A Comprehensive Guide to the Three Biosimilar Markets (Europe, US, Japan) and The Regulatory Pathways

by

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ARCHIVES

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ABSTRACT

Generics in the pharmaceutical industry have been instrumental in reducing overall healthcare cost and allowing for greater dispersal of life saving drugs to the general population. The Hatch-Waxman Act of 1984 played a critical role in changing the landscape of the pharmaceutical industry and providing legislation for an abbreviated regulatory pathway for generic drugs. The conversation has shifted to the need to implement similar regulatory paths for generics of biologics. First generation biologic patents have or are geared to expire within the next five years, providing a great opportunity for generic companies in this space to enter. Biologic generics, termed biosimilars or follow-on biologics, are more difficult to evaluate due to the complex nature of the molecule and the variables involved in the development and manufacturing process. This research seeks to understand the current debate in the biosimilar conversation, and examine whether there is a clear regulatory path to market for biosimilars using epoetin as a case example across the three main markets; US, Europe and Japan.

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Chapter 1: Introduction

Generic forms of biologic products are now developed and discussed as key products to reduce overall cost and help maintain profitability for healthcare companies. These generic products are termed 'biosimilars' or 'follow-on biologics." Many pharmaceutical and biotechnology companies face the strategic decision whether to enter the biosimilars marketplace. A number of key factors, including the "patent cliff" paradox for current branded biologics and the shift in medical practice to utilize targeted high-value biologic therapies, make the biosimilar market a very attractive possibility.

The current questions for companies concerned with pursuing biosimilars are:

- Is there a "path" to market for biosimilars?
- How do these paths differ across the three most developed regulatory markets; US, Europe and Japan?

One fundamental question is whether or not pharma and/or biotech companies should pursue biosimilar therapies based on the regulatory 'cost' associated with entry. Beyond just the monetary cost of drug evaluation, there is also the risk of uncertainty with biosimilars. This thesis examines whether there is a clear regulatory path to market for biosimilars using epoetin as a case example across the three main markets; US, Europe and Japan. An in-depth analysis of the regulatory documents will be conducted and presented in a case study framework.

The structure of the thesis is as follows:

- **Chapter 2:** A historical look at the pharmaceutical regulatory pathway development for generics and an in-depth analysis of the key regulatory milestones that molded the direction of the generic conversation. Then, a robust outline will be provided as to how small molecules generics are compared to their branded equivalent through a product driven method.
- **Chapter 3:** A historic look at the biologics industry and regulatory pathway for both branded products and biosimilars.
- **Chapter 4:** Identifies the key areas (scientific, clinical, and political) that are hotly contested in the biosimilar debate. This chapter will take a look at the strong opinions held by the

research-based companies (Large Pharma/Branded Biologics companies) and how those differ from those of generic companies that wish to enter the biosimilar space.

Chapter 5: One of the missing links in the biosimilar conversation is a comprehensive checklist for biosimilar companies interested in entering the main world biologics markets. In theory, a global biosimilars approval pathway would greatly reduce cost for biosimilar manufacturers, thereby encouraging more players in the market and spurring competition to reduce biosimilar price. However, with the complexities and uncertainties of determining biosimilar equivalence, there is a slim chance that a global regulatory pathway would ever develop due to lack of consensus. Therefore, biosimilar manufacturers will need to gain approval through the complex regulatory processes for each market they wish to enter. With biosimilar guidelines in its infantry, there has been a lack of transparency as to what steps are needed to be takein within each country to gain approval (Figure 1). This chapter will provide potential biosimilar companies a checklist of key submission criteria for each of the three regulatory pathways (EU, US and Japan). Human Erythropoietin, or epoetin as it is referred to as a biologic product, will be the case example used to discuss the regulatory pathway throughout the thesis. A background will be provided about epoetin here.

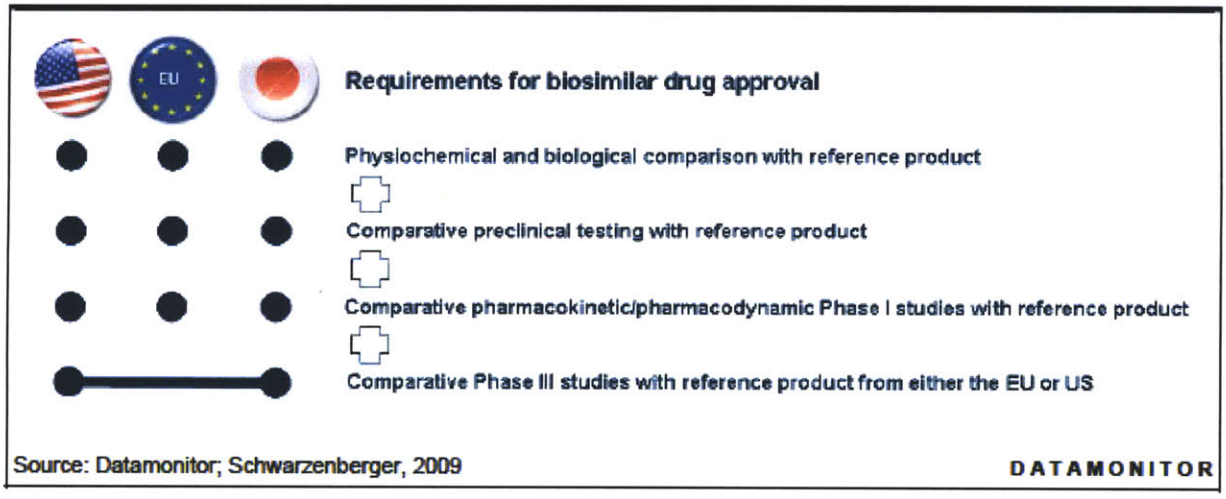


Figure 1: Requirements for Biosimilar Drug Approval in the US, EU and Japan: The connecting line for the fourth component, comparative phase 111 studies, is implying that phase 111 study results from these three countries could be interchangeable for regulatory approval if a global biosimilars pathway is created.

- **Chapter 6:** A discussion of what learning's have been gained in the biosimilar regulatory space and what actions must be taken that are known with certainty to provide information about how 'similar' a biosimilar is to its reference product. A revisit of the biosimilar debate and a discussion of key areas of biosimilars that are creating value in the market will be presented. In conclusion, a final regulatory guideline will be provided.
- **Appendices:** A robust analysis of the biosimilar market for both the short and long-term.

Chapter 2: History of Pharmaceutical Regulatory Pathway

Introduction of Generics

Generic is a common term in the prescription drug business, and is defined as a drug that is produced and sold without patent protection under its chemical name. The generics market (Gx Market) is largely included as a branch of the pharmaceutical industry known as the small molecules industry. Although sales have generally soared in recent years, generics are predominantly adopted in countries with high healthcare expenditure. In the US for example, healthcare expenditures exceeded $2.2tn in 2007, accounting for 16% of GDP. Prescription medication was over $200bn of that expenditure (5). With the cost-cutting pressure within the healthcare system over the past few decades, generics have risen as a key player in aiding to reduce the cost burden.

Generics are able to extract a greater value from the drug than what is current being offered by the branded version usage levels. They provide access to the average individual to medications through lower costs that are driven by high competition and high volume uptake. Patients are given further incentives to use generics through payer provisions such as waiving generic co-payment as seen in the US Medicare system. However, the mission of generics is very similar to that of its innovator. It maintains its first priority to ensuring patient safety, and does this through understanding the drug's characteristics and its impact on patient safety. Generic companies also maintain a principle of respecting the innovator's intellectual properties (29,30,31,30).

The 100 Year Evolution of Pharmaceutical Drugs

The small molecule/pharmaceutical drug industry is relatively speaking more mature, with medieval literature referencing alchemist as developers and distributors of chemically synthesized drugs. These drugs were defined and regulated in the U.S. in 1906 with the enactment of the Food and Drugs Act of June 30, 1906 (24,26). The defining of a drug and more specifically, a 'new drug', is critical in understanding the evolution of the generics industry and the criteria in which generic vs. branded drugs are compared to one another.

A 'drug' is identified as the grouping of products that are subject to regulation, and are 'articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases in man and

articles (other than food) intended to affect the structure or any function of the body of man..." More clarity was given to this definition through the 'grandfather clauses' of 1938, in which the New Drug Application (NDA) was introduced (24,26).

Based on this regulatory knowledge at the time, end product testing of chemically synthesized drugs was used to determine product performance and safety. Since these drugs were either produced through chemical reactions, or isolated and purified from plants, the purity of these drugs can be easily determined. Since 1938, the new drug application (NDA) has been the vehicle in which pharmaceutical drug makers have used to gain approval and marketing/sales authorization in the US. Table 1 provides a checklist for parties interested in bringing a product through this approval process.

		New Drug: Small Molecule
Product Characteristics/ Non-clnical	Physical Characteristics: molecular weight, primary & secondary structures, etc.	X
	Chemical Characteristics: molecular formula, chemical strucutre	X
	Specifications of drug substance (active ingredient)	X
	stability	X
	purity	X
	pharmacokinetic/pharmacology/toxicology	X
	studies for absorportion, distribution, metabolism and excretion of the drug in animals	X
Good Manufacturing Practice (GMP)/Quality	list of all components used in the manufacture (synthesis/isolation/purification) of drug substance, their tests and specification/drug development plan	X
	Rationale for development plan (dosage forms, etc.)	X
	Container/Closure System	
Clinical	Bioavailability/bioequivalence studies (very few biologics will have such data)	X
	Description and analysis of each clinical pharmacology study of the medicinal product(comparison of human data with animal data)	X
	Pharmacokinetic & Toxicology Studies	X
	Description and analysis of each controlled clinical study	X
	Clinical Effectiveness for the clinical indications. Evidence for dosage and administration required.	X
	Clinical Safety: studies of assessment of absorption, distribution, metabolism, and/or elimination of drug	X
	Summary of benefits and risks of the medicinal product in its intended use	X
Other	Patent information on any patent that claims the drug	X
	Microbiology	X
	Safety update Reports (four months post NDA's submission)	X

Table1: Regulatory Checklist for New Drug Application (NDA)(26): A breakdown of the key regulatory categories; product characteristics, GMP, Clinical and other.

Historically, there has been ambiguity with the FDA's definition of 'new drug'. This has been critical in the confusion of what a generic drug is and how it is later evaluated. The definition of a 'new drug' can be interpreted in three ways:

1. Every drug that is introduced is a 'new drug'. (Therefore generics would be required to pass stringent general recognition among experts to escape new drug classification.)
2. Drugs are classified as 'new' if the active ingredient is different. (Therefore any generic copy of the drug that contains the same active ingredient can escape the new drug classification, and pre-market approval requirement)
3. A group of drug products that have the same active ingredient, same dosage form, and the same indication (26).

The major controversy with this legislation was whether the term new drug was intended to refer to all manufacturer's version of the same active ingredient marketed in the same dosage form and sold for the same indication or any variation of these three criteria (i.e. same dosage and same indication but not same active ingredient).

Continued revisions by the FDA have tried to address the issues around what is a new drug. Key legislation passed in 1984 paved the way for the generic entrance into the pharmaceutical industry. The Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Act, explicitly permitted drug approval based on an abbreviated new drug application (ANDA) and allowed for generic copies of FDA approved pioneered products to apply without full safety and efficacy testing. The Hatch-Waxman Act provided guidelines for generics to enter the market through an approval process that required bioequivalence studies as opposed to clinical data, and granted additional market exclusivity (not to exceed five years) in lieu of not having patent protection in the development process. Figure 2 provides a sampling of the requirements of the 505 regulatory pathway family, which is the regulatory path established for generic entrance (26).

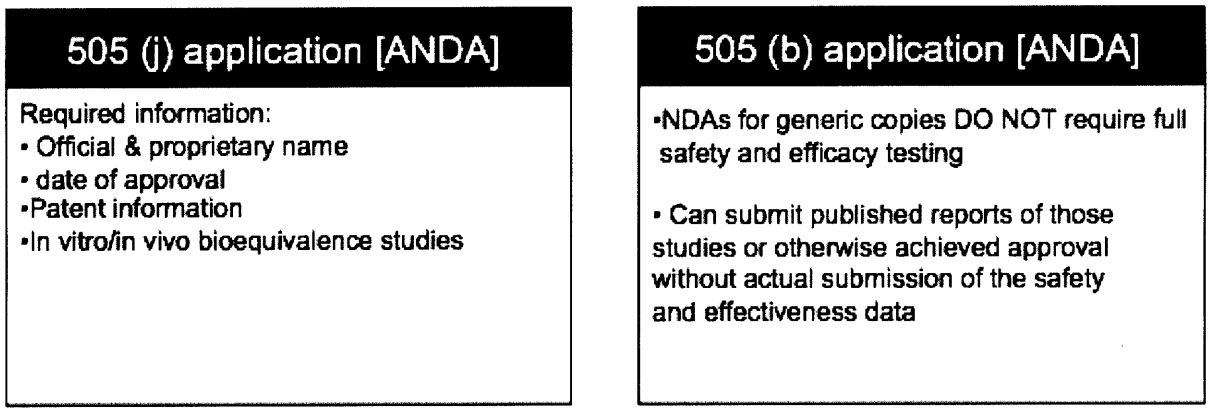


Figure 2: Abbreviated New Drug Application Pathways for Pharmaceutical Candidates (26): The 505 pathways were created through the Hatch-Waxman Act, which allowed for abbreviated new drug applications for generic drugs.

The Hatch-Waxman Act, specifically the 505(b) provision that allowed generics to submit literature and external clinical data as evidence of the safety and efficacy of their drug, was strongly opposed by the pharmaceutical industry. Pharmaceutical companies argued that external data was not sufficient to prove safety and efficacy of generics and that full-scale clinical trials should be required for regulatory approval. However, the FDA rejected the challenge and continues to allow clinical trial data to be submitted as part of the application process that was not collected directly by the generics company (26).

The positive effect of the Hatch-Waxman Act was astounding. Prior to the introduction of this act, the market saw very little penetration of generic products, which meant fewer drivers to decrease the overall healthcare cost burden. Less than 40% of all top-selling drugs post patent expiration had a generic option available prior to 1984, and less than 20% of all prescriptions were generic. The benefit to society, both in terms of lowering healthcare costs and providing accessibility of life saving therapies to a greater population was enormous. The introduction of these guidelines have allowed for generic drugs to be more easily distributed and prescribed to patients. In 2007, generics accounted for 65% of total prescriptions, with a steady growth rate of 8-10% per year(5). It is evident that generic drugs in the small molecule industry have been a proven success and has positively impacted the US (25).

In 2001, a global initiative took place to allow for submission of data in the same format and content across the three major markets (Europe, US, Japan) for regulatory approval. In the past, submission

requirements vary depending on the function of a drug. However, regulatory bodies across these three markets came to a consensus on how to create a structured framework for drug manufacturers to follow in order for them to collect the necessary data and product research to gain approval (25,26).

Therefore, a new drug pathway and an abbreviated pathway have been created for regulatory approval of small pharmaceutical molecules. Table 2 provides a checklist and comparison of the regulatory pathway between new drugs and generics. Generics have greatly benefited from the abbreviated pathway, as they are not required to invest in high cost studies (clinical trials, non-clinical trials) that therefore decrease the high barrier to entry and allow for cost savings to be enjoyed by the entire healthcare system. The commercialization of generics requires 3-5 years to develop at a cost of $1-5million, 200-fold less than the cost to innovate and develop a new small molecule drug (31).

		New Drug: Small Molecule	Generic: Small Molecule
Product Characteristics/ Non-clinical	Physical Characteristics: molecular weight, primary & secondary structures, etc.	X	X
	Chemical Characteristics: molecular formula, chemical strucutre	X	X
	Specifications of drug substance (active ingredient)	X	X
	stability	X	X
	purity	X	X
	pharmacokinetic/pharmacology/toxicology	X	X
	studies for absorportion, distribution, metabolism and excretion of the drug in animals	X	
Good Manufacturing Practice (GMP)/Quality	list of all components used in the manufacture (synthesis/isolation/purification) of drug substance, their tests and specification/drug development plan	X	
	Rationale for development plan (dosage forms, etc.)	X	
	Container/Closure System		
Clinical	Bioavailability/bioequivalence studies (very few biologics will have such data)	X	
	Description and analysis of each clinical pharmacology study of the medicinal product(comparison of human data with animal data)	X	
	Pharmacokinetic & Toxicology Studies	X	
	Description and analysis of each controlled clinical study	X	
	Clinical Effectiveness for the clinical indications. Evidence for dosage and administration required.	X	
	Clinical Safety: studies of assessment of absorption, distribution, metabolism, and/or elimination of drug	X	
	Summary of benefits and risks of the medicinal product in its intended use	X	
Other	Patent information on any patent that claims the drug	X	X
	Microbiology	X	
	Safety update Reports (four months post NDA's submission)	X	

Table 2: Branded and Generic Regulatory Approval Pathway Checklist that is a product driven process

Chapter 3: The Evolution of Biologics and the Regulatory Pathway

The Birth of the Biologics Industry

Biologic therapies have in essence been in existence since the turn of the 20th century to combat infectious disease epidemics such as polio, typhoid, and cholera. They differ from small molecules in that they are "complex mixtures that are not easily identified or characterized" and are derived from living sources, such as humans, animals, plants and microorganisms (24). In the past century, the definition of biologics has expanded to include viruses, therapeutic serum, toxin, antitoxin, vaccine, blood, and blood components or derivative allergenic products or analogous product applicable to the prevention, treatment, or cure of a disease or condition of human beings. Biologics can be found in two forms: as a drug or medical device.

