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Market entry of biosimilar monoclonal antibodies;
current barriers, how they could be removed and what will be
the economic and other impacts of their removal

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Synopsis

The impressive market success of monoclonal antibody drugs (mAbs) and their upcoming patent expiry, have lead many companies to start biosimilar mAb development. They all seek to gain share in the multibillion-dollar mAb market. For healthcare payers biosimilar mAbs promise a great savings opportunity and may contribute to sustaining the increasing cost of medical treatment. The European Medicines Agency (EMA) has designed a regulatory pathway to support biosimilar mAb development but multiple barriers stand in the way of their potential market success. Complex production, clinical trials, marketing and compulsory post-authorization safety studies make biosimilar development expensive, compared to the development of small molecule generic drugs.

The South Korean company Celltrion demonstrated that with the right combination of resources and capabilities a biosimilar mAb can be developed and its biosimilar infliximab gained market approval in 2013. Subsequent market entry and success are dependent on intellectual property (IP) challenges, reach of the innovator, the impossibility of substitution and interventions by healthcare policymakers. The absence of a worldwide regulation on market entry and patent issues limits the potential market size. The removal of market entry barriers will lead to increased biosimilar competition and possibly a generic-like market, where competition is price driven. The biosimilar developer can make the highest profit in a brand-like market with a small number of competitors and competition driven by differentiation. The availability of biosimilar mAbs will lead to healthcare savings in the medium- term but this might not be sustainable in the long-term if price erosion occurs.

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Notation and glossary

Big pharma	A group term for large globalised pharmaceutical companies
Bioequivalence	The absence of a significant difference in the rate and extent to which the active ingredient in pharmaceutical equivalents or alternatives becomes available at the site of action under appropriately designed study conditions.
Biologic	Class of medications produced by living cells using recombinant DNA technology.
Biosimilar	Copy version of an already authorized biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy and safety, based on a comprehensive comparability exercise.
Biotechnology	A process using biological systems to create or modify products
Blockbuster (medicine)	A product that achieves annual revenues of over US\$ 1 billion at global level.
BMWP	The Biosimilar Medicinal Products Working Party
CHMP	Committee for Medical Products for Human Use
CRO	Contract research organisation
Da	Dalton, unified atomic mass unit
DFS	Disease free survival
EC	European Commission
EGA	European Generic medicines Association
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
Extrapolation of indication	The approval of a drug for indications for which it has not been evaluated in clinical trials.
FDA	Food and Drug Administration
GaBI	Generics and Biosimilars Initiative
Generic	A medicine that is developed to be the same as a medicine that has already been authorised, an exact copy of a small-molecule product.
ICER	Incremental cost effectiveness ratio
Immunogenicity	The potential or ability of a substance or antigen to cause an immune reaction or response.
INN	International Non-Proprietary Name
Interchangeability	Therapeutical equivalence makes that a product can be interchanged with its comparator in clinical practice.
IP	Intellectual Property
MA	Market Authorization
mAb	Monoclonal antibody

MS	Member State
ORR	Overall response rate
OS	Overall survival
PASS	Post-authorization Safety Studies
PFS	Progression free survival
Pharmacovigilance	Science and safety control procedures to which medicines are subject before, during and after their approval by regulatory authorities with the aim of detecting, assessing and understanding the benefit: risk profile of a medicinal product.
PSY	Patient Safety Years
QALY	Quality-adjusted life year
RA	Rheumatoid Arthritis
Reference product	Authorized, patented product of which other manufacturers are attempting to create a copy.
Substitution	Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.
Switching	Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.
US	United States
WHO	World Health Organization

1. Introduction

The introduction of new drugs in numbers per year has only changed slightly over the past 30 years (Ward et al, 2013). The time, money and technology required for innovative drug development have increased substantially. As a result the return on research and development investment has decreased (Scannel et al, 2012). Revenues in the innovative drug industry are further challenged by generic drug competition and cost containment policies implemented by third party healthcare payers (Belsey et al, 2006).

Biotechnology has been widely adopted by big pharma in the development of new drugs (EC, 2009) and the associated complex and costly manufacturing processes lead to expensive innovative drugs. Drugs produced using biotechnology, biologics, represent a growing share of all drugs worldwide. Monoclonal antibodies are a great contributor to this growth (Rickwood, Kleinrock & Núñez-Gaviria, 2013).

The discovery of the principle for production of monoclonal antibodies (mAbs) was rewarded in 1984 with the Nobel Prize in physiology or medicine (Nobel Prize, 2013). Today they represent a multibillion-dollar industry of drugs used mainly in autoimmune diseases and cancer treatment. In 2012 seven of the top ten blockbuster biologics were monoclonal antibodies with combined sales of US\$ 53 billion (La Merie, 2013).

The first blockbuster mAb patent expired in 2013 with many to follow in the coming five years (see figure 1, GaBI, 2013a). This opens the market to non-innovator versions of these successful drugs. A wide range of companies has acknowledged this opportunity and started or is planning to develop biosimilar mAbs, see overview in the appendix.

For small molecule drugs the patent-cliff is a known phenomenon. After the patent on a branded drug expires a sharp downturn is to be expected for product sales (Jessop, 2013). Multiple generics enter the market and the price plunges to sometimes 20% or less of the original (Calo & Martínez, 2012). For biologics it was long thought that the complexity of the production process would not allow for the development of non-innovator versions (Hirschler, 2010, Ellery & Hansen, 2012). Advances in analytical technology

changed this and in 2003 the concept of “biological similarity” for biologics was introduced in the European Union (EU) legislation under the European Commission Directive 2003/63/EC followed in 2005 by the guideline on similar biological medicinal products (EMA, 2005) published by the committee for medicinal products for human use (CHMP). The term biosimilar rather than generic is used for the non-innovator version of a biologic. In 2006 the European Medicine Agency (EMA) granted market approval to the first biosimilar, Sandoz’ Omnitrope®.

