be discovered by analysing more markets for biosimilars and a wider range of biologics. However, this thesis still provides a starting point for viewing potential threats and opportunities for new entrants, in Taiwan or other jurisdictions.

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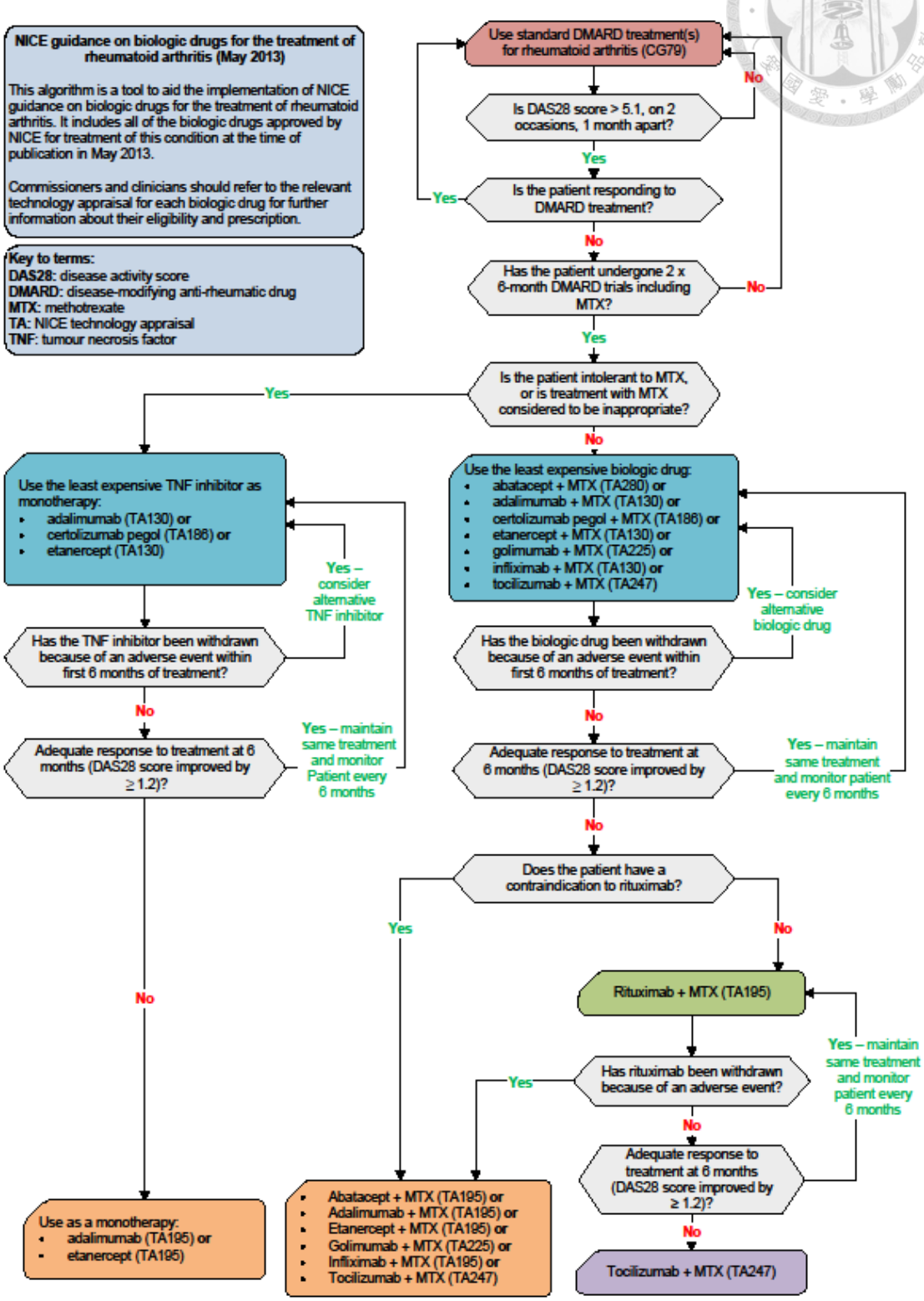
Appendix 1: NICE Treatment Algorithm for Rheumatoid Arthritis



Source: National Institute for Health and Clinical Excellence, 2013 (60)

Appendix 2: Detailed Summary of Company Actions in Response to Biosimilar Competition