The discovery of vaccines was the first biologic to come to market. At this time in history, there was a lack of understanding of immunology and microbiology. Therefore, there was very little understanding of the variables involved in the manufacturing of these biologic products and the effects of those variables on safety and efficacy. The crude manufacturing methods predominately used animal models to produce the vaccines, and these methods were poorly understood. Only after the 1901 antitoxin episode, where 10 children were given diphtheria antitoxin contaminated with tetanus contracted from horses used in production, did the FDA step in to regulate biologics(24).

Due to the early tragedies such as the diphtheria antitoxin incident, regulators quickly learned that end product testing was not sufficient to determine product performance and safety. Many biologics work through immune response systems, and therefore a very small amount of active substance is required to trigger these responses. Hence, the extent to which a biologic had to be free of all impurities was in question and dependent of clinical safety profiles. Another issue was that until the most recent past, analytical methodologies and protein chemistry were not sensitive enough to characterize these complex products. Because of these intricacies in safety testing, a new regulatory approach was developed specifically for biologics. Regulatory bodies focused on controlling the product's manufacturing facility and method of manufacturing, since the variables in these processes highly influence safety and effectiveness of the biologic (24).

The process of regulating biologics began with The Biologics Control Act of 1902, which was passed to regulate the manufacturing process of biologics. This act began a series of future legislation that focused on the manufacturing process of biologics to determine safety and efficacy, rather than mirror the product-driven regulation of the pharmaceutical industry (Refer to Figure 3)(24).

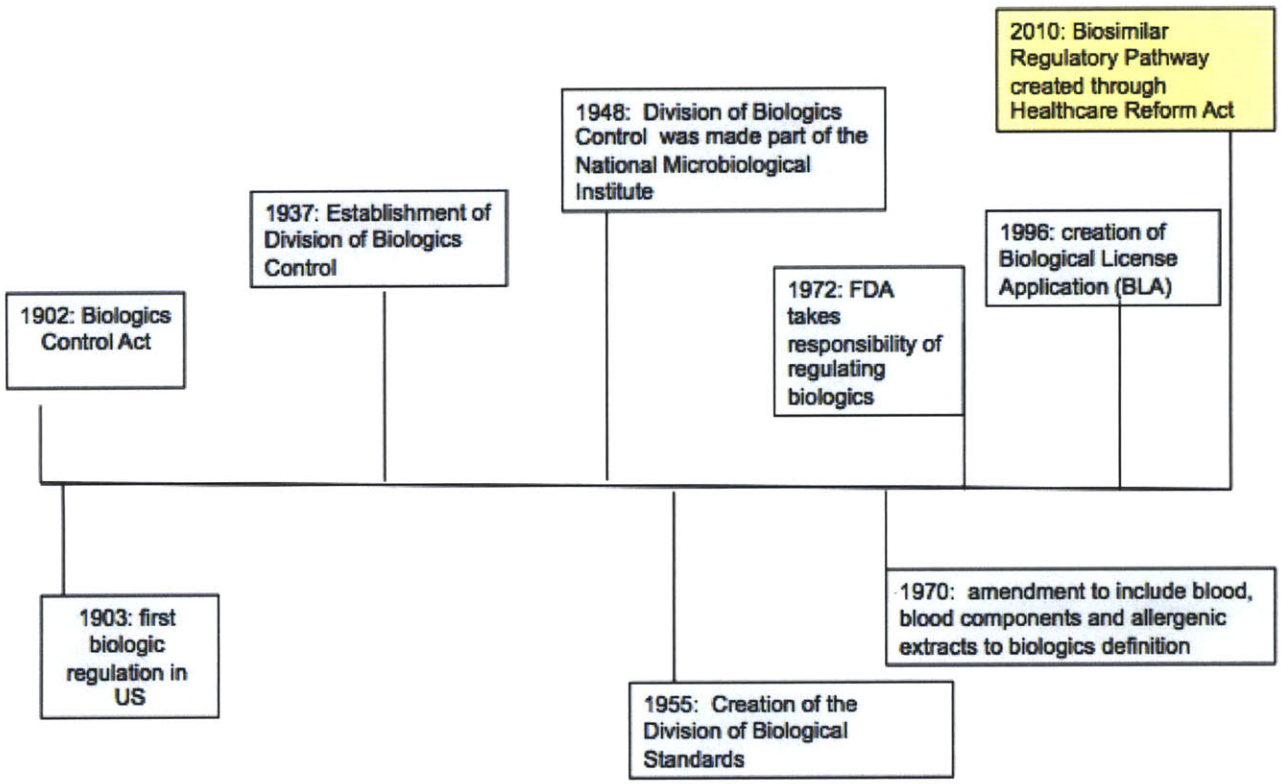


Figure 3: Timeline of Biologic Regulation in the US(24,26) : All the previous legislation and events leading to the Biosimilar Regulatory Pathway created through the Healthcare Reform Act of 2010.

The further understanding of immunology coupled with the genomics era in the 1970s and 1980s led to the explosion in scientific advancement and the creation of the biotechnology industry. The complexity of these new products led to significant debate and restructuring in regulator's thought process in monitoring these products. Different regulatory approval processes were put in place to deal with the fundamental differences between chemically derived drugs and biologics.

Biotechnology and the biologics industry is a fairly young industry with a limited number of past experiences to build on. It was introduced into mainstream medicine in the early 1980s, with the arrival of recombinant insulin, human growth hormone, and erythropoietin. The key to biologic regulation is to be able to prove that it the therapy is 'safe, pure and potent'. Biologics require the same evidence of safety and effectiveness, publication of clinical trial data, post-approval testing and risk evaluation and mitigation strategies as is required for pharmaceutical drug approval (Table 3). However, biologics are unique because its' manufacturing process is the key vehicle required for characterization rather than its' precise composition. Therefore, by definition, two biologic agents from different production systems can never be identical (12).

		New Drug: Biologic
Product Characteristics/ Non-clnical	Physical Characteristics: molecular weight, primary & secondary structures, etc.	X
	Chemical Characteristics: molecular formula, chemical strucutre	X
	Specifications of drug substance (active ingredient)	X
	stability	X
	purity	X
	consistency of manufacturer of the drug substance	X
	Description of analytical testing performed on the manufacturer's referece standard lot and qualitying lots to characterize the drug substance.	X
	pharmacokinetic/pharmacology/toxicology	X
	studies for absorportion, distribution, metabolism and excretion of the drug in animals	X
Good Manufacturing Practice (GMP)/Quality	Floor diagram of general facility layout	X
	list of all components used in the manufacture (synthesis/isolation/purification) of drug substance, their tests and specification/drug development plan	X
	Rationale for development plan (dosage forms, etc.)	X
	Visual Representation of the manufacturing process	X
	Cell Line Information	X
	In process controls: fermentation, harvesting and downstream processing	X
	Specification/analytical Methods	X
	Container/Closure System	X
Clinical	Bioavailability/bioequivalence studies (very few biologics will have such data)	?
	Description and analysis of each clinical pharmacology study of the medicinal product(comparison of human data with animal data)	X
	Pharmacokinetic & Toxicology Studies	X
	Description and analysis of each controlled clinical study	X
	Clinical Effectiveness for the clinical indications. Evidence for dosage and administration required.	X
	Clinical Safety: studies of assessment of absorption, distribution, metabolism, and/or elimination of drug	X
	Summary of benefits and risks of the medicinal product in its intended use	X
Other	Patent information on any patent that claims the drug	X
	Microbiology	X
	Safety update Reports (four months post NDA's submission)	X

Table3: Regulatory Checklist for New Drug Application for Biologics: The biologic regulatory pathway expands on the small molecule pathway by including good manufacturing practices. Due to the difficulties in analyzing the end product of biologics, bioequivalence and bioavailability tests are not always submitted because they can not be obtained.

Biologics have accounted for 10% of the new molecule entities (NMEs) from the period of 1950-2008 in the US(27). (During this period, ~1200 NMEs were approved in the US). It is important to note that biologics did not enter the market until 1982 (Figure 4).

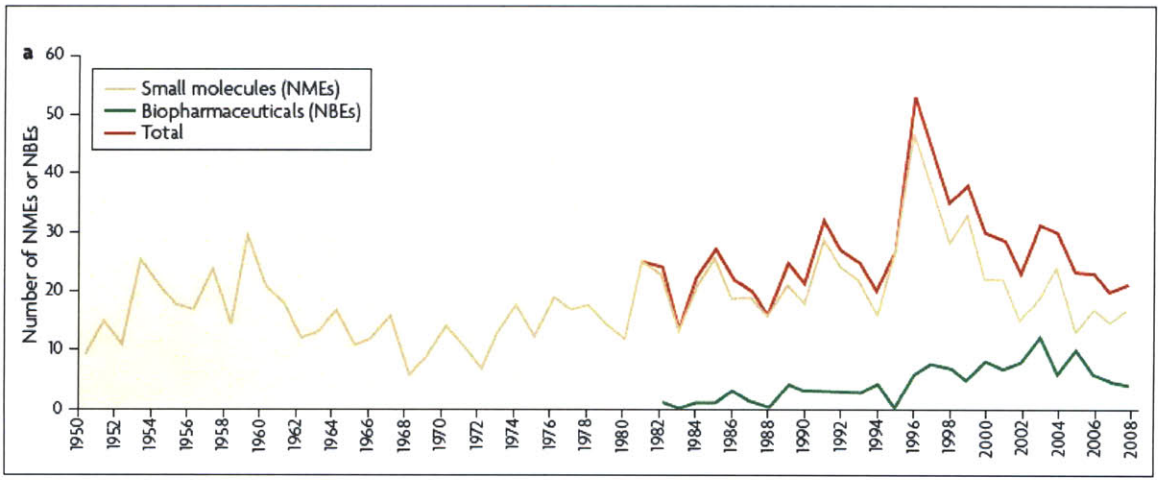


Figure 4: History of New Drug Approval (27): Timeline of approvals of new molecular entities (NMEs) and new biological entities (NBEs) by the US Food and Drug Administration (FDA) between 1959 and 2008.

Biologics are the wave of the future for medical therapies. The pharmaceutical industry is transitioning away from its strategy of small molecule products towards more specialized, secondary care indications with the use of biologic therapies. Biologic sales currently account for $75bn worldwide, with annual growth projections of 15%. Biologics are perceived to be a lucrative industry due to its ability to target unmet needs for life threatening and rare diseases such as cancer, HIV, and rheumatoid arthritis to name a few. With the average biologic costing more than 22x per dose in comparison to pharmaceutical drugs, it has become a lucrative proposition for both entrenched pharmaceutical players and new entrants. In summary, biologic therapies will drive future sales growth because they focus on unmet disease areas, demand a high price point, and incumbents maintain a high barrier of entry due to the difficulty in manufacturing formulation (29,30,31,32). Figure 5 shows the projected growth in biologics therapies.

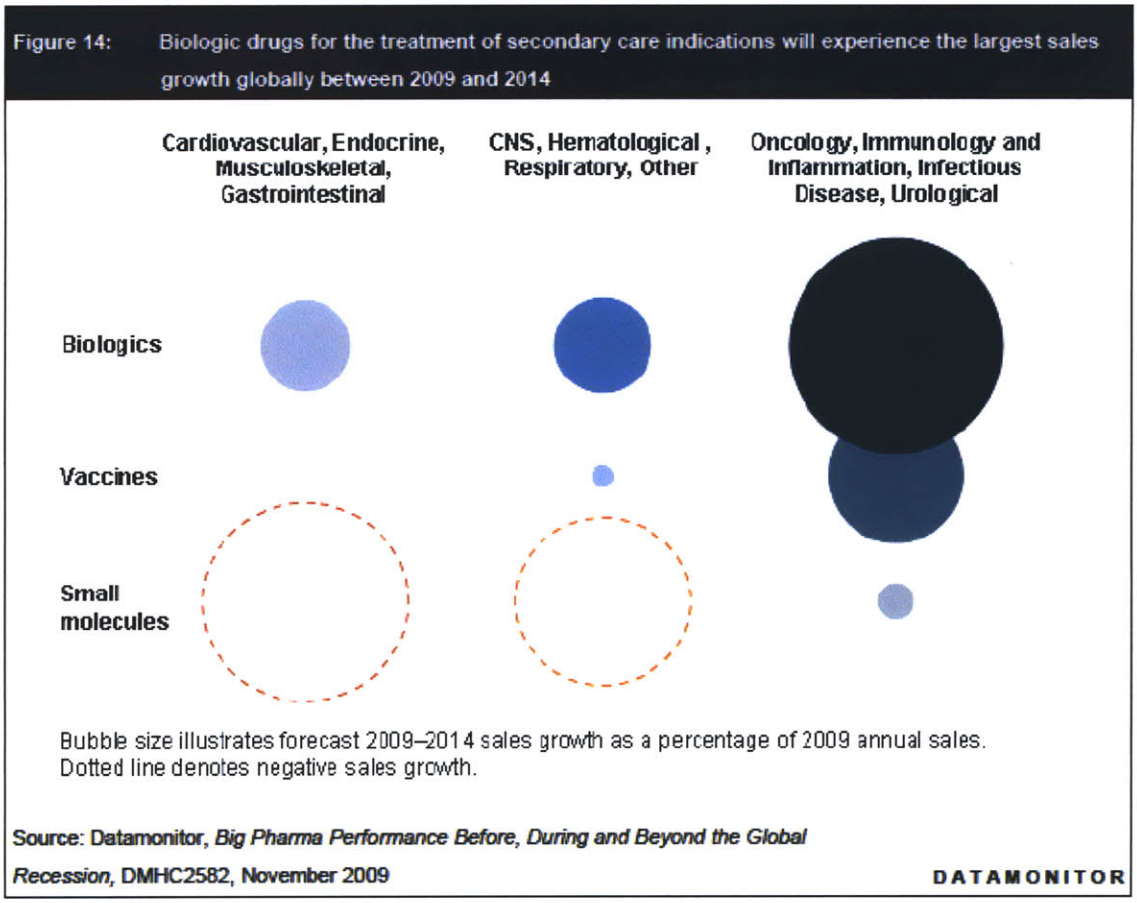


Figure 5: Forecasted Sales Growth for Pharmaceutical/Biologic Drugs from 2009-2014 (29,30,31,32)

Drivers of Biologic Growth

In 2009, 27% of all new drug applications represented biologics (29). Incentives to continue this growth in biologic entrants include the following:

Large Pharmaceutical Focus: Large pharma is facing a loss of sales in the immediate future due to patent expiration of key blockbuster drugs and the healthcare trend away from primary care, small molecule therapy. Biologics market is an expanding market, with a shift in medical practice towards secondary care through use of these high-value biologic therapies. Key therapeutic growth drivers for 2010-2014 include monoclonal antibodies, injectable drugs, and oncology related therapies (29). Therefore, the pharmaceutical industry is seriously exploring the biologics space as an area where they hope to make investments to offset their future profit losses.

Regulatory Incentives: Regulatory bodies such as the FDA and EMEA are encouraging companies to focus on unmet disease areas, also defined as 'orphan drugs', through tax credits, regulatory assistance and the potential to gain access to an accelerated approval system (29,32).

Customer Perception: The hot social topic in medicine is the concept of 'personalized medicine', in which medicines are tailored to individual patients based on their own unique profile. Biologic therapies cater to this increasing social need to take modern genetic and science knowledge to create medications that are applicable to a unique individual and/or population (21).

The Introduction of Biosimilars

Biosimilars, commonly referred to as biogenerics and follow-on biologics, are a biological product that is highly similar to a reference product in terms of safety, purity and potency (24,25). In essence, biosimilars are the generic form of biologics. Biosimilars have the potential to decrease the burden of the high cost of biologic therapies by providing alternatives to the branded products. Given the proven success and overall benefit of generics in the US small molecule industry, why has the adoption of generics biologics been so controversial? This highly debated topic has been on the forefront of medical discussion for the past five years.