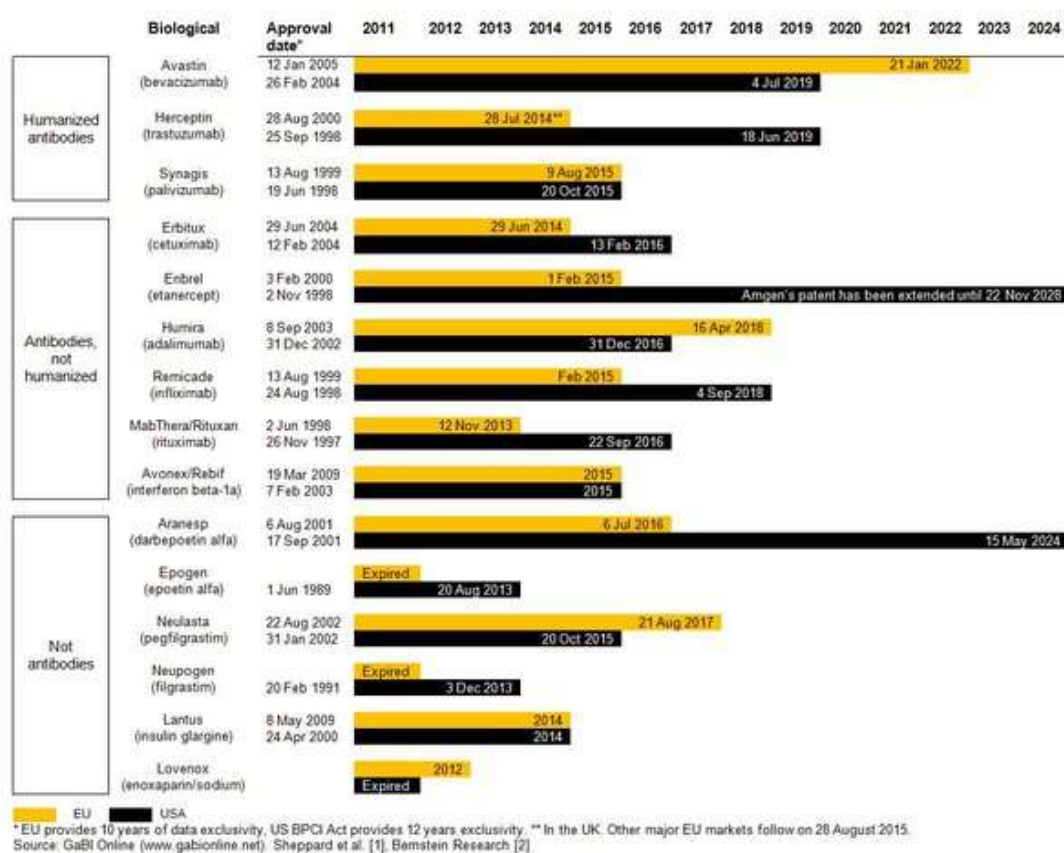


Figure 1. Expiry dates for major patents on best-selling biologics (GaBI, 2013a).

A biosimilar is not the same as a generic due to the difference in reference product, see table 1. A generic is based on a small molecule medicine and a biosimilar on a biological medicine. A biosimilar requires different resources, e.g. biotechnology and clinical trial expertise, to develop and market than a generic drug (Belsey et al, 2006, Ellery & Hansen, 2012). The approval

process for a biosimilar is more complicated and the final market share, due to national laws and physician acceptance, is much smaller (Cornes, 2012a, Rovira et al, 2013, Blackstone & Fuhr, 2008).

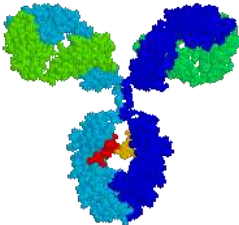

	Biological medicine	Small molecule medicine
Nature	<ul style="list-style-type: none"> Complex molecule 20,000–200,000 Da. Biological basis, fragile stability 	<ul style="list-style-type: none"> Small molecule 100-200 Da. Chemically derived, stable
Manufacture	<ul style="list-style-type: none"> Recombinant technology, for example, gene, via vector to synthesis by cell line. Certain steps not fully predictable, impossible to ensure identical copy. 	<ul style="list-style-type: none"> Chemical synthesis Fully predictable and understood, identical copy can be made.
Life-cycle	<ul style="list-style-type: none"> Innovation rewarded with a period of market exclusivity. At loss of exclusivity, biosimilars are launched through referencing an original product and proving comparability in clinical efficacy and safety studies. Biosimilar development takes 6-8 years and costs \$80-120 million.* 	<ul style="list-style-type: none"> Innovation rewarded with a period of market exclusivity. At loss of exclusivity generics are launched when pharmaceutical equivalence and bioequivalence is proven. Generic development takes 18-24 months and costs around \$2 million.*
Substitution	<ul style="list-style-type: none"> In the EU the national authorities decide; not allowed in any country and some have laws prohibiting biosimilar substitution. 	<ul style="list-style-type: none"> In the EU the national authorities decide. It is encouraged and even mandatory in several EU countries.
Example	 <p>Monoclonal Antibody ~25,000 atoms 150,000 Mol Wt</p> <p><small>© 1996 Mike Clark</small></p>	 <p>Aspirin 21 atoms 180 Mol Wt</p>

Table 1. Major differences between biological and small molecule medicine (based on IMS 2012 p6) *(Ellery & Hansen, 2012).

The EMA provides the following explanation of the concept of biosimilars;

‘A biosimilar medicine is a biological medicine that is developed to be similar to an existing biological medicine (the ‘reference medicine’). Biosimilars are not the same as generics, which have simpler chemical structures and are considered to be identical to their reference medicines’ (EMA, 2009).

In 2012 biosimilars accounted only for 0.5% of the value of the mature markets spend on biological medicine (Rickwood, Kleinrock & Núñez-Gaviria, 2013). This can increase with the arrival of biosimilar mAbs, as their higher price will result in greater savings from biosimilar competition for the third party payers.

The biosimilars that are currently on the market in Europe are relatively small (20-30 kDa) and less complex than the mAbs. The regulatory pathway for biosimilar mAbs is longer, the physician acceptance is expected to be lower and competition from innovative products is high (Lepage-Nefkens et al, 2013, Declerck, 2013). The huge market potential nevertheless resulted in many pharma companies investing in biosimilar mAb development. In 2011 activity and expectations were high, the EMA reviewed 35 biosimilar mAb products for scientific advice (Schneider et al, 2012). But recent reports are more cautious and several companies, e.g. Samsung and Teva, have halted their biosimilar mAb development or ended the development partnership, like Teva and Lonza did (Barnes, Kim & Park, 2013). The actual sales of biosimilars of \$0.6 billion in 2012 were nowhere near the estimation made in 2007 of \$16 billion for 2011 (Sheppard, 2013). The estimates of future size of the biosimilars market range widely from \$2 billion to \$20 billion in 2020, much depends on the change in the different barriers to market entry that biosimilars currently face (Dalgaard, Evers & Santos da Silva, 2013).