Brand Name (molecule name)	Company	Market	Detailed Summary of Company Actions
Avastin (bevacizumab)	Roche	US	New indication approvals: approvals for the treatment of malignant glioma (a type of brain tumor) and ovarian cancer. Phase III new indications: Breast cancer (adjuvant)
		EU	Phase III new indications: HER2-neg. BC adj; NSCLC adj, high-risk carcinoid, ovarian cancer 1 st line, relapsed ovarian cancer, platinum-sensitive, cervical cancer recurrent, rel. ovarian ca. Pt-resistant, glioblastoma 1 st line. Phase I new biologics: Ang2-VEGF MAb Newly diagnosed glioblastoma multiforme (AVAglio); other Anti-VEGF for oncology (Phase I)
	Chugai	Japan	Phase III new indications: HER2-neg. BC adj; NSCLC adj, high-risk carcinoid, ovarian cancer 1 st line, relapsed ovarian cancer, platinum-sensitive, cervical cancer recurrent, rel. ovarian ca. Pt-resistant, glioblastoma 1 st line. Phase I new biologics: Ang2-VEGF MAb Newly diagnosed glioblastoma multiforme (AVAglio); other Anti-VEGF for oncology (Phase I)
Enbrel (etanercept)	Amgen	US	Phase 2 programs on Mabs for inflammatory diseases; biosimilars for bevacizumab, infliximab, adalimumab
	Pfizer	EU	Approved new biologic (in Japan) Xeljanz (Tofacitinib) for Rheumatoid Arthritis; Phase 3: A JAK kinase inhibitor for the treatment of psoriasis, ulcerative colitis and psoriatic arthritis
		Japan	Approved new biologic (in Japan) Xeljanz (Tofacitinib) for Rheumatoid Arthritis; Phase 3: A JAK kinase inhibitor for the treatment of psoriasis, ulcerative colitis and psoriatic arthritis
Humira (adalimumab)	AbbVie	US	Patent ingringement against Centocor Ortho Biotech, Inc.'s (now Janssen Biotech, Inc.'s) product Simponi. New indications Phase 3 trials for uveitis and hidradenitis suppurativa. New biologics: Phase II for tregalizumab, GLPG0634, a next-generation, oral Janus Kinase 1 (JAK1) inhibitor, anti-IL-6R Nanobody, ALX-0061, to treat inflammatory diseases,
		EU	Patent ingringement against Centocor Ortho Biotech, Inc.'s (now Janssen Biotech, Inc.'s) product Simponi. New indications Phase 3 trials for uveitis and hidradenitis suppurativa. New biologics: Phase II for tregalizumab, GLPG0634, a next-generation, oral Janus Kinase 1 (JAK1) inhibitor, anti-IL-6R Nanobody, ALX-0061, to treat inflammatory diseases,
	Eisai	Japan	New indication: Regulatory approval in 2013 for intestinal Behçet's and treatment of moderate to severe ulcerative colitis.

Appendix 2: Continued

Brand Name (molecule name)	Company	Market	Detailed Summary of Company Actions
Lucentis (ranibizumab)	Roche	US	Phase I: Lucentis sust. deliv.
	Novartis	EU	New Indication: Phase III development for the treatment of visual impairment due to choroidal neovascularization and macular edema secondary to conditions other than age-related macular degeneration, diabetic macular edema, retinal vein occlusion and pathologic myopia. New Biologic: Phase II for Anti-VEGF for wet macular degeneration. Sandoz (Novartis generics company) has biosimilar rituximab, etanercept and adalimumab in pipeline
		Japan	New Indication: Phase III development for the treatment of visual impairment due to choroidal neovascularization and macular edema secondary to conditions other than age-related macular degeneration, diabetic macular edema, retinal vein occlusion and pathologic myopia. New Biologic: Phase II for Anti-VEGF for wet macular degeneration. Sandoz (Novartis generics company) has biosimilar rituximab, etanercept and adalimumab in pipeline
Remicade (infliximab)	Johnson & Johnson	US	Patent infringement: REMICADE® patent in question is valid and has responded to the Office Action to defend the patent. New biologics already approved: Simponi, Stelara
	Merck	EU	New biologics already approved: Simponi; Phase II MK-8457 for rheumatoid arthritis, Phase III tildrakizumab for psoriasis
	Mitsubishi Tanabe	Japan	New Indication: Phase III: Refractory Kawasaki disease, Behcet's disease, Pediatric Chrohn's, and Ulcerative colitis. New biologics already approved: Simponi. New biologic in Phase I for inflammatory and autoimmune disease.
Rituxan / MabThera in EU (rituximab)	Biogen Idec	US	New biologic: Approval for Gazyva for chronic lymphocytic leukemia. Applied for new patents for Rituxan. Agreement with Samsung Bioepis to commercialize anti-TNF biosimilar product candidates in Europe
	Roche	EU	Approved new indication: active GPA and MPA (two types of ANCA-associated vasculitis). Approved new biologic: Actemra for RA. Phase III new biologics: Gazyva (obinutuzumab) for DLBCL; iNHL relapsed; iNHL front-line. Phase III new formulation: NHL sc formulation
	Chugai	Japan	Approved new biologic: Actemra for RA. Phase I new biologic: Rheumatoid arthritis. Phase I new biologic: Systemic lupus erythematosus SLE)