Biosimilars are considered a cost-reducing strategy for healthcare systems, therefore providing a great deal of societal value. The U.S. Congressional Budget Office (CBO) estimated that establishing a regulatory pathway for biosimilars would reduce U.S. expenditures on biologics by a stunning $200 million over the period of 2009-2013, and use of biosimilar would create a cost savings of $25bn from 2009-2018 (24). The wave of first generation biologics have, or will, expire prior to 2014, thereby creating a platform for the entrance of biosimilars. The next chapter attempts to decipher the current debate on introducing biosimilars regulation.

Chapter 4: Biosimilar Regulatory Pathway Debate

Biosimilars are debated globally due to many factors including the scientific complexity of biologics, safety and efficacy issues, and lastly political struggles between the incumbents and the generic entrants. The two main opponents in the debate are led by:

- research-based industries, including large pharma and organizations such as the Biotechnology Industry Organization (BIO), US's PhRMA, The European Federation (EFPIA) and Japan's Manufacturers' Association (JPMA
- generic companies, led by Generic Pharmaceuticals Association (GPha) in the US and European Genetic Medicines Association (EGA) (15,16)

The debate is broken down into three main categories; scientific, clinical and political (Table 4).

	Select Key Component	Debate	
		Research-Based Industry (Large Pharma)	Generics
Scientific	Interchangeability/ Substitution	Choice between Patient & Physician. The variations in the clinical impact of biosimilars and its reference product influences the choice of what should be used for medical treatment.	Determined on a product by product basis. However, decision power should be in the hands of the regulatory bodies and not each physician/patient relation.
	Non-proprietary Name	Biosimilars receive a distinct,non proprietary name for safety purposes (issues of pharmacovigilence).	Biosimilars retain name of original product.
Clinical	Clinical Trials	Human Clinical Trials must be mandated to establish that biological product is safe, pure, and potent because it is not the same as its reference product.	Determined on a case by case basis.
	Immunogenicity	Immunogenicity testing required for each indication and postmarketing studies should be required.	Determined on a case by case basis by the regulatory bodies
Political	Data/Market Exclusivity.	14yrs + to ensure an incentive for research-based companies to continue developing innovative biological products.	No market exclusivity, or as minimal as possible to ensure their entrance into the market.

Table 4: Key areas of Biosimilar Debate between Research based Industry and Generics (6)

Scientific Debate: When is "similar" similar enough?

Most of the concerns revolve around the general view of proteins and how to compare the biosimilar with its reference product. Defining what 'similar' means and trying to interpret what tests and analysis need to be performed to demonstrate bio-equivalence will be critical in paving the path for biosimilar entry into multiple markets worldwide. There are two main factors to consider when evaluating biosimilars from a scientific point of view: comparability and substitution/interchangeability (2,37).

Comparability: While considering the R&D and manufacturing for biologics, Professor Charles Cooney at MIT noted that the key question to ask is why would a product fail. In the biosimilar industry, what does it mean for a product to fail? The choice of a reference product becomes critical in understanding the biosimilar and the specifications it must meet. Determining bioequivalence is a difficult task in the biologics space. Not two products (innovator's and biosimilar) will share exact comparability because they are produced by two different manufacturing methods. (Note: The manufacturing process of the reference product is proprietary information, and therefore not disclosed to the biosimilar companies. Biosimilar companies are forced to debated topics is how will regulatory bodies will evaluate comparability without having the manufacturing process details of the reference product. Large pharma is concerned about having to provide their trade secret manufacturing information as well as safety and effectiveness tests to regulatory bodies in order for biosimilars to be fully evaluated.

Substitution/Interchangeability: Since the biosimilar is 'similar' but not identical to its reference product, can it be interchangeable with the same guidelines as pharmaceutical generics? Because of the current limitations of analytical methods and difficulties in manufacturing a consistent product, a biosimilar product cannot be determined to be identical to its reference product. Therefore, in order for interchangeability between the innovators product and the biosimilar, therapeutic equivalence data will need to be provided. However, there is still the debate as to what the equivalence data should consist of. A strong understanding of the structural relationship of a protein will be critical key for regulators to determine bioequivalence. This structural-activity relationship (SAR) plays such a pivotal role in multiple product-quality attributes (Figure 6)(37,39).

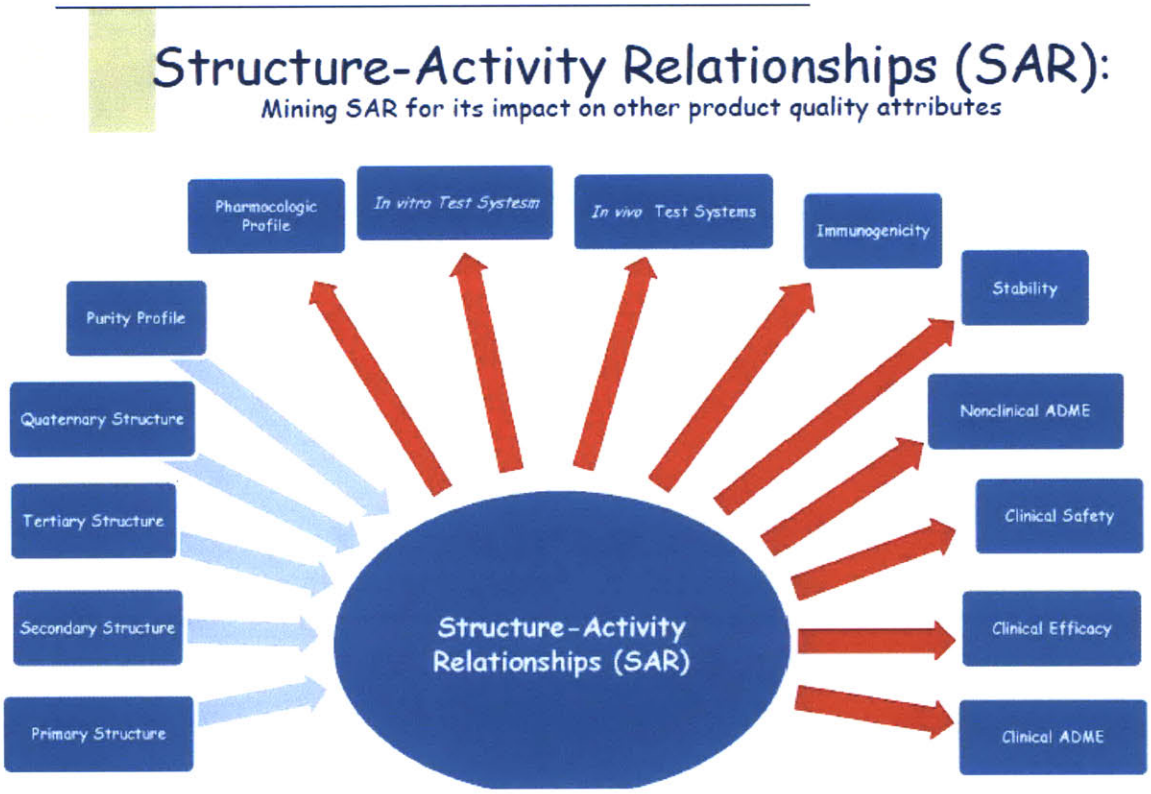


Figure 6: Structure-Activity Relationship as defined by Robert L. Zeid(39)

Table 5 provides a list of the main factors to compare between innovator and biosimilar, and standard industry analytical tools. There is no standard guideline for analytical tools that must be used to characterize proteins, which makes comparisons between proteins extremely difficult.

How to Characterize a Protein	
Main Factors to Compare	Analytical Tools
Is the Amino Acid Sequence the same?	Mass Spec
Does it have the same tertiary (3D) structure?	X-ray Chrystallography, multi-dimensional NMR
Sensitivity/Specificity	Flourescent tricoscopy

Table 5: Main Factors for Characterization of a Protein to determine Bioequivalence between Reference Product and Biosimilar.

Glycosylation: Stumbling Block for Determining Bio-Equivalence

Glycosylation is an example of biologic differences between the innovator and biosimilar that hinder the ability to decipher similarity between the two products. Glycosylation is a form of post-translational modification that causes structural and functional changes in proteins. Glycosylation adds complexity when comparing reference products and biosimilars, and makes characterization extremely difficult. The main issues are that there are no precedents on how to evaluate changes in glycoslyation in the protein, and an understanding of which form of the molecule has the greatest impact on the clinical profile exists. Glycosylation can occur at multiple sites within the molecule. Here are the issues in evaluating glycosylation changes:

- Do companies take the average of glycoslation across the entire molecule?
- Evaluate the glycosylation at each site and look at the percentage change from site to site between the reference product and the biosimilar?

The details of glycosylation and its direct impact to the clinical profile of biologics have not been examined in detail and therefore no actual guidance on how to analyze and evaluate these changes in terms of safety and efficacy are available. Glycosylation is only one of many examples that cause difficulties in understanding the true meaning of the changes between the reference product and the biosimilar. (Appendix A, Interview with William Egan).

Clinical Debate

Since biosimilars are not identical to their reference products, there is consensus that some form of clinical data will need to be submitted to show safety and efficacy. But how much? Will biosimilar companies have to submit a full clinical trial development plan and data (preclinical, phase I, II, III)? This is a challenging question to answer. Even though the physical-chemical profile and differences in biological activity is known between the innovator and biosimilar product, there is still no conclusive knowledge as to how this affects the patient. Therefore, clinical programs need to be in place to determine how safe the biosimilar is and whether or not it has the same indications as its reference product. The size and complexity of these programs will be dependent on the level of understanding and interactions of the protein structure, impurity profile, and other characteristics.

Immunogenicity: Imunogenicity plays a critical role in biological products. Proteins are more likely to engage the immune response than smaller molecules. Therefore, these immune responses can

impact the therapeutic effect of the biologic therapy and has the potential to decrease or block the clinical effect. Research based industries call for biosimilars to provide robust post-marketing studies to regulators, thereby ensuring that there are no adverse events secondary to the immune system that could be potentially life-threatening.

Political Debate: Market/Data Exclusivity

Another contested conversation is the requirement for additional data and market protection beyond the scope of a patent. In the generics market, generic companies favor none to limited data & market exclusivity periods since they are interested in entering the market as quickly as possible. They argue that the cost to the healthcare system increases the longer generics are kept out of the market. However, research-based players (large pharma etc.) state that the long, costly and high risks associated with gaining FDA approval for the innovator product warrants some sort of 'insurance policy' to guarantee it recovers its costs. They argue that patent protection does not offset the extensive cost to bring the biologic to market due to the length of time it takes to meet the regulatory requirements (5,7,14,20). The same arguments seen in the generics market apply to biologics and biosimilars.

From past precedents set by the pharmaceutical generics regulation (Hatch-Waxman Act of 1984), data and market exclusivity have been given to the innovators to ensure the development of new therapeutic products in the future. In the biologics space, the length of time of data exclusivity is being challenged. Research-based companies claim that a 14 year period is necessary where as other more moderate legislation supporting a 5 year market & data exclusivity. Setting a sufficient data and market exclusivity time limit will be critical in maintaining investments in the biologics research while still ensuring biosimilar entrance (5,7,14,20).

Chapter 5: Biosimilar Regulation

Regulatory agents require robust monitoring systems to be in place to evaluate safety and efficacy profiles of biosimilars. However, these agents have struggled with developing regulatory pathways for biosimilars because of the complexity of determining bioequivalence. The risks involved in biosimilars include a higher probability of differences in efficacy between the biosimilar and its original counterpart, and a potential increase in toxicity due to impurities and immunogenicity(28). Scientific technologies with the ability to determine the differences between the reference biologic and the biosimilar do exist. However, as Bob Zeid stated, the main question is what do these differences mean to safety and efficacy? Europe, the US, and Japan have been some of the first movers in the global regulatory landscape to establish biosimilar pathways and develop a rationale for establishing bioequivalence. Below is a comprehensive explanation of these three pathways and how a biosimilar company should address the regulatory requirements.

Europe's Regulatory Guidelines for Biosimilars

The EU has the longest established biosimilars regulatory pathway, with the creation of The European Medicines Agency (EMEA) Biosimilar Regulatory process, enacted in 2005, which is overseen by the Committee for Medicinal Products for Human Use (CHMP). Since its inception in 2005, there has been successful entrance of biosimilars in the following categories: recombinant human growth hormone, epoetin alfa and fligrastim.

The structure of the EMEA approval process is strategically framed to adjust for each individual biosimilar. According to Lorna Brazell esq., the approval process is still fairly new and there are very few past precedents to determine the timescales for development and assessment of biological medicinal products. Therefore, it is still in nature a case-by-case process. There is still uncertainty from both the regulators and companies of what information is needed in respect to a new application based on claimed comparability to a reference product. Since the regulatory body does not mandate specific reference products, each application may introduce a new biologic product as a 'reference product' that has not been used in previous biosimilar applications. Therefore, it will require time before the EMEA has a better understanding of how to determine bioequivalence between two products. The regulatory pathway also allows for continued dialogue between the

biosimilar innovator and the regulatory body to carefully monitor the process, which includes manufacturing process guidelines, pre-clinical and clinical guidelines.

The regulatory approval process functions as follows (Figure 7):

1. Companies submit an application for "Similar Biological Medicinal Products".
2. Companies must prove their biosimilar products demonstrate bioequivalence and pass safety & efficacy tests. The biosimilar producers must choose a reference product. (Refer to Choice of Reference Product pg. 32)(9)
3. Quality Standards: The CHMP guidelines (BWP/49348/2005) provide robust guidelines for quality standards of the biosimilar in the manufacturing process, formulation studies, comparability studies and analytical methods (Refer to Quality Standards pg. 33-34) (11).
4. Non-Clinical/Clinical Issues: Due to the fact that biosimilar are 'similar' to their reference product and not identical, it is crucial to have data on both animal and human reactions to the product. Guidelines are provided under CHMP/BMWP/42832/2005. [Refer to Non Clinical and Clinical Issues pg. 34-36) (10).

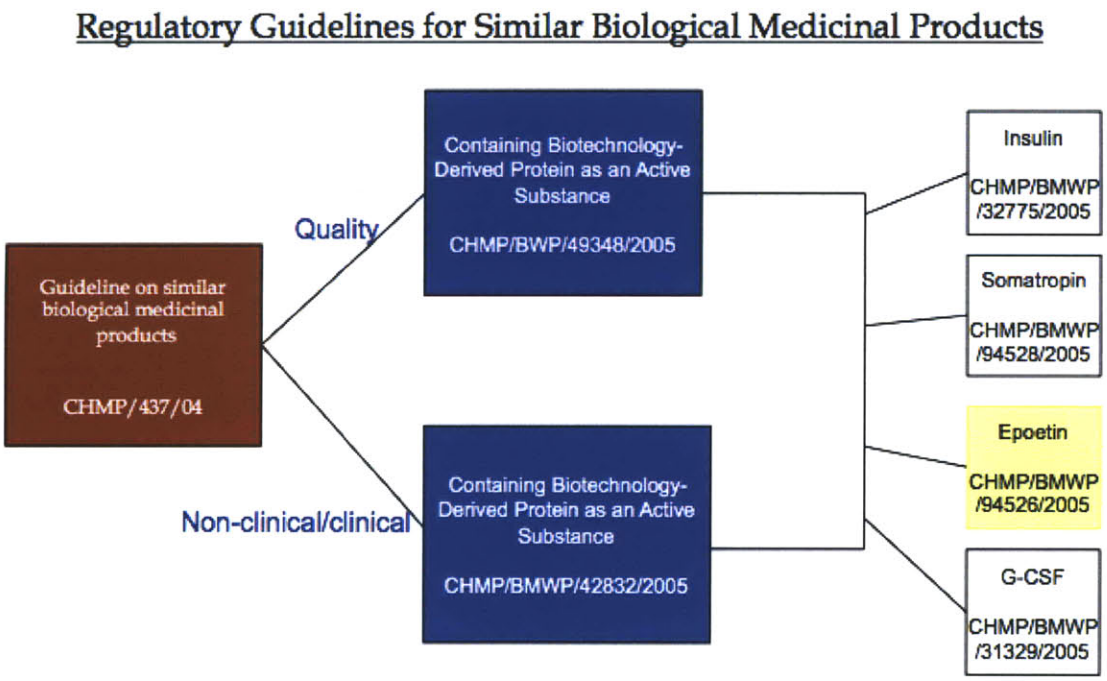


Figure 7: The Regulatory Guidelines for Similar Biologic Medicinal products as instructed by the European Medicines Agency (EMEA)(9,10,11).