In September 2013 the first biosimilar mAb for infliximab developed by Celltrion was approved by the EMA as Inflectra[®] (by Hospira) and Remsima[®] (by Celltrion) (GaBI, 2013b). These products could not directly enter the greater part of the European market due to a recent patent prolongation of the innovator drug Remicade[®] of six months until February 2015 for filing an extra indication for paediatric use. Currently 15 companies have 40 biosimilar development programs of which 20 in a clinical phase (Gal et al, 2013 and see appendix for an overview). Six of these companies are developing a biosimilar rituximab. In the EU the patent on Roche's rituximab expired in November 2013 without any biosimilar rituximab approved that could enter the market (McBride, 2013). At the time of writing (May 2014) no product has even been filed at the EMA. This clearly indicates the existence of high barriers to market entry. Aside from the regulatory pathway, patent strategies are one of many barriers to market entry that biosimilar developers face. This thesis will focus on the foreseen market entry of biosimilar mAbs in Europe. Europe has a regulatory pathway in place for biosimilar mAbs and with its generally high uptake of generic medicine and high spending on biologics, is an interesting market for potential success. This in contrast to the largest market for biologics, the United States (US), where the food and drug administration (FDA) has not yet approved any biosimilar through a biosimilar pathway (Rickwood & DiBiase, 2013).

With the ever-increasing cost of healthcare and the economic pressure to reduce or sustain healthcare expense (Thomson, Foubister & Mossialos, 2009), biosimilars could be instrumental in reducing cost for medication and increasing patient access to treatment (McCamish & Woollett, 2012a; McCamish & Woollett, 2012b, Cornes, 2012b, Haustein et al, 2012, Dingerman, Windisch & Cornes, 2012, Gascón et al, 2013). Especially the cost for cancer treatment is becoming unaffordable even for wealthy countries, due to higher prevalence of cancer and more expensive biological and targeted therapies (Cornes, 2012a).

The advancement in technology makes biosimilars possible and the pressure on healthcare budgets makes them desirable. Therefore both a technological push and a market pull mechanism are facilitating biosimilar mAb development.

From the company perspective the huge market potential is a valid reason to develop biosimilars. The reference products that are targeted are all blockbuster drugs and the market share of biologics worldwide is still growing (Rickwood & DiBiase 2013). Some companies, like Boehringer Ingelheim (2012), explain their choice to develop biosimilars mAbs as helping to meet the challenge of rising treatment costs, emphasising their corporate social responsibility. Merck motivates its choice to enter the biosimilar market with its belief that it will improve patient accessibility to potentially lifesaving lower-cost drugs (Mintz, 2011).

From the users' or payers' perspective the main rationale for using or promoting the use of biosimilars is cost saving (Cornes, 2012a).

2. Research question

This thesis will identify the barriers to market entry for biosimilar mAbs in Europe and analyse how they can possibly be removed. It will then discuss the economic and other consequences of barrier removal. The focus will be on consequences for the company developing the biosimilar and for the healthcare expense in different EU countries. This thesis is an attempt to answer the following questions:

- What are the barriers to market entry and success for biosimilar mAbs in Europe?
- Could these barriers possibly be removed?
- What is the impact of barrier removal and what can be the economic consequences for biosimilar mAb developers and healthcare expense in different EU countries?

3. Literature

'Barriers to entry are the factors that need to be overcome by new entrants if they are to compete in an industry' (Johnson, Whittington & Scholes, 2011 p55). The industry concerned here is the biotech pharma industry, which is characterized by high R&D expense and profits derived from few blockbuster biologics. The biosimilar mAb is a novel concept in itself but it directly competes for market share with its reference product, the blockbuster biologic. Therefore the barriers to entry for biosimilar mAbs can be determined on the basis of the general industry barriers, which are scale and experience, access to supply or distribution channels, expected retaliation, legislation or government action and differentiation (Johnson, Whittington & Scholes, 2011).

The following keywords were used to search for literature on the Internet, in the Imperial College e-library, on Pubmed and in Factiva; 'biosimilar monoclonal antibody', 'biosimilar pipeline' and 'biosimilar market entry'.

Sources found, were supplemented manually with related papers from their reference list and with papers recommended by experts in the field.

Data on companies and their biosimilar pipeline was taken from company and business news web sites. This is a highly actual topic and the cut off date for the literature search was 31st January 2014. News up to May 2014 is mentioned as recent developments in paragraph 11 at the end of this thesis. The literature on the subject of biosimilar mAbs is abundant and diverse in subject approach. Because of the differences highlighted in table 1, many parties see a challenge in solving the difficulties in producing biosimilar mAbs and the uncertainties about their efficacy and safety. Of the selected sources 72 discuss biosimilars in general, most of them mentioning biosimilar mAbs explicitly and 17 are dedicated to biosimilar mAbs.

Research on the chemical and pharmaceutical properties emphasises efficiency gains in mAb production (Whitford, 2012) and also the development of highly specific analytical techniques to assess similarity between innovator and biosimilar products (Calo & Martínez, 2012).

Research on the use of mAbs in treatment and the foreseen acceptance of biosimilar mAbs by physicians and third party payers, emphasises the risk of

immunogenicity and the differences in mechanism of action for the different mAbs and in the different indications (Weise et al, 2012b, Dörner et al, 2013, Vulto & Crow, 2012, Noaiseh & Moreland, 2013, Mellstedt, 2013, Lapadula & Ferraccioli, 2012).

Business literature focuses on the market potential, the company resources that are needed to develop and commercialise a biosimilar and the response of innovator companies to the threat of biosimilar competition (Blackstone & Fuhr, 2008, Dalgaard, Evers & Santos da Silva, 2013, GBI, 2009, Yang, 2010, Sheppard, 2010, Sheppard, 2011, Ramachandra & Davies, 2013, Rader, 2013, Barkalow, 2011, McBride, 2013, McCamish & Woollett, 2012a, Walsh, 2013).

Forecasts of the biosimilar mAb market are mainly written up in commercially available business reports, which could not be included in this research project. An abstract of these reports does state a high potential for biosimilar mAbs and an expected market entry for biosimilars of leading mAbs by 2018 (ASDR, 2013). Ariyanchira (2012) describes the different sentiments toward biosimilars in semi- and unregulated countries, which are embracing the more affordable copies where regulated markets are more cautious. She predicts biosimilar mAb acceptance will grow when already approved biosimilars demonstrate safety and efficacy.