Choice of a Reference Product

Choosing a reference product is critical for biosimilar innovators to successfully manuever the regulatory approval process in any market. Specifically in the EMEA, the choice of the comparable reference product is given to the biosimilar innovator. The reference product must already be an approved biologic in accordance with Article 8 of Directive 2001/83/EC (Figure 8)(9). Once the reference product is established, comparability tests including quality, safety and efficacy testing must be completed.

Strict guidelines must be adhered to in regards to the reference product. They include:

- In terms of the molecular nature of the biosimilar, it must have the same active substance as the reference medicinal product.
- Pharmaceutical form, strength and route of administration must be identical.

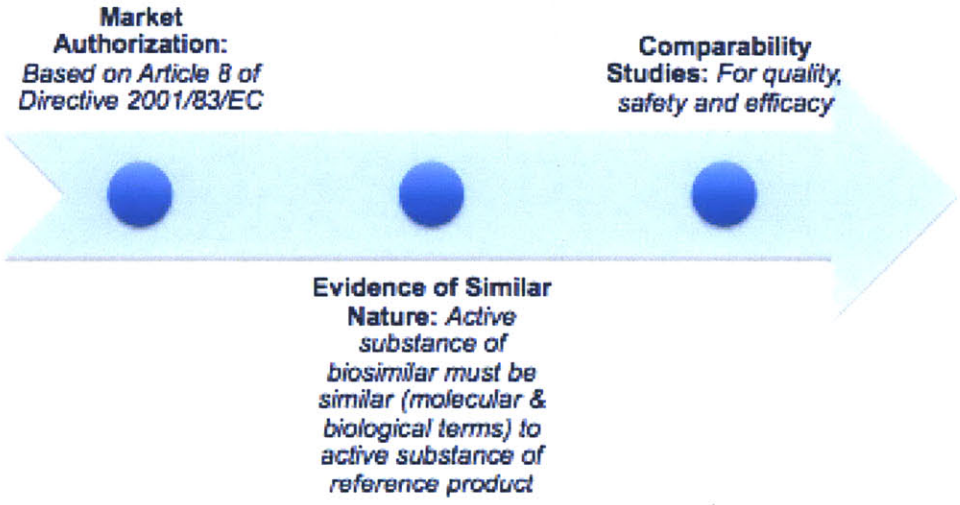


Figure 8: The Three Step Filter Process to Choosing a Reference Medicinal Product(9). First, a biosimilar innovator will have to narrow down its choices of reference products to those that have already gain approval through the biologics new application process in the EMEA (based on Article 8 of Directive 2001/83/EC). Second, the reference product and biosimilar must have the same active substance. Last, comparable tests, both in term of biological analysis and clinical studies, need to be performed to show similarities and differences between the two.

Quality Standards

The EMEA provides quality guidelines throughout the biosimilar development process. The following is a breakdown of the requirements and guidance given for each of the steps.

Manufacturing process: The manufacturing process must be developed and optimized with *state of the art* technology and accumulated knowledge up to the present time of development. The quality of the biosimilar will be defined by the characteristics of the molecule compared to the reference product and the process, and it must demonstrate consistency and robustness throughout the process (11).

Formulation Studies: Studies will need to be conducted to test the formulation of the biosimilar. These studies will need to prove stability, compatibility and integrity of the substance for its indicated medicinal use (Figure 9)(11).

Figure 9(11): Three Deomnstrable Features of the Forumlation Studies: The studies should be able to demonstrate that the proposed formulation is stable, is compatible in regards to excipients, diluents and packaging material and lastly, that the integrity of the substance be maintain in regards to its biology and physico-chemical.

Comparability Studies: Comparability test with the reference product must be conducted and submitted to the EMEA. It is not expected that the quality attributes of the biosimilar and reference product will be identical. However, the biosimilar manufacturer must submit justification for any minor structural differences and/or impurity profile of the two biologics (11).

Analytical Methods: One of the key requirements for generics is its similarity with the branded product. It is critical in the case of biologics that robust analysis is done to evaluate as many different factors to ensure quality of the product. Figure 10 showcases the five main areas that need to be consider while determining which analysis to conduct(11).

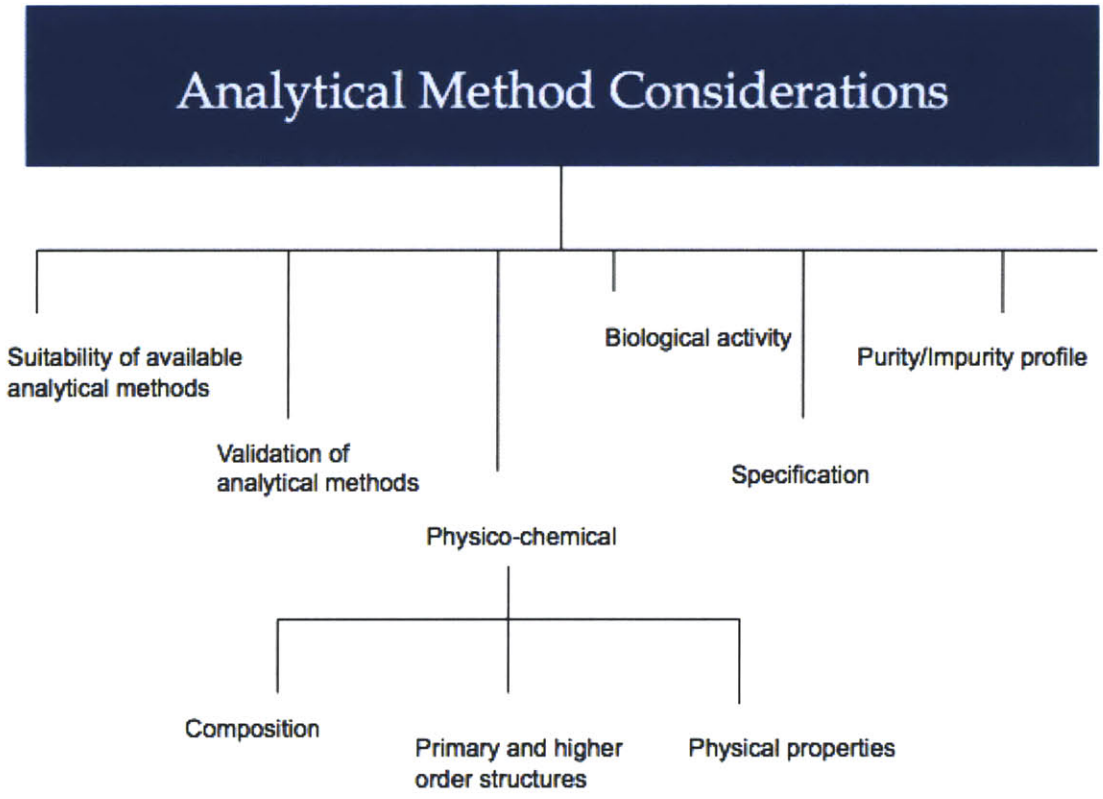


Figure 10: Main considerations on analytic procedures(11)

Non-Clinical and Clinical Issues

Non-Clinical Studies: The purpose of non-clinical studies is to understand the structural components of the product and use this information to detect any possible differences between the biosimilar and the reference product. Some of the key variables that will be monitored in these studies are stability, characterization, toxicology, mechanism of action, absorption, and metabolism. Although the EMEA recommends providing both in-vitro and in-vivo data (Table 6), they grant

biosimilar developers the final scientific decision of what type of assays, animals models, and test would be most sufficient in providing data for safety and efficacy profiles (10).

In Vitro Studies	Require assays such as receptor-binding studies or cell-based assays
In Vivo Studies	Pharmacodyamic and toxicity studies; concern with dose regiment

Table 6: Non-Clinical Studies: In Vitro and In Vivo(10)

Clinical Studies: These requirements are dependent on past knowledge gained through the reference product's experience in clinical trials. It is strongly recommended that the clinical trial strategy be developed with the data from the final manufacturing process, which represents the most robust information on the quality profile of the batches that will be used in commercialization. The clinical comparability studies are a three-step process (figure 11)(10).

Step 1: Design and conduct pharmacokinetic (PK) studies that investigate the dose design (single, steady-state or repeated). Factors for biosimilar companies to be aware of during these tests are differences in half-life, absorption and bioavailability and lastly differences in the elimination characteristics between the two products (biosimilar and reference).

Step 2: Design and conduct pharmacodynamic (PD) studies that demonstrate therapeutic efficacy.

Step 3: Either PK/PD or efficacy studies will be required. Comparative PK/PD studies can demonstrate clinical comparability if the following conditions for the reference product are well characterized: PK, PD, relationship between dose/exposure, and one PD marker is accepted as a surrogate marker that is compared to the dose/exposure of the biosimilar.

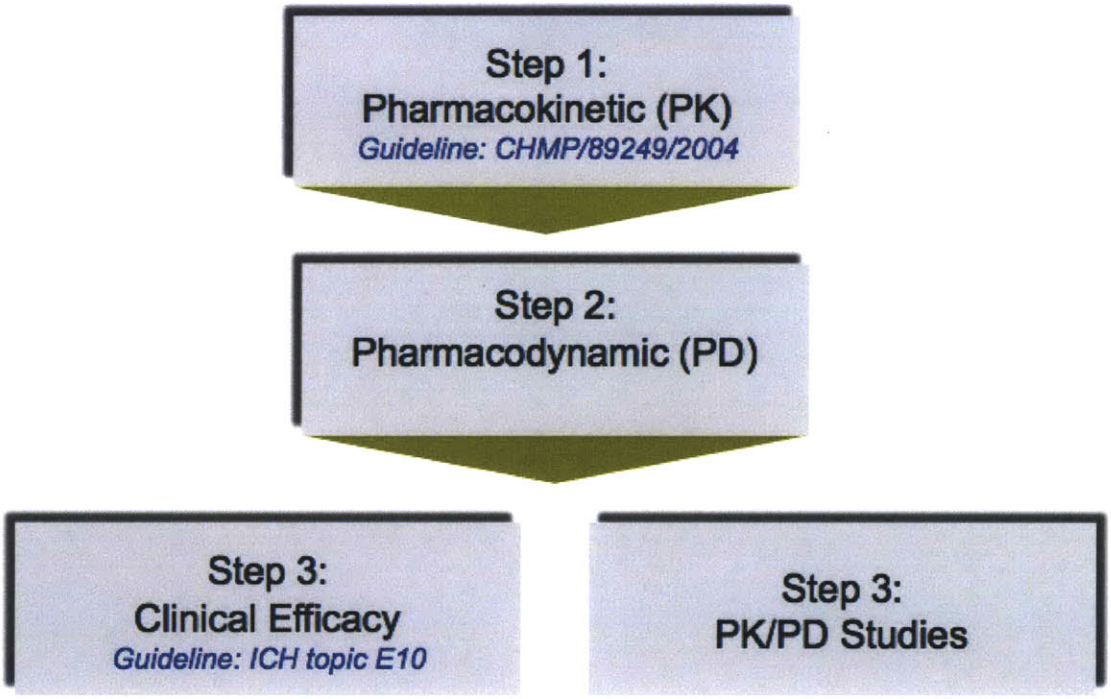


Figure 11: Three Stepwise Comparability exercise(10)

The pre-authorization clinical studies are normally insufficient for all potential differences and adverse effects to be realized. Therefore, to ensure full safety to patients, post-approval phase monitoring will need to be continued and the data collected will be submitted to the EMEA. Biosimilar companies are required to submit a risk management strategy and pharmaco-vigilance plan to the EMEA that maps out the course of action the company will take in the case that potential risks are realized post-commercialization (10).

Immunogenicity: Antibody-Testing Strategy

The immune response against these therapeutic biologics plays a critical role in how safe they are for patients. The immunogenic potential is greatly influenced by multiple factors, including the nature of the active substance, impurities, stability of the product, and route of administration.

The role of immunogenicity needs to be considered in all clinical trial designs, specifically in events such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. Table 7 provides a list of all the factors that need to be considered in the antibody-testing strategy, as directed by the EMEA(9,10,11).

Antibody Testing Strategy	
1	Must use *state of the art* methods
2	Tests must optimize for sensitivity & specificity
3	Screening test must detect low titre and low affinity antibodies
4	Follow domestic and international standard
5	Justify periodicity and timing of sampling for testing of antibodies
6	Require one-year follow up data for pre-licensing

Table 7(9,10,11): Antibody Testing Strategy per EMEA Regulation: Provides six requirements that need to be include in the submission of the antibody testing strategy to the EMEA for biosimilar approval.

Full Regulatory Guidelines as Provided by the EMEA

In the five years since the introduction of biosimilar guidelines in the EU, there has been continuous re-evaluation of the process and introductto determine bioequivalence. Table 8 provides a comprehensive list of the updated CHMP guidelines for each of the biologics product categories. As each new reference product is evaluate for the major bucket categories, new guidelines are introduce to address some of the findings found in that process. The EMEA has categorized biosimilars as follows:

- Biological products containing biotechnology derived proteins as active substances, which cover the first generation biologics (Epo-alfa, G-CSF, recombinant human insulin)
- Immunologicals such as Vaccines and Allergens: These biologics are highly complex, and therefore the ability to characterize at a molecular level may not be possible under current technology norms. The EMEA is will keep a sharper eye on these biosimilar applicants to ensure patient safety.
- Blood or Plasma-Derived Products and their Recombinant Alternatives: Biologics under this category are required to meet stricter safety and efficacy requirements as required for 'new products' due to the complex and variable physico-chemical, biological and functional characteristics of the products.

EMEA Guidelines: Documents to Consult While Considering Submitting a Biosimlar Application	
Guidelines for All Similar Biological Medicinal Products	
Name	**Document**
Development Pharmaeutics for Biotechnological and Biological Products	CPMP/QWP/155/96
Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products	CPMP/ICH/138/95
Guidance on Specifications: Test Procedures and Acceptance Criteria for Biotechnological Biological Products	CPMP/ICH/365/99
Preclinical Safety Evaluation of Biotechnology-Derived Product	CPMP/ICH/302/95
Biological Products Containing Biotechology-Derived Proteins as active Substance	
Name	**Document**
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances Quality Control	CHMP/BWP/49348/2005
Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues	CHMP/BWP/42832/2005
Annex Guidelines: Non clinical & clinical Issues- guidance on products containing Recombinant Human Insulin	CHMP/32775/2005
Annex Guidelines: Non clinical & clinical Issues- guidance on products containing Somatropin	CHMP/94528/2005
Immunologicals such as Vaccines andAllergens	
Name	**Document**
Guidance on Pharmaceutical and Biological Aspects of Combined Vaccines	CPMP/BWP/477/97
Guidance on Cell Culture Inactivated Influenza Vaccines	CPMP/BWP/2490/00
Guidance on Harmonisation of rEqquirements fo Influenza Vaccines	CPMP/BWP/214/96
Points to Consider on the development of Live Attenuated Influenza Vaccines	CPMP/BWP/2289/01
Guidance on Allergen Products	CPMP/BWP/463/97
Note for Guidance on Clinical Evaluation of New Vaccines	CPMP/EWP/463/97
Blood or Plasm-Derived Products and Their Recombinant Alternatives	
Name	**Document**
Note for Guidance on Plasma-Derived Medicinal Products	CPMP/BWP/269/95
Note for Guidance on the Clinical investigation of Human Normal Immunoglobulin for Subcutaneous and Intramuscular use	CPMP/BPWG/283/00
Note for Guidance on the Clinical Investigation of Human Plasma Derived Factor VIII and IX Products	CPMP/BPWG/198/95
Note for uidance on the clinical Investigation of Recombinant Factor VIII and IX Products	CPMP/BPWG/1561/99
Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous and/or Intramuscular Use	CPMP/BPWG/575/99

Table 8: A comprehensive list of the published EMEA guidelines for biosimilar development and manufacturing for submission for approval(8,9,10,11). For full viewing of the guidelines, refer to ww.emea.europa.eu.

Case Study: Human Erythropoietin

Epoetin-Alfa is a biologic that has had successful biosimilars counterparts. A thorough analysis of the molecule and path to market through these newly created biosimilars regulatory pathways is provided below.

Background of Epo

The discovery of erythropoietin, or commonly referred to as Epo, occurred in the nineteenth century through observations of blood viscosity of individuals living in high altitude climates. It was later proposed by Friedrick Miescher that erythropoietin directly stimulates the production of red blood cells (RBCs) by the bone marrow. Since these early observations, it has been confirmed that this hormone, Epo, is produced in the kidneys and plays an integral role in the production of RBCs. Epo is a glycoprotein that consists of 165 amino acid with a molecular weight of 34,000.

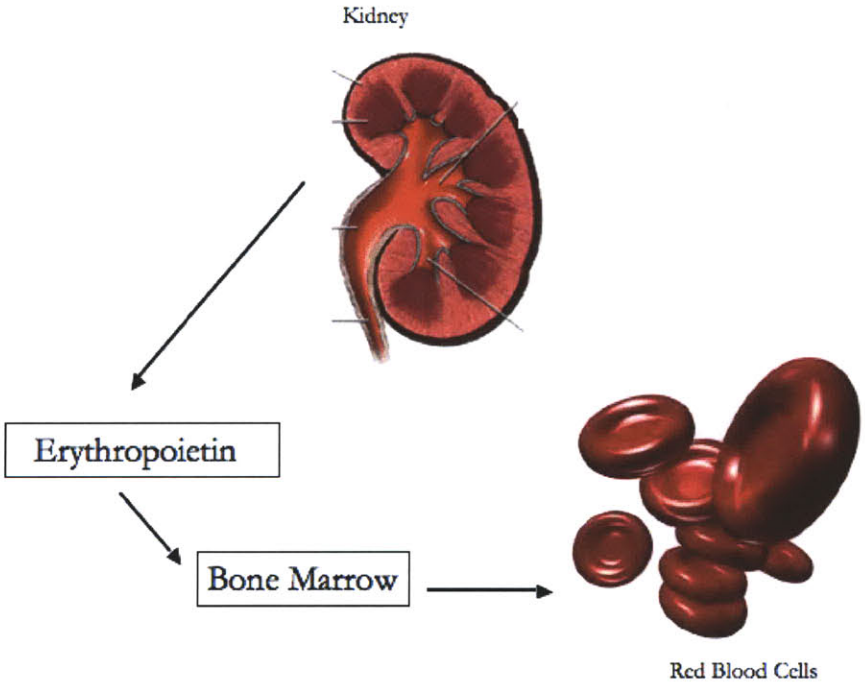


Figure 12: Erythropoietin Production Pathway: The hormone erythropoietin is produced by the kidneys. It stimulates the bone marrow to produce red blood cells.

Epo's therapeutic advantages are critical in the treatment of anemic patients. Anemic patients are deficient in an adequate number of red blood cells, and therefore respond to Epo by stimulating the

molecular mechanisms of the production of RBCs. From its initial discovery, Epo's clinical uses have increased to include the treatment of the following:

- Individuals with low hematocrit or hemoglobin counts
- Allogeneic blood transfusion patients: The administration of Epo reduces transfusion requirements. For example, the introduction of Epo to autologous blood in a pre-donation program can increase the yield

Overall, the introduction of Epo into medical strategies have increased the quality of life for patients affected by low RBCs(1,8).

Amgen was the first mover in the therapeutic development of (darb)epoetin-alfa, bringing its first generation branded product Epogen, followed by Aranesp to market in 2001. The mechanism of action for Aranesp is that it stimulates erythropoiesis by the same mechanism as endogenous erythropoietin. It is indicated for anemia with chronic renal failure and metastasis non-myeloid malignancies due to chemotherapy. Since its initial introduction by Amgen, the market has been dominated by three major players; Amgen, Johnson & Johnson and Roche (Table 9). Amgen developed and out-licensed the European rights to Johnson & Johnson, and co-marketed the drug as Procrit in the US. Roche's Mircera, introduced in 2007, is a longer lasting product in comparison to Aranesp and requires monthly administration (1).

Development and marketing of epoetin in the US and Europe, 2009

Product	US market	European market
Epoetin alpha	Procrit (Johnson & Johnson) Epogen (Amgen)	Eprex (Johnson & Johnson) Not marketed
Epoetin beta	Not marketed	NeoRecormon (Roche)
Darbepoetin alpha	Aranesp (Amgen)	Aranesp (Amgen)
Pegylated epoetin beta	Mircera (Roche)*	Mircera (Roche)
Epoetin delta	Not marketed	Dynepo (Shire)

* yet to launch

Source: Datamonitor DATAMONITOR

Table 9: Key Leaders in the Epoetin Market, European and US(29): Amgen, Johnson & Johnson, and Roche are the three key players in both the US and European market with their products respectable Aranesp, Procrit/Eprex, and Mircera.

Story of a Successful Biosimilar Epo-Alfa: Binocrit

The EMEA approval of Binocrit, a biosimilar Epoetin-alfa , is an example of the successful introduction of biosimilar through the newly formed regulatory pathway. Binocrit, HX575, was approved on the 28th of August 2007. It underwent the recently published EMEA guidelines, which required an application submission for "Similar Biological Medicinal Products" and strict adherence to the clinical development program guidelines on recombinant erythropoietin. Binocrit was compared against its reference product, Eprex, a J&J marketed therapeutic. Eprex is the European branded name for the US products, Epogen and Procrit. Binocrit received the same indication as Eprex, which allowed for its use in the treatment of anemia associated with chronic renal failure in pediatric and adult patients on peritoneal dialysis. The standard method of treatment for Binocrit is by injection using pre-filled syringes containing 1000-10000 IU of epoetin alfa(8).

The data points required by the EMEA for Binocrit to gain approval were as follows:

- Justification based on biosimilar concept: Binocrit is identical in its primary structure to the endogenous human erythropoietin. In developing binocrit, it is produced in Chines Hamster Ovary Cells, or commonly referred to as CHO cells.
- Biosimilar PK/PD data on Binocrit
- Studies that showed equivalent efficacy and safety data

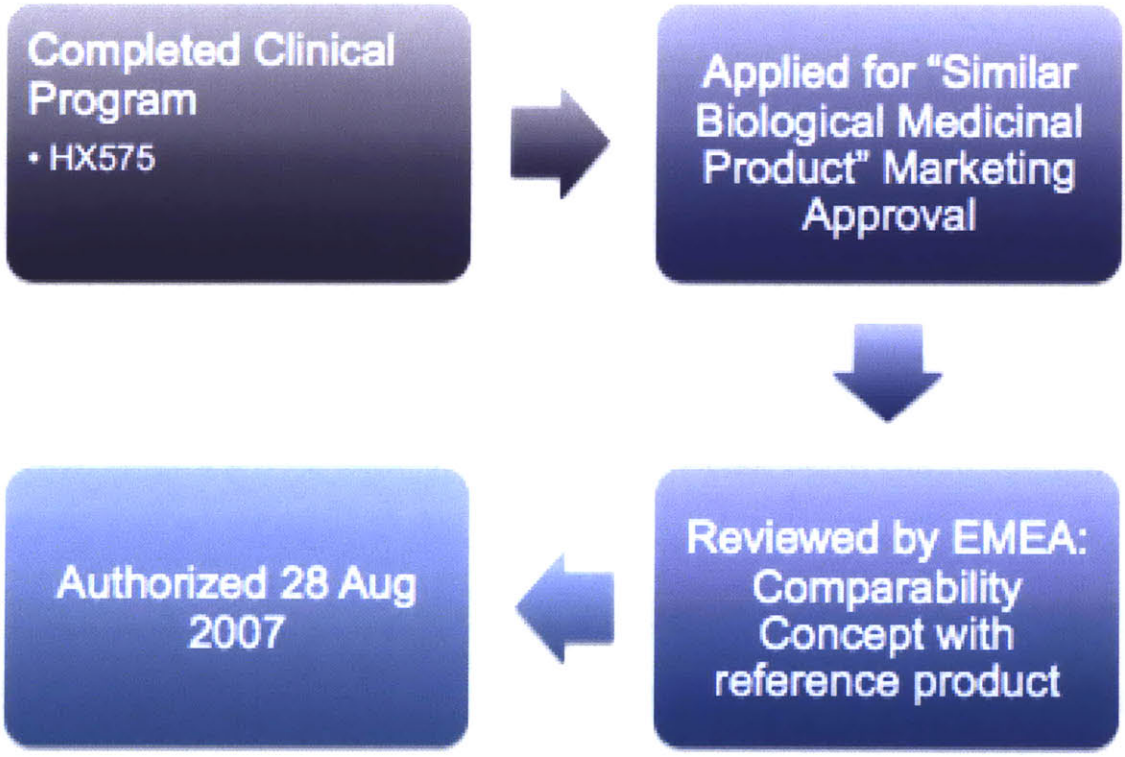


Figure 13: Binocrit Regulatory Application Process in the EMEA(8)

Binocrit is a highlighted example of the first successful biosimilar Epoetin-alfa that was introduced to the European market. Figure 13 provides Binorit's path to market. As Table 10 indicates, in the past five years since the introduction of biosimilar guidelines, there have been six successful biosimilar entrants including a second Epo-alfa biosimilar, Retacrit. Retacrit was developed from a joint collaboration of Stada and Hospira. Retacrit is also an Epo-alfa that was referenced against Eprex and introduced to the biologics market in December of 2007(4).

Table 5.5 Biosimilar Approvals by the EMEA, 2006-2009

Drug Type	Product	Reference Product	Development Companies	Date of EMEA Approval
Growth hormone	Omnitrope (somatropin)	Genotropin (Pfizer)	Sandoz	April 2006
	Valtropin (somatropin)	Humatrope (Eli Lilly)	LG Life Science/ BioPartners	April 2006
Erythropoietin	Binocrit/Epoetin Alfa Hexal/ Abseamed (epoetin alfa)	Eprex/Erypo (Johnson & Johnson)	Sandoz/Medice	August 2007
	Silapo/Retacrit (epoetin zeta)	Eprex/Erypo (Johnson & Johnson)	Stada/Hospira	December 2007
CSF	Tevagrastim/Ratiograstim/ Filgrastim Ratiopharm/ Biograstim (filgrastim)	Neupogen (Amgen)	Teva/Ratiopharm/ CT Arzneimittel	September 2008
	Zarzio/Filgrastim Hexal (filgrastim)	Neupogen (Amgen)	Sandoz	February 2009

Table 10: Approved Biosimilars in the European market (4). There are two growth hormone biosimilars, Omnitrope and Valtropin, both introduced in April of 2006. The next biosimilars to be approved were Epo-alfa candidates, Binocrit and Silapo, respectably in August 2007 and December 2007. More recently, G-CSF candidates such as Tevagrastim and Zarzio were approved.

US's Regulatory Guideline for Biosimilar

On March 23, 2010, a monumental healthcare reform bill was passed in the United States Congress that hoped to curb healthcare costs and grant more Americans access to much needed care. As part of this bill, an abbreviated regulatory pathway for biosimilars (Biologics Price Competition and Innovation Act of 2009) was finally defined; significantly late in comparison to its European counterparts (2). One of the key hindrances for the US in developing its regulatory strategy for biosimilars was having to navigate the murky waters of the different opinions of the stakeholders. These stakeholders include the FDA, Congress, innovators, generic companies (Biosimilar entrants) and payers. Table 11 provides the key outcomes for each of the stakeholders with the passing of the US's biosimilar pathway (33).

Key Players	**Role/Agenda**
FDA	With the passing of the Healthcare Reform Act, the FDA will need to put in place a pathway for biologics in the near term. They have committed a budget of $5.7 million in 2011 to develop drug review standards and other necessary preparations. This will include developing the abbreviated guideline for biosimilars.
Congress	Passed the *Health Care and Education Affordability Reconciliaton Act of 2010* on March 23, 2010, which included *The Biologics Price Competition and Innovation Act of 2009*.
Innovators	Previously were lobbying against the introduction of biosimilars and a regulatory pathway. Innovators protected with extended branded exclusivity given for 12 years. Most recently, more innovators are commiting to engaging in the biosimilar market including Eli Lilly, Merck, and Astrazeneca.
Generic Companies	Previously were lobbying US government and FDA for an appreviated regulatory pathway for biosimilars. Engaged in M&A activityand collaboration efforts with large Pharma (including Sanofi Aventis, Pfizer,etc.) to bring biosimilars to market. Have found that biosimilar R&D developed, coupled with pharma's large scale manufacturing knowledge and marketing penetration is critical to success in this space.
Payors/Reimbursement	The Centers of Medicare and Medicaid will dictate the billing code for biosimilars. At entry, the biosimilars will most likely receive the same billing code as its reference brand. This could be potentially positive for the uptake of biosimilars, since initially physicians will receive a higher selling price based on the current systems's Average Selling Price (ASP) system. This may be negative if the branded companies raise their price, thereby maintaining the ASP, to allow for physicians to continue prescribing their brand.

Table 11: Key Stakeholders in the Biosimilar Regulatory Landscape(20,21,33)

Key Outcomes of The Biologics Price Competition and Innovation Act of 2009

The Biologics Act provided a strict definition of a biosimilar, which is 'a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and reference product in terms of the safety, purity and potency' (2). Based on this legislation, the FDA can accept, review and approve license application for biosimilars through a newly formed administrative office within the Office of New Drugs. Dr. Leah Christi was appointed in May, 2010 as the Acting Associate Director for Biosimilars and will lead the effects to implement a biosimilar regulatory pathway. The current regulatory pathway that has accepted biosimilar applications, 505 (b), will be slowly phased out to allow for the biosimilar regulatory pathway (currently still in development) to be the gold standard (Figure 14). Reference products are once again chosen by the biosimilar company, however the FDA mandates that the reference product must be both approved and distributed in the US. (This differs from the EMEA standards, which only require that the reference product be approved in the EMEA).

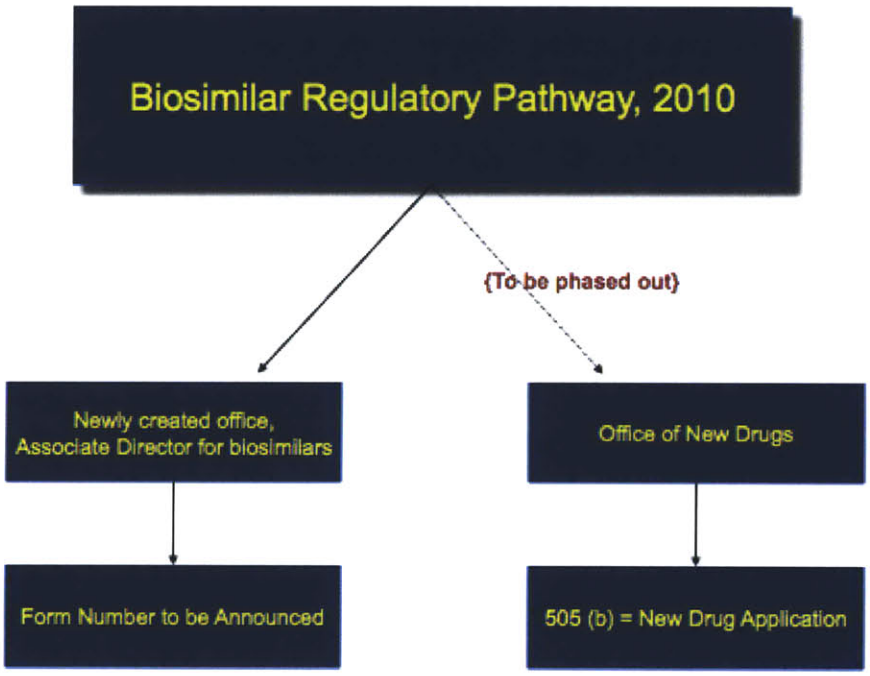


Figure 14: US Regulatory Pathways for Biosimilars: Prior to 2010, Biosimilars were applying through the New Drug Application (NDA) 505 (b) pathway. This pathway allows for submission of new molecular entities and drugs that had changes to previously approved drugs. Biosimilars fit both of these categories. With the introduction of the Biologics Price Competition and Innovation Act , a new office has been created under the direction of Dr. Leah Christi that will implemented a biosimilar regulatory pathway and all administration required for regulatory approval.

One of the major topics of discussion that the new biosimilar legislation tackled is the concept of interchangeability. In order for a biosimilar to be interchangeable with its reference product, it must meet the following three criteria:

1. Through analytical methods, it is established to be a biosimilar to the reference product.
2. It has the same clinical results as the reference product in any given patient.
3. The risk in terms of safety or diminished efficacy in alternating or switching between use of the biological and reference product is not greater than the risk of using the reference product without such alteration or switch.

The concept of interchangeability is still being debated. The question remains, can a biologic, especially a complex biologic, be determined to be interchangeable with today's technology? According to Dr. Janet Woodcock, former Chief Medical Officer of FDA, the answer is no. Technology does not allow us to be able to predict the clinical comparability, which is dependent on an understanding of the structural characteristics of a protein and its function. Even with the leaps and bounds science has made in understanding the complexity of biologics, and innovated technology that has been developed to tackle these complexities, science has not yet reached a point to adequately determine these differences and understand what it means from a clinical sense (2).

The main problem of the new pathway is that it creates a wide range of uncertainty as to what criteria needs to be met in order to gain approval. Biosimilar companies will need to meet with FDA regulators during their initial formulation of a biosimilar development strategy to get a firmer understanding of how to proceed forward at this time. The reality of the situation is that the FDA is in the learning process of taking the biosimilar legislation and translating it into a functional regulatory pathway (2,37). Figure 15 outlines the key stumbling blocks for biosimilar companies in navigating the US regulatory space.