Academic research on market entry barriers for biosimilar mAbs is limited. Most research was done before the EMA guideline on biosimilar mAbs was published (Towse and Mestre-Fernandez, 2010, Simoens, Verbeken & Huys, 2011). Other research describes market entry for biosimilars in general (Lepage-Nefkens et al, 2013, Calo and Martínez, 2012, Declerck & Simoens, 2012) or for one specific biosimilar (Simoens & Huys, 2013). Laslop briefly discusses challenges and opportunities for biosimilar mAbs specifically in her 2013 commentary. She mentions regulatory procedure, reimbursement decisions and physician acceptance as main obstacles to market access and underlines the importance of post-marketing safety data.

Since biosimilar mAbs have not entered the market at the time of writing the experience with and knowledge on biosimilars in general and those currently available will be taken as a basis for the assessment of biosimilar mAb specific market entry barriers.

The market entry of biosimilars is in some aspects comparable to that of generics. The main comparison is in the ways that governments can stimulate uptake of these non-innovator drugs as described by Dylst, Vulto and Simoens (2012).

The contribution of biosimilars to the containment of healthcare expense in Europe has been researched for the currently available biosimilars (Haustein et al, 2012, Farfan et al, 2013, Rovira et al, 2013). From this research it is evident that savings will not be as large as achieved with generics and so far no clear pattern of market dynamics can be determined (Rovira et al, 2013). The uptake of biosimilars has been slow and therefore data on cost savings are limited, the high expectations for cost savings are based on the not yet available biosimilar mAbs (Farfan et al, 2013). The limited data available point to actual cost savings that differ depending on the type of biosimilar and that will be higher with the trend of increasing uptake throughout the EU (Rickwood & Di Biase, 2013). The biosimilar mAb, once available on and accepted by the market, will contribute to cost savings mainly because of the high prices of the reference product, this makes that a mere 20% discount leads to a large absolute cost advantage. In the EU the use of biosimilars for the top 7 reference biologics could result in yearly savings of 2 billion euros (EGA handbook, 2011).

All literature sources on biosimilars refer to the regulatory pathway, which has been unclear for a long time and is still in development worldwide. The requirements of and overlap between different international pathways are relevant to biosimilar mAb developers as they determine the total market size for their product. The focus of this thesis lies with the European market for

biosimilar mAbs. The European regulatory pathway is therefore most relevant and will be highlighted as the basis of further discussion.

The European Medicine Agency guideline for 'similar biological products containing monoclonal antibodies' became effective on December 1st 2012 (EMA, 2012b). The guideline proposes a stepwise approach, where the extent and nature of the non-clinical and clinical programme depends on the level of evidence obtained in the previous steps. All studies should aim to detect any potential differences between biosimilar and reference product. The necessity for and extent of studies will be determined on a case-by-case basis. Herein lies a trade-off for sponsors to invest in early analysis and process development to decrease future cost by regulatory relief regarding requirements for animal and clinical studies (McCamish & Woollett, 2012b).

'The guiding principle is to demonstrate similar clinical efficacy and safety compared to the reference medicinal product, not patient benefit *per se*, which has already been shown for the reference medicinal product.' (EMA, 2012b: p.12)

Clinical trials need to show therapeutic equivalence, the biosimilar cannot perform worse or better than the originator drug. To be approved as a biosimilar it needs to allow use of the same dosage for the same indication (Weise et al, 2012b). Phase II dose finding clinical trials are therefore not needed.

The guideline mentions the possibility of extrapolation of clinical efficacy and safety data to other indications of the reference mAb, not specifically studied during the clinical development of the biosimilar mAb, but this should be supported by scientific arguments. This means that the effort an innovator company puts into getting new indications approved does not need to be replicated by the biosimilar developer (Ellery & Hansen, 2012).

Market authorization (MA) may involve the obligation to perform post-authorization safety studies (PASS) that exceed routine pharmacovigilance. To facilitate PASS and pharmacovigilance the specific mAb, whether it was biosimilar or innovator, administered to the patient needs to be identified. Identification can be done through name and batch number, provided that biosimilars will be named differently from the innovator drug. International non-proprietary names are assigned by the World Health Organization (WHO) and meant to ensure global recognition of pharmaceutical substances. After MA the biosimilar may carry the same international non-proprietary name (INN). A naming debate is still on going about whether or not this is acceptable, since having the same name makes it seem as if the two products can be interchanged and that decision lies with the national authority. Innovator companies are generally against assigning the INN of the reference product to the biosimilar, while generic companies argue that biosimilars should have the same INN as the reference products (Lovenworth, 2012).

For biosimilars however using only the INN for prescribing or pharmacovigilance would possibly result in the untraceable switching between reference product and biosimilars and between different biosimilars with the same INN (Chu, Torstensson & Pugatch, 2010). To ensure a secure track and trace of biosimilar use and protect patients from unintended switching the manufacturer's name should always accompany the INN (Zuñiga & Calvo, 2010a, Niederwieser & Schmitz, 2011). This is an opportunity for manufacturers to brand their biosimilar, but also represents an extra marketing cost, favouring the reference product (Rader, 2013).

Many of the successful mAbs targeted by biosimilar developers are used in the treatment of cancer. Endpoint evaluation is affecting physician acceptance of biosimilars with cancer indications.

‘According to the “Guideline on the evaluation of anticancer medicinal products in man” (CHMP/EWP/205/95) the preferred endpoint to prove

efficacy in cancer indications would be either progression free / disease free survival (PFS / DFS) or overall survival (OS). ' (EMA 2012b: p.12)

These preferred endpoints, PFS/DFS and OS, can take a long time to reach and are not suitable for establishing comparability between biosimilar and reference product (Ebbers et al, 2013). For detecting product-related differences, endpoints measuring drug activity are usually more sensitive and may be acceptable if they are clearly related to the desired clinical effects (Weise et al, 2012b). When sensitive enough, the overall response rate (ORR), or other novel endpoints, can be accepted as a primary endpoint for clinical studies of the biosimilar mAb. The physicians however have learned to choose treatments on the basis of PFS/DFS or OS data and will be reluctant to prescribe a biosimilar on the basis of ORR data alone (Mellstedt, 2013). Especially since the treatment result should not be better than with the innovator drug of which all the data is known.

The main safety risk for biological medicines is immunogenicity, which together with other rare adverse events may go undetected in a clinical study of limited sample size (Weise et al, 2012b, Laslop, 2013, Dörner, 2013). Immunogenicity is the potential or ability of a substance or antigen to cause an immune reaction or response.

The root cause of immunogenicity of a biologic is hard to find and is related to both the complexity of its production and its final structure (Schellekens & Jiskoot, 2006). Immunogenicity of biosimilar mAbs is more complex and more difficult to predict by analytic assays than that of the previously approved simpler biosimilars (EMA, 2012c, Declerck, 2013).