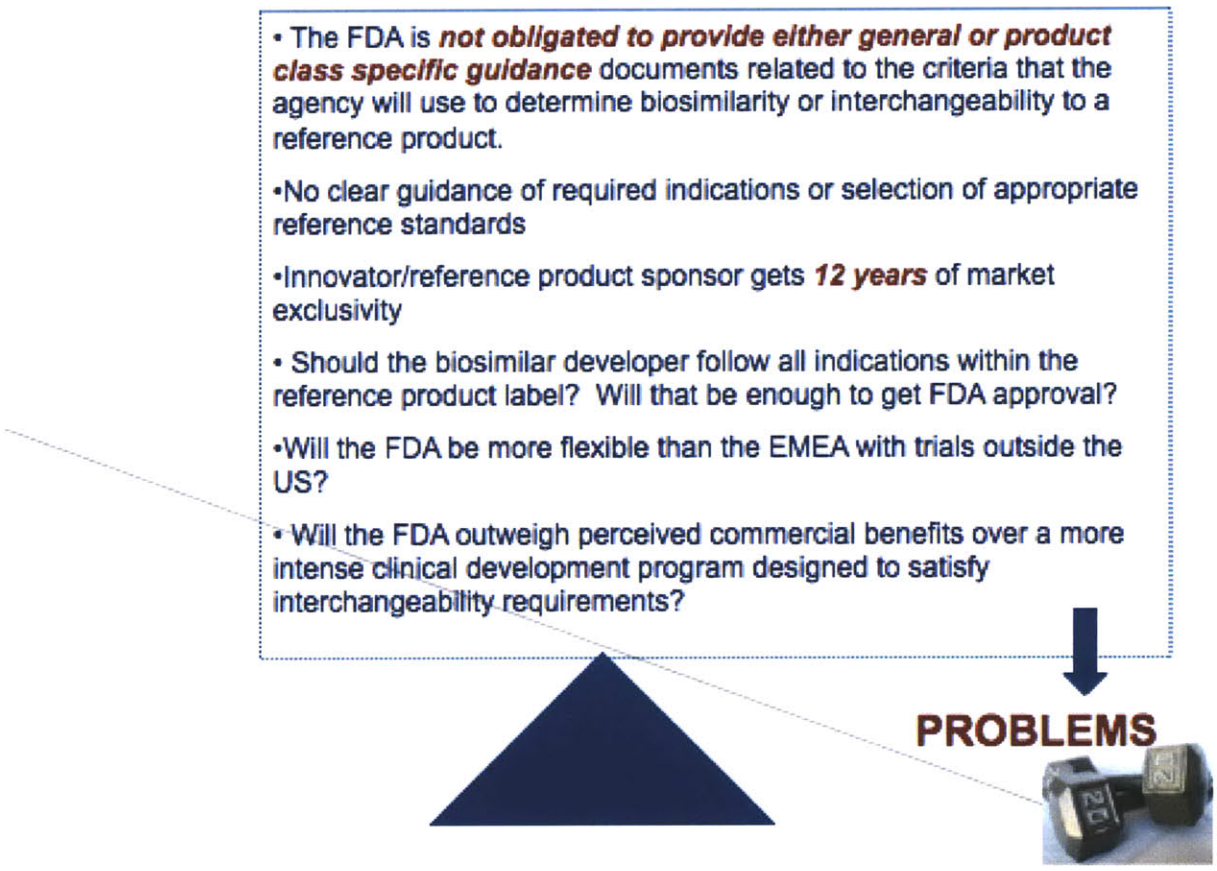


Figure 15: Problems with the 2010 US Biosimilar Regulatory Legislation(2): Concerns arise due to the vague language and lack of specific guidelines for biosimilars to follow to ensure approval. Additionally, the biosimilar companies will be disclosing much of their proprietary information since they will have to engage the FDA throughout their development process to ensure approval and will have to wait a significant time interval (12 years) for the innovator's market exclusivity period to end.

Key Pointers to for Biosimilar Companies to be Successful in the US

As a company interested in pursuing a biosimilar path, the key to success will be continued dialogue with the FDA regulators as early in the process as possible. Providing full transparency and creating a collaborative atmosphere with the FDA in the development strategy of biosimilar manufacturing and non-clinical/clinical tests will prevent rejection due to insufficient data or testing.. It is crucial for companies to plan for optimal timing in their conversations with the FDA. Those companies that already have successful biosimilars outside the US should research what additional requirements are needed for approval by the FDA. Those in the early stages should engage the FDA in their biosimilar development planning to obtain feedback on their choice of reference product to quality

and clinical design. They key stages at which biosimilar companies should get feedback from the FDA is outline in Figure 16. This is in alignment with the nature of the biosimilar development plan. The US guidelines are very vague, and therefore it will be in the best interest of biosimilar companies to keep in close contact with the regulators throughout the biosimilar development process(2,12).

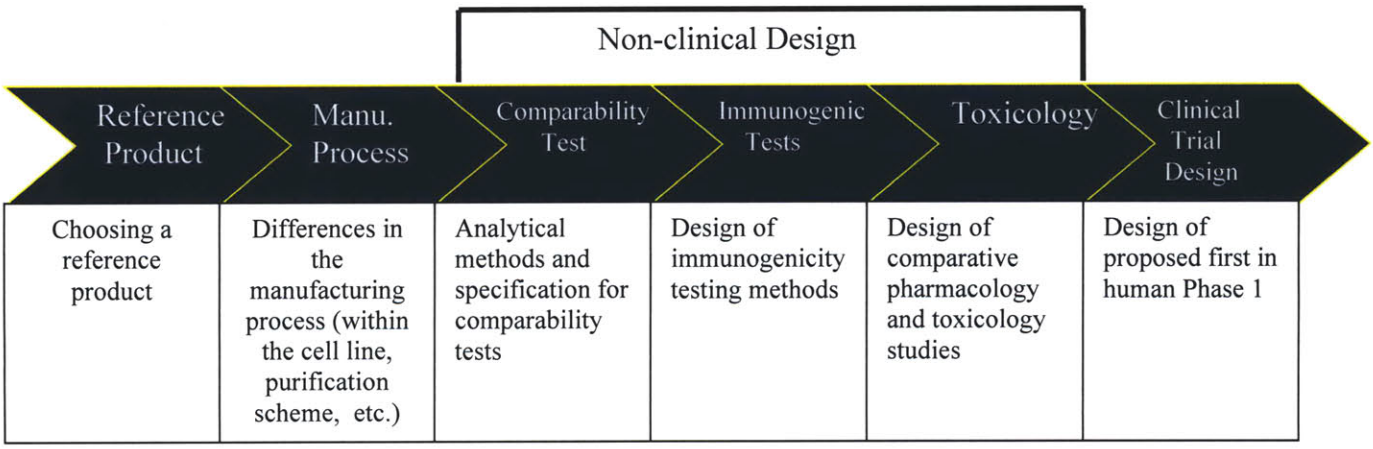


Figure 16: The Six Topics to Discuss with the FDA(2): Due to the lack of specifics of the current biosimilar pathway in the US, it will be critical to engage with the FDA throughout the biosimilar development process and get feedback on data from the manufacturing phase, non-clinical and clinical phases.

Japan's Regulatory Guideline for Biosimilar

In March 2009, Japan's regulatory agency, PMDA, issued a final guidance for biosimilar approval. It was second behind the EMEA to provide vigorous guidelines for biosimilar companies interested in entering the Japanese market. However, it matched its predecessors in developing a guideline that allowed for flexibility to incorporate evolving science technology and openness to industry wishes while still maintaining public safety as its number one concern (15,16,28,30). Table 12 provides the Japanese regulatory checklist for biosimilar entrants.

Japanese Regulatory Checklist for Biosimilar Entrants			
Steps	Action Required	Description	Checked
Step 1	Manufacturing Guidelines		
1a	Manufacturing Process Development Plan	Develop plan based on prior knowledge. Need to site previous cases with significant glycan heterogeneity, established manufacturing processes and characterization results.	
1b	Characterization	Need to address structure analysis, physicochemical properties, and bioactivity	
1c	Drug Product Design		
1d	Stability Testing	Stress and acceleration testing required	
Step 2	Reference Product Studies Guidelines		
Step 3	Evaluation Studies of Bio-equivalence and Quality-Equivalence		
3a	Types of Comparative Studies		
3ai	Structural Analysis and Physicochemical Properties	Evaluation of impact of varation in heterogeneity from higher order structures of posttranslational modicification. Compared to results from bioactivity, in vivo kinetics and immunologic properties results.	
3aii	Bioactivity	Required to conduct in vivo bioactivity studies	
3aiii	Immunologic Response		
3b	Specifications and Test Procedures		
3c	Non-Clinical Studies		
3ci	Toxicology	Provide report on toxicity of antibodies - are they neutralizing? What are the new pharmacokinetics? Impurity profie required	
3cii	Pharmacological Studies		
Step 4	Clinical Studies Guidelines	Required because of difficulty proving bio-equivalence through biological analysis. Results of PK/PD studies will determine length & number of clinical trials required.	

4a	PK/PD studies (Pharmacokinestic and Pharmacodynamic)	Verify pharmacokinetic bio-equivalence and compared to reference product	
4b	Comparison of Clinical Efficacy	To validate efficacy and safety of biosimilar on humans. To demonstrate bio-equivalence/quality-equivalence	
4c	Verification of Clinical Safety	Further studies of immunogenicity. Power study to be able to see results of impurity profile.	
Step 5	Post-marketing Surveillance		
	Patient follow up	Post immunogenecity studies	

Table 12: The Five Requirements for Biosimilar Approval through the Japanese Regulatory Agency(28): The first step is the manufacturing guidelines, which requires a strict adherence to the manufacturing process plan and gaining structural knowledge on the biosimilar. The next step 2 and 3 is doing comparative non-clinical studies with the reference product. The step 4 is the clinical trial design. Last, Japan's regulatory agency requires post-marketing data.

Successful Biosimilar Entrants in the Japanese Market

Japan has seen the introduction of two biosimilars in the past year: the introduction of Omnitrope (somatropin) and an epoetin alpha. The biosimilar epoetin alpha was developed through a collaboration between Japan Chemical Research (JCR) Pharma and Kissel in January 2010 (15,16,30). As of yet, no officiall data has been released to show the market up take of these biosimilars. However, the regulatory pathway in Japan has successfully provided guidelines that enable biosimilar products to enter the market.

Commonalities among all the Regulatory Pathways

The EMEA, FDA and PMDA have all committed to biosimilar guidelines to allow biogenerics in the market. Although each pathway differs in its requirements, there are a few common threads among all three.

It is a learning process for all regulatory agencies. Biologics are extremely complicated and defined by the manufacturing process rather than the components of the molecule. Since this is a new venture for all the regulatory agencies, there is a 'learn by experience' philosophy on how to determine bioequivalence and what data points are required to make these conclusions.

Patient safety comes first. All the regulatory agencies have been conservative and cautious in their approach to giving full entrance to biosimilars. The concerns of variations in clinical profile and immunogenicity have caused regulatory bodies to not automatically grant interchangeability between the reference product and the biosimilar.

Clinical tests will be required. Noting the above, clinical test will be required to ensure that it is safe within the patient population and that it behaves in the same manner as its reference product.

Chapter 6: Discussion

Returning to the main thesis questions, it can be confidently stated that in the major global markets there is a regulatory path for biosimilars. Taking into considerations all the different variations in the market specific regulatory pathways, the biologics and biosimilars requirements are outline in Table 8. There is continued debate as to the test requirements for biosimilars and what the results will need to be in order to gain interchangeability status. These debated topics are highlighted in Table 8.

		New Drug: Biologic	Generic: Biologic
Product Characteristics/ Non-clinical	Physical Characteristics: molecular weight, primary & secondary structures, etc.	X	X
	Chemical Characteristics: molecular formula, chemical strucutre	X	X
	Specifications of drug substance (active ingredient)	X	X
	stability	X	X
	purity	X	X
	consistency of manufacturer of the drug substance	X	X
	Description of analytical testing performed on the manufacturer's referece standard lot and qualitying lots to characterize the drug substance.	X	X
	pharmacokinetic/pharmacology/toxicology	X	X
	studies for absorportion, distribution, metabolism and excretion of the drug in animals	X	X
Good Manufacturing Practice (GMP)/Quality	Floor diagram of general facility layout	X	X
	list of all components used in the manufacture (synthesis/isolation/purification) of drug substance, their tests and specification/drug development plan	X	X
	Rationale for development plan (dosage forms, etc.)	X	X
	Visual Representation of the manufacturing process	X	X
	Cell Line Information	X	X
	In process controls: fermentation, harvesting and downstream processing	X	X
	Specification/analytical Methods	X	X
	Container/Closure System	X	X
Clinical	Bioavailability/bioequivalence studies (very few biologics will have such data)	?	?
	Description and analysis of each clinical pharmacology study of the medicinal product(comparison of human data with animal data)	X	?
	Pharmacokinetic & Toxicology Studies	X	?
	Description and analysis of each controlled clinical study	X	?
	Clinical Effectiveness for the clinical indications. Evidence for dosage and administration required.	X	?
	Clinical Safety: studies of assessment of absorption, distribution, metabolism, and/or elimination of drug	X	?
	Summary of benefits and risks of the medicinal product in its intended use	X	?
Other	Patent information on any patent that claims the drug	X	X
	Microbiology	X	X
	Safety update Reports (four months post NDA's submission)	X	X

Table 13: Regulatory Checklist for Biologics and Biosimilars

Do biosimilars create value to the healthcare system? Absolutely! The key driver for success of biosimilars and decreasing costs is that they capitalize on past biologic experience. It is agreed upon by both parties (research-based industry and generics) that biosimilars contribute to cost-savings in the following areas:

Prevention of Failed products: Biosimilars have a 'blueprint' that was created by the reference/innovator's product experience for the entire process including R&D, manufacturing protocol, clinical trial development and data, and marketing/sales. Therefore, the risks associated with failing at different milestones during the development phase are significantly decreased, if not obsolete. Therefore, biosimilars add insurance for developers that their investment will not carry the high risks that are usually associated with biologics. The cost associated with failed products can reach the **upward limits of $1.5bn** if taken through phase 111 trials, which is the average cost of new biologics in 2005(37). The success of a new biologic passing a clinical trials is still relatively low, ranging 11.5%-21.5% (37).

Time: The majority of time is spent in the development process, and trial and error approach to innovation. The average innovative biologic product takes 10-20 years to develop. Biosimilars are decreasing this timeline by at least half! The biosimilar savings from eliminating failed products and decreasing time to market represents in the upward range of 80% of the overall total cost of biologics.

The areas that are still debated are how much clinical trial data will be needed to ensure safety and the issue of interchangeability and substitution. More emphasis is being placed on these two areas than is realistically justified.

Clinical Trials: From the perspective of the generics companies, they are trying to avoid the additional cost involved in clinical trial studies. Cost savings for generic companies occur in R&D expenditure (or lack thereof), and an abbreviated timeline. Therefore, the ' additional cost' argument of having to do clinical trials, which their counterpart generics in the pharmaceutical industry avoid, is trivial. The need to provide confidence to the regulatory agencies that their biosimilar product is safe for public use appears to outweigh the cost argument.

Interchangeability/Substitution: In terms of interchangeability/substitution, opponents claim that the current science technology does not support automatic interchangeability or substitution. They also state that variations in immunogenecity are too great of a risk to allow for interchangeability. These once again are faulty roadblocks that are being used to prevent branded biologics from losing their market share and high margins. First, within the original reference products are variations in compositions that occur from one batch to another. This is inherent in the making biologics. Recent advancement in biologic analytical tools allow for a robust understanding of the molecular composition of these complex molecules. According to Dr. Martin Schiestle from Sandoz and additional respected members of the science community (Refer to Appendix A), 'the regulatory bodies have created approval processes for biosimilars and rigorous comparatives testing at all stages of development that provide a sound scientific basis for interchangeability' (16). In other words, we have the information to allow for pharmacist to interchange between branded and biosimilars drugs comparable to that for small molecules and their generic counterpart.

A question to ask while discussing interchangeability is why do biologics continue to be evaluated through a process driven method instead of a product driven method. As discussed earlier, historically biologics were too complicated and the molecular & cell biology was poorly understood to be able to evaluate with confidence the originator and generic product. However, as modern technology has evolved to be able to characterize biologics, regulators should consider whether the process driven method of evaluating biologics is necessary. Interchangeability could potentially be determined by comparing the end active substance, thereby causing greater ease in creating regulatory guidelines.

Future of Biosimilar Regulation

So what is next for biosimilars regulation? As of 2010, there are three established biosimilar regulatory pathways. The FDA, EMEA and PDMA all share the common goal of placing the patient safety above all other criteria when designing the benchmarks within their approval process. Is creating a global regulatory pathway feasible in the future?

One key issue is the nature of the reference product from one country to the next. First there is the question as to whether or not the reference product is approved and/or distributed in the country. Europe requires that a chosen reference product for a biosimilar must be both approved and distributed, while the US only requires that it be approved in the US market. A second issue is whether the reference product, even under the same name, is an identical product throughout different regions.

In order to confidently resolve this issue, countries will have to return to their country specific reference product and determine whether the biosimilar and reference product are comparable in each region. Therefore, the value add of a global regulatory path is lost since both clinical and non-clinical tests will need to be conducted in each region where the same reference products are actually different.

In conclusion, regulatory paths have been established, therefore providing greater incentives for companies to develop biosimilars. Although there is still much uncertainty in the debate as to how to regulate these molecules, a comprehensive checklist based on the current known information is created in Table 14. Therefore, a checklist for biosimilars milestones has been created that incorporate the three regulatory agencies' rules (Europe, US and Japan). The next step for the future of biosimilars is to determine a consensus for the specifics in characterizing biologics and clinical trials (highlighted in yellow).

Completed Regulatory Guideline Checklist

		New Drug: Small Molecule	Generic: Small Molecule	New Drug: Biologic	Generic: Biologic
Product Characteristics/ Non-clnical	Physical Characteristics: molecular weight, primary & secondary structures, etc.	X	X	X	X
	Chemical Characteristics: molecular formula, chemical strucutre	X	X	X	X
	Specifications of drug substance (active ingredient)	X	X	X	X
	stability	X	X	X	X
	purity	X	X	X	X
	consistency of manufacturer of the drug substance			X	X
	Description of analytical testing performed on the manufacturer's referece standard lot and qualitying lots to characterize the drug substance.			X	X
	pharmacokinetic/pharmacology/toxicology	X	X	X	X
	studies for absorportion, distribution, metabolism and excretion of the drug in animals			X	X
Good Manufacturing Practice (GMP)/Quality	Floor diagram of general facility layout			X	X
	list of all components used in the manufacture (synthesis/isolation/purification) of drug substance, their tests and specification/drug development plan	X	X	X	X
	Rationale for development plan (dosage forms, etc.)	X		X	X
	Visual Representation of the manufacturing process			X	X
	Cell Line Information			X	X
	In process controls: fermentation, harvesting and downstream processing			X	X
	Specification/analytical Methods			X	X
	Container/Closure System			X	X
Clinical	Bioavailability/bioequivalence studies (very few biologics will have such data)	X		X	?
	Description and analysis of each clinical pharmacology study of the medicinal product(comparison of human data with animal data)	X		?	?
	Pharmacokinetic & Toxicology Studies	X		X	?
	Description and analysis of each controlled clinical study	X		X	?
	Clinical Effectiveness for the clinical indications. Evidence for dosage and administration required.	X		X	?
	Clinical Safety: studies of assessment of absorption, distribution, metabolism, and/or elimination of drug	X		X	?
	Summary of benefits and risks of the medicinal product in its intended use	X		X	?
Other	Patent information on any patent that claims the drug	X	X	X	X
	Microbiology	X		X	X
	Safety update Reports (four months post NDA's submission)	X		X	X

Table 14: Regulatory Checklist for Small molecules and its Generic Equivalent, and Biologics and its Biosimilars

References

1. Aranesp (darbepoetin alfa) For Injection. Thousand Oaks: Amgen. May 2010.

2. Babbit, Bruce. "The Dawn of Biosimilar Development in the US: Key Legislative Aspect and Next Steps for BioPharma Manufacturers." PAREXEL Consulting, June 20, 2010.

3. Basu, Prabir et.al. "Analysis of Manufacturing Costs in Pharmaceutical Companies." J Pharm Innov. 2008. 3:30-10

4. "Biosimilars and Follow-on Biologics: The Global Outlook 2009-2024." Visiongain. 2009.

5. Brill, Alex M. "Proper Duration of Data Exclusivity for Generic Biologics: A Critique." November 2008.

6. Doyle, K. and K. Barnett. "Preparing for the Arrival of Follow on Biologics". RPM Reports, Aug 2009. <http://www.therpmreport.com>

7. Engelberg, Alfred B. et.al. "Balancing Innovation, Access, and Profits – Market Exclusivity for Biologics." The New England Journal of Medicine. November 4, 2009.

8. European Medicines Agency. Assessment Report for Binocrit (EMEA/590881/2008). London: GPO, 23 October 2008.

9. European Medicines Agency. Guideline on Similar Biological Medicinal Products (CHMP/437/04). London: GPO, 30 October 2005.

10. European Medicines Agency. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005). London: GPO, 22 February 2006.

11. European Medicines Agency. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality (EMEA/CHMP/BMWP/49348/2005). London: GPO, 22 February 2006.

12. Genazzani A.A. et.al. "Biosimilar Drugs: Concerns and Opportunities." Biodrugs 2007: 21 (6); 351-256.

13. "Germany – Biologics & Biosimilars."Espicom Business Intelligence. 2010. February 8, 2010. <www.espicom.com/Extranet/Profiles.nsf/Profile_ID_Lookup>

14. Grabowski, Henry. Re: Emerging Health Care Issues – Follow-on Biologic Drug Competition Comment on Final Report (Originally Identified as Project No. Po83901). July 6, 2009.

15. Haydock, Ian. "Japan's Biosimilar Guidelines Edge Forward." Informa UK Ltd 2009. February 27, 2009.

16. Haydock, Ian. "Stakeholders grapple with biosimilars issues at Japan Meeting." Informa UK, Ltd 2009. Febrauar 27, 2009.

17. "India – Biologics & Biosimilars."Espicom Business Intelligence. 2010. February 8, 2010. www.espicom.com/Extranet/Profiles.nsf/Profile_ID_Lookup

18. Kanter, James. "Europe is Studying Delays in Access to Generic Drugs." The New York Times. July 9, 2009. September 21, 2009. <http///Users/susan/documents/WA/European%20Generic%20.webarchive>

19. Kelley Brian. "Very Large Scale Monoclonal Antibody Purification: The case for Conventional Unit Operations." Biotechnol. Prog. 2007, 23, 995-1008.

20. Kotlikoff, Laurence J. Biosimilars, Data Exclusivity, and the Incentives for Innovation: Response to Grabowski. March 17, 2009.

21. Kotlikoff, Laurence J. Stimulating Innovation in the Biologics Industry: A Balanced Approach to Marketing Exclusivity. September 2008.

22. Langer, Eric S. " Trends in Capacity Utilization for Therapeutic Monoclonal Antibody Production."Landes Bioscience March/ April 2009. 2:2, 151-156.

23. Lin, Amy C. " Understanding and Managing Profitability in a Competitive Environment: An Application in Biotechnology." SM Thesis. Massachusetts Institute of Technology, 2010.

24. Mathieu, Mark P., ed. Biologics Development: A Regulatory Overivew. Waltham, MA: PAREXEL International Corporation, 1997.

25. Mathieu, Mark P, ed. PAREXEL'S Bio/Pharmaceutical R&D Statistical Sourcebook 2009/2010. Waltham, MA: PAREXEL International Corporation, 2009.

26. Mathieu, Mark. New Drug Development: A Regulatory Overview Seventh Edition. Waltham, MA: PAREXEL International Corporation, 2005.

27. Munos, Bernard. "Lessons from 60 years of Pharmaceutical Innovation." Nature Reviews: Drug Discovery. Volume 8, December 2009. 959-967.

28. Nomura, Hideaki et.al. "Innovator's Perspective on Follow-on Biologics." Powerpoint.

29. Sinclair, Alistair, ed. "Biosimilars Series: Forecast Analyst Beyond the Generics Horizon (Reference Code: DMHC2477)." Datamonitor. June 2009.

30. Sinclair, Alistair, ed. "Generics Series: Generics Overview in the Seven Major Markets: Market Pressures Drive Down Margins (Reference Code: DMHC2581)." Powerpoint. Datamonitor. December 2009.

31. Sinclair, Alistair, ed. "Pharmaceutical Key Trends 2010: The Patent Cliff Dominates but Growth Opportunities Remain (Reference Code: DMHC2599)." Datamonitor. March 2010.

32. Sinclair, Alistair, ed. "2009 Pharmaceutical M&A review: Access to emerging markets and biologics remain key drivers for Big Pharma M&A (DMHC2574)." Powerpoint. Datamonitor. December 2009.

33. Sonnier, J. et.al. "Biogenerics". William Blair & Company. January 19,2006.

34. Strickland, Debbie. " News Analysis: Biotech and Generic Industries Lock Horns over Biosimilars." Genetic Engineering & Biotechnology news. March 4, 2009. March 6, 2009. <http://www.genengnews.com/news/bnitem_print.aspx?name=50576293>

35. Symank, Katheryn. "Are Biosimilars on the U.S. Horizons? Healthcare & Life Sciences: Vital Signs, Strategic Insights for Healthcare Executives." Frost & Sullivan. June 23, 2008

36. Tumulty, Karen and Michael Scherer. " How Drug-Industry Lobbyists Won on Health-Care." Time. Oct 22, 2009. November 4, 2009. <http://www.time.com/time/printout/0,8816,1931595,00.html>

37. "Understanding the Challenges of Biosimilar Medicines." Paraxel Consulting 2010.

38. "United States– Biologics & Biosimilars."Espicom Business Intelligence. 2010. February 8, 2010. <www.espicom.com/Extranet/Profiles.nsf/Profile_ID_Lookup>

39. Zeid, Robert L. "Paradigm Shift in Comparability Assessment: How Quality by Design (QbD) and Process Analytical Technology (PAT) can improve Structure-Activity Relationship (SAR) evaluation and its relevance to comparability protocols and biosimilars". Powerpoint. June 30, 2010.

Appendices

Appendix A: Interviews

Name (Last, First)	Title	Company
Brazell, Lorna	Partner, Intellectual Property	Bird & Bird LLP, UK
Builder, Stuart PhD	CEO	Strategic BioDevelopment
Cooney, Charles PhD	Robert S. Haslam Professor of Chemical Engineer	MIT
Egan, William	Vice President	PharmaNet Consulting
Ertel, Shara	Director, Business Planning	Alnylam Pharmaceuticals
Gottschalk, Adrian	Sr. Director, Global Oncology & Cardiopulmonary Commercialization and Business Intelligence & Operations	Biogen Idec
Kotlikoff, Laurence	Professor of Economics	Boston University
Pollard, Stuart	Vice President, Scientific and Business Strategy	Alnylam Pharmaceuticals
Rossi, Christina	Sr. Director	Biogen Idec
Rossomando, Anthony PhD	Senior Director	Alnylam Pharmaceuticals
Sensabaugh,Suzanne	VP, Regulatory Affairs	Panacea Pharma
Sinclair, Alistair	Head of Strategic Analysis	Datamonitor
Thompson, Paul	Account Manager, Customer Strategy	PAREXEL Consulting
Zeid, Robert	Principal Consultant	TLI Development

Appendix B: Assessment of Biosimilars Market 2010

Overview of Generics Market

The worldwide generics market continues to exist and maintain its stronghold in the 'mature generics market', which consists of the US, Germany, and the UK. The US and Western European markets are expected to grow at 7% in the upcoming years, with the emerging economies showing an even more promising landscape with a growth rate of 16%. These three countries account for over $70bn in generic sales, which accounts for 90% of total major market generic sales(29,30,31,32).

The US continues to be a prime market for uptake of generics because of customer acceptance. According to Datamonitor, the average erosion of first generics entry after three quarters in the market was approximately 80%. Germany and the UK followed in second place in terms of volume erosion (Figure 17).

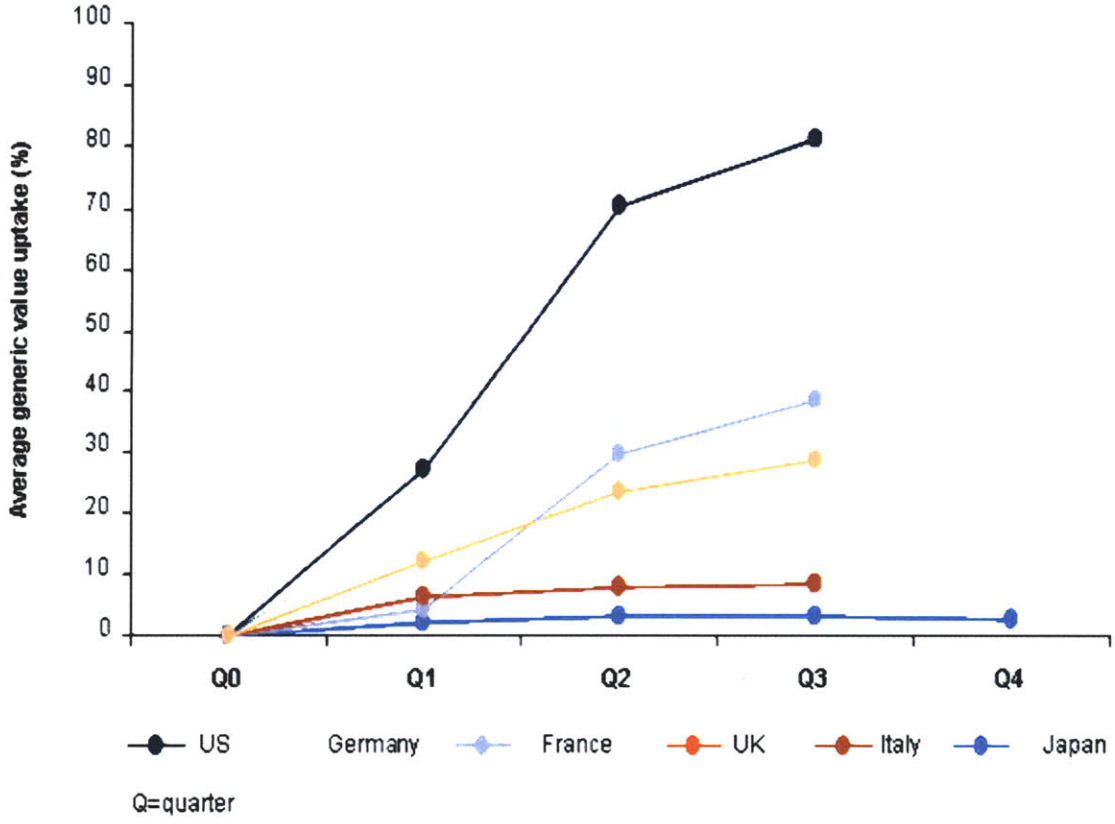


Figure 17: Quarter by Quarter Summary of Generics Uptake after Initial Launch(29): The US has the fasted uptake of generic drugs, representing 85% of the market after 3 quarters. Japan has the slowest uptake, representing the population's loyalty to branded products and distrust of generics.

Opportunity for Biosimilar Growth: Patent Cliff

2010-2014 opens the door for generic players with key patents expiring in this timeframe. Estimates in the upward range of $110bn in global sales are exposed to generic competition through 2014. Of this estimated profitability exposure, $40 bn represents biologics erosion. This is a key driver of the emerging biosimilar market, especially since biologic therapies are rapidly growing with extraordinary high prices. With biosimilars, priced at about 30% discount to the brand product, healthcare payers are expected to make a huge savings across all major markets(4,29,30,31).