Brinks (2013) concludes in a review on immunogenicity of biosimilar mAbs, that immunogenicity between reference and biosimilar product are similar but data is limited and it remains a major concern for biosimilar mAb development. Manufacturing changes in European Eprex® a decade ago were the cause of a severe immunogenic adverse reaction, pure red cell

aplasia, in several patients (Schellekens & Jiskoot, 2006). Such incidents result in tighter regulation and increased cautiousness among patients and physicians that also affects the way these end-users perceive the safety of biosimilars (Vulto & Crow, 2012).

The unknown safety risk combined with small cost savings, 20-30% compared to 80% for generics may not incentivise physicians and patients to switch to biosimilar use (Schneider et al, 2012, Cornes, 2012). It is generally believed that a larger price difference is required to drive the market (BioTrends, 2012, BioTrends, 2013).

An increase of objective information to the healthcare provider about the quality, risk and experience with biosimilars can greatly enhance uptake (Lucio, Stevenson & Hoffman, 2013). Studies comparing the safety and efficacy of biosimilar filgrastim in the actual therapeutic setting show no difference between originator and biosimilar drug (Publicover et al, 2013). But filgrastim is not representative of the potential risk for biosimilar mAbs, because it is a compound known to have a low immunogenic potential and its use is limited to a short period of time in patients that are in most cases less likely to experience an immune reaction.

The uptake of biosimilars in the EU varies per country and across the three initial therapy areas but shows a strong annual growth (Rickwood & Di Biase, 2013, European Commission, 2013). The biggest success so far is for biosimilar filgrastim, which in five years has gained large market share, produced cost savings and increased access without loss of effectiveness or greater safety risks (Gascón et al, 2013). Biosimilar growth-hormone somatropin has seen the lowest uptake, which may be related to its use in long-term therapies and the difference in administration device (Farfan et al, 2013).

Due to the complex production process of mAbs, based on partially unpredictable biological reactions, any change in this process, e.g. up scaling

or starting up at a new production facility, will result in larger or smaller differences in properties between the end product before and after the change (Mellstedt, Niederwieser & Ludwig, 2007). The EMA has experience in assessing these differences for the innovator products. For innovator products this creates an allowed quality bandwidth (McCamish & Woollett, 2011).

To negotiate all development stages including regulatory pathway and commercialization, companies have chosen to form alliances and partnerships to extend their capabilities (Mathur, Shankar & Bhargave, 2013, Sheppard, 2010). Generic companies have capabilities in small molecule medicine production and bioequivalence testing and compete for market share in a price driven market. To facilitate biosimilar mAb development they need to acquire or ally with partners who have experience in biotechnology, clinical development and marketing support (Calo & Martinez, 2012). Sandoz receives this support from its mother company Novartis. Big pharma companies have acquired or set up biotechnological capabilities, Pfizer has acquired Wyeth, Amgen acquired Watson (Calo & Martínez, 2012) and Merck originally set up Merck Bioventures as joint venture with contract research organisation (CRO) Parexel (Barkalow, 2011). A wide array of companies and joint ventures or alliances is currently trying to exploit the opportunity of biosimilar mAbs with even some not traditionally pharma companies, like Samsung and Fujifilm entering the industry. The alliances combine capacities and spread risk and will need to have enough stamina to survive the combination of high initial investments with slow market uptake that characterize biosimilar development.

The high upfront investments, \$200m-\$500m with average development time 6-8 years (GBI Research, 2009), required to prepare the company for a successful biosimilar launch can be recouped when only few biosimilars enter the market and the market will stay brand-driven with only a minor decrease in price of the reference product. This means a major first mover advantage, as price erosion will occur when more players enter the market.

The partnerships needed to develop biosimilars can change the current status of big pharma, with many players in emerging markets gaining experience in biosimilar development and some receiving governmental backing to capture global market share (Rickwood & Di Biase, 2013). Big pharma companies operate globally and while the European market is large and with its high adoption of generics likely susceptible to biosimilars, it is only a percentage of the global mAb market. Figure 2 illustrates from the perspective of biosimilar developer Hospira, the global division of the biologics market (Ramachandra & Davies), of which mAbs are a main component.

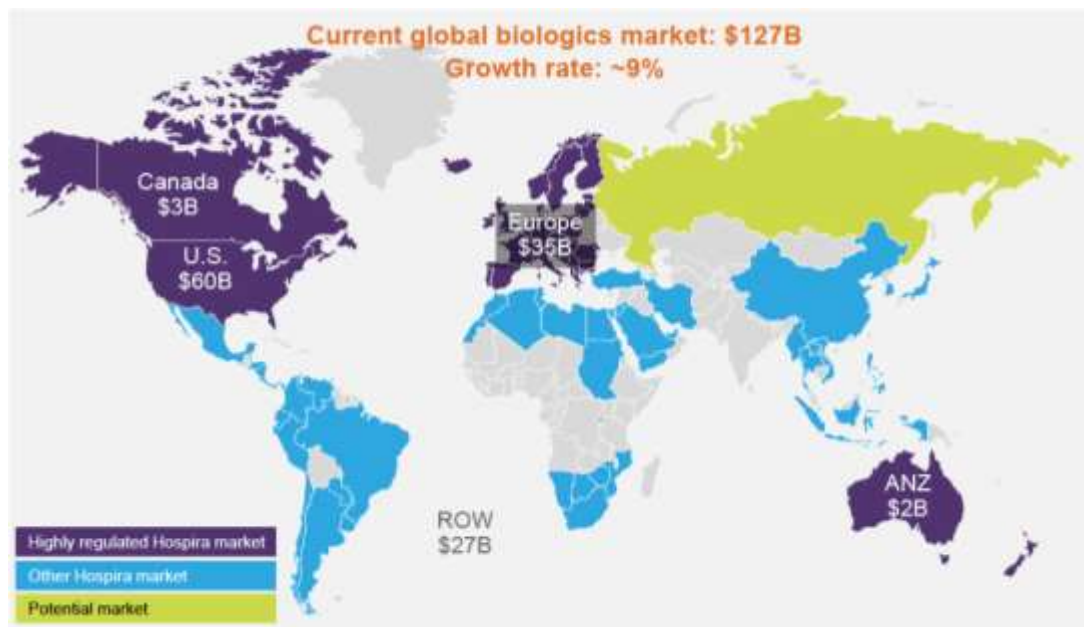


Figure 2. Local Market Values based on 2012 data (Ramachandra & Davies, 2013 slide 11).

Ideally a company would like to develop a biosimilar mAb that will be alleageable for market authorization worldwide (McCamish & Woollet, 2011). An indication that guidelines are becoming more supportive of global development is the conditional acceptance by the EMA of reference products from outside the EU as from June 2012 (Laslop, 2013). The EMA guidelines are the most developed regulatory guidelines and other regulatory authorities, e.g. in Canada and Australia, use them as a basis for their own guidelines (Niederwieser & Schmitz, 2011). The food and drug administration

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(FDA) in the US did this as well when they proposed their guideline. However it still differs from the EMA guideline in a way that makes it uncertain if biosimilars approved under one guideline will also satisfy the requirements of the other (McCamish & Woollett, 2012b, Lepage-Nefkens et al, 2013).

South Korea based its regulatory pathway on that of the EMA, this may partly explain the success of the South Korean company Celltrion in being the first to have a biosimilar mAb approved in the EU (Rickwood & Di Biase, 2013).

In other parts of the world, like Brazil and India, the market is much less regulated and many copy mAbs have entered the market (Misra, 2012). In company reports and other sources these copy mAbs are often confusingly named biosimilars. They are clearly not biosimilars because they have not obtained market approval after passing a comparability exercise as demanded by the EMA. The misuse of the term biosimilar confuses the public (Weise, 2012a) and complicates the assessment of company development pipelines. The WHO has adopted a guideline to determine the minimal requirements for a similar biologic to assure global quality, safety and efficacy of biologics (WHO, 2013).

Some companies, who market similar biologics in less regulated countries, have the intention to produce dossiers and products suitable for regulated markets (Sheppard, 2011). The research into which companies are involved in biosimilar mAb development is further complicated because the companies change names, merge, are taken over, make and break alliances. The company websites differ greatly in the amount and detail of knowledge they share about their pipeline development. Through licensing agreements a biosimilar mAb manufactured by one company can be further developed for market approval and commercialised by several other companies. All the above complicates the assessment of the exact number of biosimilar mAbs in development at any moment in time. An overview in the appendix lists the biosimilar mAbs in development and the associated companies in November 2013. It shows that most companies target biosimilars for rituximab, etanercept and trastuzumab. These are all highly successful mAbs of which the patent has or will soon expire, see figure 1. For several of these

biosimilars development has progressed to the phase III clinical trial stage, but so far (May 2014) not one has been filed for market approval with the EMA.

4. Methodology

From the literature described above the main barriers to market entry and success are identified for biosimilar mAbs in the European market. These barriers are further analysed and experts have been asked to comment on the findings from literature. The personal network of the author provided the experts, whose opinion was asked in informal and unstructured conversations, which were not transcribed. The experts were qualified as such because of their close involvement with biosimilar development, academically, commercially or from a market research perspective, see appendix 2 for names and current positions. Based on literature and expert opinion, the possibility of barrier removal is discussed.

The discussion on economic and other consequences of barrier removal is based on reports and research of biosimilar market penetration and associated cost benefits in Europe. When choosing a forecasting method it is important to understand the novelty of a product. The biosimilar mAb is different from previously marketed biosimilars in that it is more complex, is used for different indications, its mechanism of action is not fully known and it represents a greater immunogenicity risk. However the concept of biosimilarity and the rigorous regulatory requirements are the same. Trend extrapolation based on data from currently marketed biosimilars is valuable in forecasting biosimilar mAb market penetration and price development. The cost savings obtained from the use of the filgrastim biosimilars are used to forecast cost savings for the use of biosimilar trastuzumab instead of the reference product. No adjustments are made for discounting in the purchase or reimbursement process, or for any other parameters of the time value of money. The assumption is made that reference product and biosimilar are interchangeable, meaning that all other treatment costs, e.g. for hospitalization or time taken off work, are equal.

Recent studies on cost savings obtained with biosimilars use IMS data (Haustein et al, 2012, Gascón, 2013). IMS unfortunately does not provide access to its database to or honors data requests from students. Therefore data used for this research project was extracted from literature and relevant websites.

Different currencies are used throughout this thesis to reflect the source referenced and the context of the monetary amount mentioned. Therefore amounts reflecting the global market are in US dollars and amounts reflecting the European market in euros, with the exchange rate at the time of writing being 1,38 US dollar to the euro. Possible other currencies are converted to either US dollars or euros.

5. Barriers to entry

It is important to understand that a biosimilar mAb will compete for market share with its specific reference product and other biosimilar mAbs that are based on that same reference product. The total market for (biosimilar) mAbs is segmented by indication, with most mAbs targeting only a few specific indications. Different biosimilar mAbs need to appeal to different patient groups and types of physicians and will face protection strategies of different innovator companies. The EU market is further segmented in different countries and sometimes regions within a country, as for example in Italy and Germany where regional authorities can make autonomous healthcare policy decisions. The specifics of each barrier will therefore need to be completed on a case-by-case basis. This section describes the barriers in general.

Before a biosimilar mAb can enter the market it needs to overcome several barriers. To subsequently obtain market success it needs to overcome several more. These barriers are grouped by their common cause under the headings in table 2. The first three, manufacturing process, regulatory process and IP challenge are barriers faced before market entry. Part of the

lack of incentive barrier, where the national authority needs to make a reimbursement decision is also situated in time before market entry. MA for biosimilar mAbs is applied for and granted centrally for the EU through the EMA. Reimbursement procedures are different in all member states. The lack of incentive for the physician and the patient, the impossibility of substitution and the reach of innovator play a larger role after market entry. They all influence the decision of companies to (continue to) invest in biosimilar mAb development and determine the overall potential for biosimilar mAbs.

Manufacturing process	<ul style="list-style-type: none"> • Challenge of biological unpredictability • Consistency after upscaling and over time
Regulatory process	<ul style="list-style-type: none"> • Unclear for long time • Different between EMA and FDA • Extrapolation of indications
IP challenge	<ul style="list-style-type: none"> • Patents on composition of matter, production process, formulation and application of end product • Patent prolongation strategies
Lack of incentive	<ul style="list-style-type: none"> • For payer • For physician • For patient
Impossibility of substitution	<ul style="list-style-type: none"> • Country specific regulation • Switching chronic patients versus only new patients • Indication specific
Reach of innovator	<ul style="list-style-type: none"> • Brand stickiness • Relationship with key physicians • Naming debate

Table 2. Barriers to market entry and success, grouped by main cause (adapted from Gal, Sonnenefeld & Blanckley, 2013).

5.1 Manufacturing process

The generic barrier of scale and experience is high in the biotech pharma industry mainly because of high investment requirements for manufacturing processes and learning curve effects.