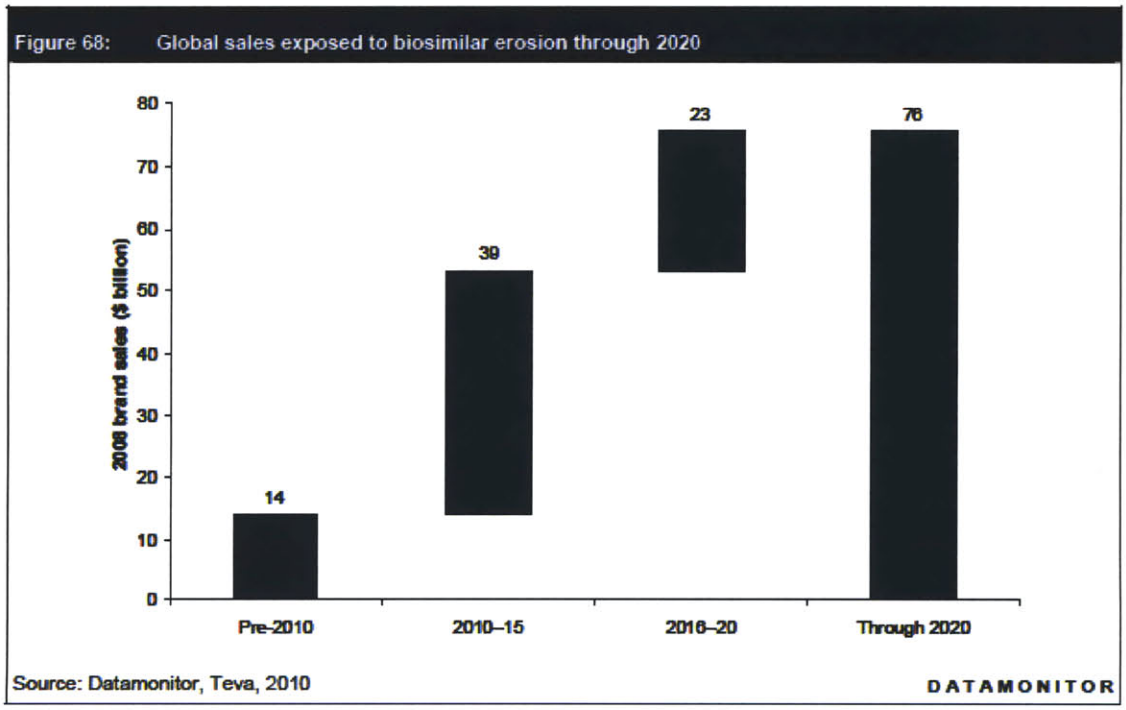


Figure 16: Global Sales Exposed to Biosimilar Erosion Through 2020(4): The global sales exposed to biosimilar is $40bn in the next five years, representing the loss of patent protection by branded biologics.

In the developed countries, innovators' biologic therapies have enjoyed patent protection, which included a period of twenty years of exclusivity rights and in some cases, additional period of data and market exclusivity from biosimilars. Epoetin Alfa, Filgrastim, GCS-F, and human growth horome are expected to lose patent protection in the near future, or already have. These first generation biologics represent the 'low hanging fruit' for generic. Table 15 clearly shows the high revenue biologics that have or are expected to expire in the near future(4).

Estimated Patent Expiry US, Major European Markets		Drug	Drug Type	2008 Sales ($bn)
Expired	Expired	Prevnar/Prevenar (pneumococcal conjugate vaccine, Wyeth)	Vaccine	2.72
Expired	Expired	Actrapid/Insulatard/Mixtard/Novolin (human insulin, Novo Nordisk)	Insulin	2.33
Expired	Expired	Avonex (interferon beta-1a, Biogen Idec)	Interferon	2.20
Expired	Expired	Rebif (interferon beta-1a, Merck KGaA)	Interferon	1.94
Expired	Expired	NeoRecormon/Epogin (epoetin beta, Roche)	Erythropoietin	1.68
Expired	Expired	Betaferon/Betaseron (interferon beta-1b, Bayer)	Interferon	1.67
Expired	Expired	Pegasys (peginterferon alfa-2a, Roche)	Interferon	1.52
Expired	Expired	Genotropin/Nutropin (somatropin, Pfizer/Genentech/Roche/Ipsen)	Growth hormone	1.34
Expired	Expired	Humulin (human insulin, Eli Lilly)	Insulin	1.06
Declared unenforceable	2011	Lovenox (enoxaparin, Sanofi-Aventis)	Heparin product	4.00
2009	2010	Enbrel (etanercept, Wyeth/Amgen)	AIFP	6.23
2010	2010	Aranesp/Nespo (darbepoetin alfa, Amgen/Kyowa Hakko Kirin)	Erythropoietin	3.58
2010	2014	Lantus (insulin glargine, Sanofi-Aventis)	Insulin	3.58
2012	Expired	Epogen/Procrit/Eprex/Erypo/Espo (epoetin alfa, Amgen/Johnson & Johnson/Kyowa Hakko Kirin)	Erythropoietin	5.07

Table 15: Biologic Drugs Expiring in the Next 10 years(4): The three top Epoetin branded biologics, Aranesp, Epogen, and Epogin have all expired as of 2010. This is a key opportunity for epoetin biosimilars in both the global, and US market.

Based on the model in table 16,and taking into considerations forecasted biosimilar sales by Datamonitor, the global and US predicted sales through 2019 are $200bn and $150bn respectably (Table 16). Even if biosimilars maintain its current market penetration of less than 2%, they will still reach $2bn in sales by 2019.

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Biologic Forecasted Global and US Shares exposed to Generic Erosion											
Global Sales (in millions)		40000	42000	44100	46305	48620	51051	53604	56284	59098	62053
PV: r= 20%		33333	29167	25521	22331	19539	17097	14960	13090	11454	10022
NPV	196513										
US Sales (in millions)		30000	31500	33075	34729	36465	38288	40203	42213	44324	46540
PV: r=20%		25000	21875	19141	16748	14655	12823	11220	9817	8590	7516
NPV	147385										
Predicted US Biosimilar Market Capture: low and high forecasts											
Predicted 1.6% market capture		96	208	381	570	716	817	858	901	946	993
PV: r= 20%		80	145	221	275	288	274	239	209	183	160
NPV	2074										
low capture at 10%		600	1302	2381	3565	4473	5105	5360	5628	5910	6205
PV: r= 20%		500	904	1378	1719	1798	1710	1496	1309	1145	1002
NPV	12962										
High Capture (25%)		1500	3255	5954	8914	11183	12763	13401	14071	14775	15513
PV: r= 20%		1250	2260	3445	4299	4494	4274	3740	3272	2863	2505
NPV	32404										

Table 16: Forecasted Biosimilar Global Sales from 2009-2010: The growth rate for the biologics industry was assumed to be at 5% through information gathered from Datamonitor pharmaceutical reports, 2010. Looked at three different potential market capture percentages to determine

predicted biosimilar revenue in the US. First, a continued market penetration of 1.6% for the future (current rate as of 2009). Second, a low market capture of 10%. The last is a high market capture of 25%, which is in line with the European biosimilar market capture percentage.

Focusing on erythropoietin biologics, the three key players that enjoy 98% market share, representing about $10bn in global sales, will all be off patent by the end of 2010(4).

- Epogin, by Roche, which took in $1.7bn in 2008, has already expired and held third place amongst its competitors.
- Arasnep, the first erythropoietin drug to enter the market, had approximately $3.8bn sales in 2008 and will expire in all major markets by the end of 2010.
- Epogen, also called by branded name Procrit, is marketed by both Amgen and J&J is the largest player in the market, with 2008 profits reaching $5bn.

Table 3.17 The Erythropoietin Market, 2008

Drug	Marketing Company	2008 Sales ($bn)	Market Share (%)	Estimated Patent Expiry US	Major European Markets
Epogen/Procrit/Eprex/ Erypo/Espo (epoetin alfa)	Amgen/ Johnson & Johnson/ Kyowa Hakko Kirin	5.07	47.8	2012	Expired
Aranesp/Nespo (darbepoetin alfa)	Amgen/ Kyowa Hakko Kirin	3.58	33.8	2010	2010
NeoRecormon/Epogin (epoetin beta)	Roche	1.68	15.8	Expired	Expired
Other branded erythropoietin drugs		0.10	0.9		
Biosimilar erythropoietin drugs		0.17	1.6		
Total erythropoietin drugs		**10.60**	**100.0**		

Source: visiongain, company annual reports and IMS Health, 2009
Notes: Data based on ex-manufacturer prices

Table 17: The Global Erythropoietin Market in 2008(4): Branded Epogen, Aranesp and Epogin represent 97% of the market. With their patents expiring, biosimilar erythropoietin drugs have an opportunity to significantly increase their market share from less than 2%.

The patent cliff has already eroded in the erythropoietin space, and it is yet to be determined how biosimilars will be able to capture the exposed market (~$10bn). Table 17 gives the forecasted revenue of epoetin, both global and in the US respectable. The total market opportunity for Epoetin globally is $142bn from 2009-2010, and $100bn in the US during that same time period. In 2008, biosimilars capture less than 2% of the market, making evident that patents play a crucial role

in deterring biosimilar activity. However, the changing landscape of patent protected products will provided great incentive for both suppliers and buyers to turn biosimilars(4,29,30,31).

	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Forecasted Epoetin Global Sales											
Epoetin Global Sales	10,000	10,500	11,025	11,576	12,155	12,763	13,401	14,071	14,775	15,513	16,289
PV: R= 20%	10,000	10,500	11,025	11,576	12,155	12,763	13,401	14,071	14,775	15,513	16,289
NPV	142,068										
Forecasted US Epoetin Sales											
US Epoetin Market	7,000	7,350	7,718	8,103	8,509	8,934	9,381	9,850	10,342	10,859	11,402
PV: use rate of return at 20%	7,000	7,350	7,718	8,103	8,509	8,934	9,381	9,850	10,342	10,859	11,402
Total NPV	99,448										

Table 18: Forecasted Epoetin Global Sales from 2009-2019: Assumptions used in this model are that the biologics growth rate is an annual rate of 5%. Therefore, there is a global opportunity to capture $142bn for biosimilar epoetins, and in the US around $100bn.

The high cost and high demand of biologic therapies, coupled with continued pressure to decrease cost healthcare cost around the globe and the lost of patent protection by branded companies, provides a perfect landscape for the emerging biosimilar market. In five years, biosimilars global sales are expected to increase by six-fold, with growth rates doubling to 57% in 2010 (Table 19)(4).

Table 3.5 World Biosimilar Market Forecast, 2009-2014

Year	2008	2009	2010	2011	2012	2013	2014
Biosimilar Market ($bn)	1.39	1.68	2.14	2.90	3.95	6.04	9.46
Growth (%, year-on-year)		*21*	*27*	*35*	*36*	*53*	*57*
CAGR (%, 2008-2014)							**38**

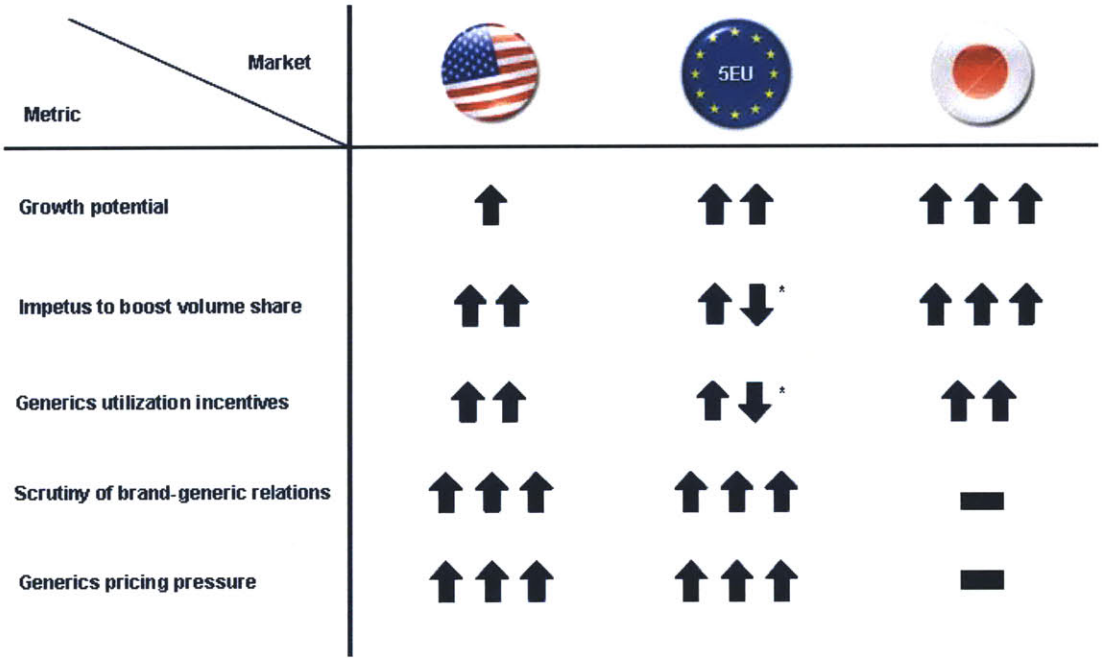
Source: visiongain, 2009
Notes: Data based on ex-manufacturer prices and exclude vaccines, 2008 figures are actual sales, other years are forecasts based on constant 2008 prices

Table 19: World Biosimilar Market Forecast(4): Expecting to reach $10bn in global sales by 2014

Key Drivers of the Biosimilar Market

Drivers that can continue to allow for growth in the generics space include

- **Overall social need to bring drugs to all society members:** Generics erosion was found to be highest in the US, with average peak volume and value uptake of 94.7% and 81.1%, respectively, in the third quarter of generics entry.
- **Cost-saving alternatives:** Both payers and the governments, as reflected in the US Healthcare Reform Bill of 2010, are looking to maximize medical savings by accelerating generic uptake in the market, thereby driving down price due to competitive pressure.
- **Large pharmaceutical and biotechnology players looking to bolster up their portfolios with profitable products:**
- **Established Regulatory Guidelines in Key Markets:** The three key markets with established regulatory pathways as of 2010 are the US (established in March 2010), Europe (2005) and Japan (2009). Table 4 provides a comprehensive outline of additional metrics to consider in the biosimilar uptake between these markets(29,30,31,32).



*Germany and the UK represent markets in which considerable generic utilization incentives exist, while the same cannot be said of France, Italy and Spain. However, these less mature markets offer greater potential for growth than Germany and the UK

5EU=France, Germany, Italy, Spain, the UK

Table 20: Metrics to Determine Generic & Biosimilar Uptake in Three Key Markets (US, EU, Japan)(29,30,31,32)

Appendix C: Additional Considerations to Improve Biosimilar Uptake

There are multiple areas of improvement that would lead to more incentives for companies to enter this space based on potential for both market penetration success and greater profitability.

1. Pricing and Reimbursement strategies need to be in place to guarantee success for biosimilars, and also provide profitable incentives for companies to get into this space. In the UK, the generic drug reimbursement is regulated under the Drug Tariff scheme. This is a complex system in which the reimbursement is re-calculated each month according to a volume weighted average manufacturer price(30). The theory behind this method is that it aligns reimbursement with changing market dynamics, however it disincentives manufacturers by causing increase pressure to lower price, which in some cases are unsustainable.
2. Conversations about the length of market exclusivity for branded products also cause concern. The faster generics get to the market, then the overall benefit to society is greater. Market exclusivity provides a barrier to generics by granting greater protection for branded products. The European Commission found that the period between branded drug launch and the first generic launch has *increased* by 3.5 years, from 10.5 years to 14 years(25). Factors that contribute to this increase timeframe included reformulation and second-generation product launches, settlements with generic companies, and brand loyalty to name a few.

Developing Frameworks and Predictive Models to Determine Bio-Equivalence

One of the continued key concerns by regulatory bodies is the overall complexity of biologics and understanding what these differences in protein structure, impurity profiles etc., actually mean when being administered to patients. There are so many variables that influence the product quality and process consistency, known as the product=process paradigm. Robert Zeid of TLI Development has proposed strategies to tackle the 'product=process' paradigm(39).

- Quality by Design (QbD): A development program that incorporates prior knowledge of the product and process characteristics to developed a framework of relationships and how these impact each quality parameter. The goal is to develop a predictive model of the impact on safety and efficacy(39).
- Process Analytical Technology (PAT): A framework that allows for designing, analyzing and controlling biosimliar manufacturing. It determines product quality by fully understanding the biological components of the drug, desigining a manufacturing process that can show reproducibility by taking into consideration therapeutic objectives, patient population, route of administration and pharmacological, toxicological and pharmacokinetic characteristics(39).

People as a key Competitive Advantage in the Biosimilar Market

Seeing that the development of biosimilar is suppose to result in a cost-saving proposition, than the question is what skills are needed to make these cost-savings tangible? Although reference products previous experience provides a framework to work within, it still requires some tailoring to match the specific development plan for the biosimilars.

People are the key differentiator for the success of a biosimilar. Biosimilar development planning requires people with a strong understanding of science and clinical medicine. They can therefore fine tune the already established reference product protocols and be able to modify them based on past results, new knowledge about the disease, and new technology.

These people are difficult to find. People established in the generics industry do not usually have the scientific background to take a fine-tune look at the scientific techniques and data previously used for the reference product and modify them based on current needs. These skill sets have not been required in the previous pharmaceutical generic industry. These skill sets are more aligned with scientific 'entrepreneurs' in the branded companies, which are used in innovating new products. However, the key ingredient required to make biosimilars a success is the ability to step back, look at past manufacturing and clinical plans from the reference product, and tailor the strategy for current regulatory approval. This may require reconsidering whether certain tests are necessary or certain

technologies can be applied/removed from the process. This is the challenge(Appendix A, conversation with Suzanne Sensabaugh).