When developing a copy of an originator drug the company does not have access to the biological production system (cells, bacteria) that was used for the reference product and therefore needs to reverse engineer. Contrary to the highly predictable chemical process, the biological production process is unpredictable. This complicates the reverse engineering of biological drugs. Already from this first reverse engineering step the development of biosimilars is more uncertain than the development of generics. The development of biosimilars starts with systematically engineering to 'match the reference product in a complex, detailed and highly controlled process that continuously assesses the quality, consistency and stability of the biosimilar mAb' (Dingermann, 2012:p.316). This process that is based on analytics and takes multiple iterations in early stage development, is illustrated in figure 3 by a pyramid (McCamish & Woollett 2012b: p.415). The effort put into the design specification stages is specific for biosimilar development. Designing a new biological medicine requires less effort in this first stage than a biosimilar, but more in the subsequent stages of (pre-) clinical development where toxicity, pharmacokinetics, pharmacodynamics and efficacy all need to be determined without the availability of reference data.

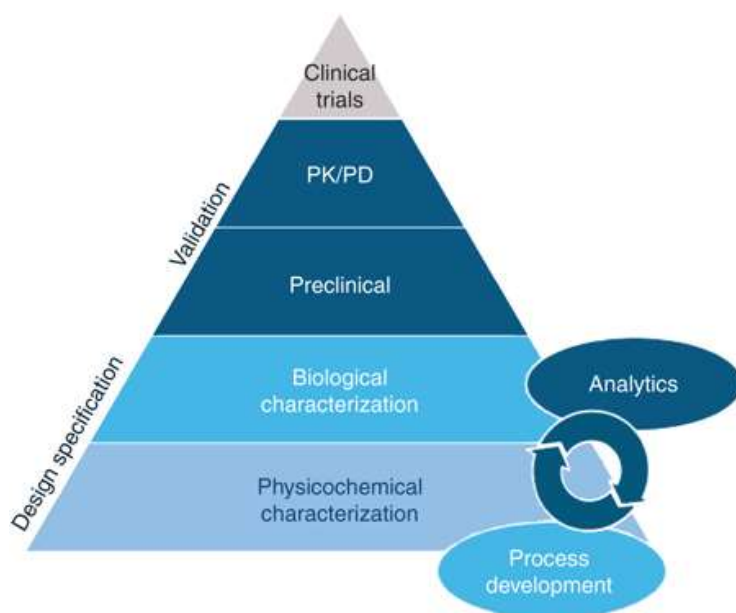


Figure 3. Biosimilar development based on analytics and multiple iterations in early stage development, Sandoz approach (McCamish & Woollett 2012b:p.415).

The cost of manufacturing has fallen over time, which is beneficial to the biosimilar developer. The innovator company will enjoy a larger profit only if it succeeds in adopting the newer, less costly, procedures while staying within the determined quality bandwidth.

Having developed and successfully tested a biosimilar mAb, the company will need to upscale production and possibly open new facilities to meet market demand. Every change in production results in a change in end product and managing the manufacturing process will be a continuous challenge for the biosimilar developer.

Ahmed, Kaspar and Sharma (2012) describe the steps of manufacturing a biosimilar and how this complex process poses a challenge to the regulatory bodies.

The access to manufacturing technologies is restricted to those companies who have been investing in biologic manufacturing platforms through the years (Calo & Martínez, 2012). There are only five different manufacturers producing eleven commercially available biosimilars, with several companies licensing a biosimilar from the same manufacturer (Niederwieser & Schmitz, 2011, Farfan et al, 2013).

5.2 Regulatory process

The regulatory process forms part of the legislative and government action barrier. Furthermore the EMA assigns MA and determines access to distribution channels.

The EMA guideline for biosimilar mAbs was approved in 2012 (EMA 2012b). Until that time biosimilar developers were unsure of the final regulatory requirements for biosimilar mAbs. In the meantime, EMA provided individual protocol-assistance and scientific consultations to companies to avoid a slowdown of the development of biosimilar mAbs. Even with the published guideline, the evaluation is still very much case-by-case and the developer has the opportunity to propose novel study techniques.

The main requirement is that similarity is proven between biosimilar and reference product by a combination of experimental analysis and clinical testing.

‘Although current methods for analyzing the structural similarity between originator and biosimilar are extremely refined and sensitive, it is very difficult or almost impossible to determine the clinical consequences of differences based on structural information only. On the other hand, the clinical comparability exercise is the least sensitive method for detecting differences.’ (Laslop, 2013:p.1)

The phase III clinical trial design needs to focus on the patient population and indication that are most sensitive for detecting differences. Phase III clinical trials are complicated by the lack of motivation for physicians to take part in them (Barnes, Kim and Park, 2013) and by the procurement of and cost for reference products (Rader, 2013).

The extrapolation of clinical study data to other indications of the reference mAb than that treated in the study is possible but challenging when a reference mAb is licensed both as an immunomodulator and as a cancer antibody (EMA, 2012b, Ellery & Hansen, 2012). If the biosimilar is only approved for the studied indication, this will decrease the potential market for the biosimilar. If extrapolation to other indications is granted, this will likely be accompanied by extended pharmacovigilance and PASS requirements (Niederwieser & Schmitz, 2011).

The PASS requirement is an additional cost for the biosimilar developer after MA. There is a trade-off between fast market approval with extended PASS requirements and extended phase III studies that will provide evidence on endpoints that are relevant to physicians or for different indications.

During the public consultation period of the EMA guideline on biosimilar mAbs industry and regulatory representatives made comments (Ebberts, 2012b, Amgen, 2014), while the medical profession did not take this opportunity to help design the guidelines. An uneven contribution to the

guideline by the different stakeholders may lead to uneven commitment of these stakeholders to the outcome of the guideline. With medical professionals especially not convinced of the quality of biosimilars after their approval (Aapro, 2011).

The EMA pathway has shown the approval of biosimilars with comparable safety and efficacy profiles to the reference product (Ahmed, Kaspar & Sharma, 2012). The FDA approval process is therefore thought to largely follow the EMA pathway. Differences in regulatory requirements between the EMA and FDA will complicate global biosimilar development and market access. The first to file will likely face more regulatory hurdles, companies have halted their trials awaiting better guidance from the FDA (Rader, 2013, McBride, 2013).

5.3 IP challenge

Patent protection is a legal restraint on new entry. Patent protection of innovative biologics and resulting market exclusivity is how the large R&D expense can be recovered. In the product life cycle of biologics the possibility of a patent cliff was not initially planned for (Ellery & Hansen, 2012).

Retaliation can be expected from innovator companies to retain market share that was previously protected by the patent. Patents on manufacturing processes can be used to block access to supply channels.

Intellectual property laws prevent the manufacturers of biosimilars from using production processes from innovators. Licensing these patents, if possible at all, can be costly as the royalties are often charged as a percentage of revenue (Gal et al, 2011). Choosing different production processes will inevitably lead to differences in the end product, which then need to be shown not to have an effect on efficacy and safety in patients. This adds to the burden and cost of validation after manufacturing.

European Commission's (2009:p.8) final report on pharmaceutical sector inquiry states: 'market entry can be affected by the deployment of the tool-box-instruments'. The report describes patent and life cycle strategies

deployed by originator companies to fight of generic and biosimilar competition.

The first approved mAb biosimilar infliximab cannot yet enter the market because the patent on the reference product was prolonged for the greater part of Europe. The possibility of patent prolongation makes the date of patent expiration more uncertain.

The earliest market entry date for a biosimilar is the latest expiration date for relevant patents as well as data and market exclusivity, but in most cases patents are the determinant blocking market entry (Rader, 2013).

While the composition of matter patent, which claims the specific amino acid sequence of the drug, block market entry, innovator patents on production processes and mAb applications complicate the development of biosimilars.

The patents are filed for nationally, therefore different countries have different patent expiration dates. The United States allow for more patents, for example on platform technology (Gal et al, 2011), than European countries. A biosimilar with MA in Europe might face patent disputes when applying for MA in the United States.

The first to file a biosimilar will likely need to resolve patent disputes and this could explain why some companies have halted their trials (Rader, 2013).

Sandoz tried to have two patents owned by Amgen on its biologic Enbrel[®] declared as invalid and unenforceable, but the US Court did not want to consider the case before Sandoz actually filed an application for MA with the FDA (GaBI, 2013c).

This leads to a complicated trade-off between investing large sums in new production processes and subsequent validation or risking the cost and possible loss of a patent dispute.

5.4 Lack of incentive

The general industry barrier of differentiation leads to the importance of providing a product with higher perceived value than the competition (Johnson, Whittington & Scholes, 2011). Where innovative biologics are

highly branded it is more difficult to differentiate biosimilars and use this to incentivise buyers.

With the high cost of development the biosimilar can only be introduced with a small discount to the originator. Many third party payers, governments and physicians indicate that they will only consider promoting and prescribing biosimilars if they can offer a significant, more than 30%, cost saving to compensate for the potential risk (Biotrends, 2012, Biotrends, 2013).

After MA is granted, the uptake of biosimilars is influenced by incentives for healthcare payers, physicians and patients to promote, prescribe and use these biosimilars.

Healthcare payers will promote the use of biosimilars when it is clear that this will lead to cost reduction without added risk. Laslop (2013) mentions the hurdle of the decision on reimbursement and how the expected small price difference will likely not be enough for payers to readily adopt the biosimilars. For generic medicine the incentive of 80% cost reduction is clear and different countries have different ways of promoting or even demanding the use of generics (Dylst, Vulto & Simoens, 2014). Biosimilars are priced at a discount of only 10-35% (Farfan et al, 2013) and have an added uncertainty because of the unknown immunogenicity risk.

Physicians as discussed above are hesitant to accept the biosimilar as equal to the reference product and they often do not directly benefit from the lower cost. They need an incentive to facilitate their transition from prescribing the familiar and trusted reference product to prescribing a biosimilar mAb with its inherent uncertainties and to compensate for the effort it will take to explain the switch to a cheaper alternative to their patient. Different medical specialisms have varying degrees of biosimilar acceptance, with oncologists being most knowledgeable and accepting of biosimilars (BioTrends, 2012). The overall slow uptake of currently available biosimilars in Europe is mainly ascribed to low physician knowledge and acceptance of the concept (Rickwood & DiBiase, 2013).

Patients will follow the advice of their physician, of patient associations and are influenced by reports in general media. Direct to consumer marketing of

prescription drugs is illegal in the EU. Patients often do not choose or pay directly for the medication in the EU, where the inpatient drug coverage is 100 % (BioTrends, 2013). This is different in Russia where patients face high out-of-pocket payments for medicines (MarketLine, 2012).

5.5 Impossibility of substitution

Where the lack of incentive barrier can partly be influenced by government action the impossibility of substitution is clearly a legislation and government action barrier. In Europe the national authorities are responsible for the legislation on substitution.

Upon patent expiry of small molecule drugs, generic versions rapidly gain high market share, due to regulations that promote substitution for the least expensive product (Lepage-Nefkens et al, 2013). Substitution is the act of replacing originator with biosimilar or one biosimilar for the other.

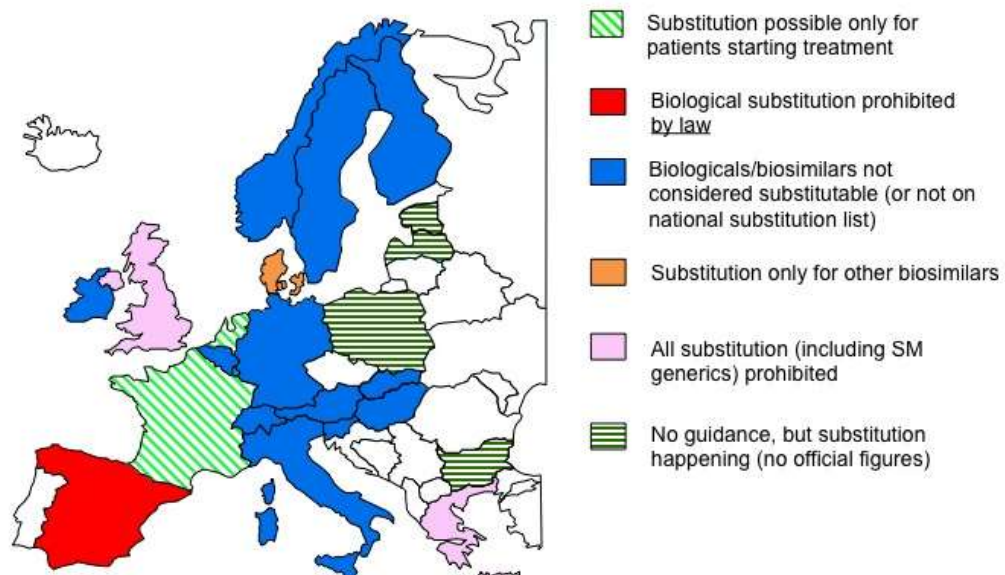
For biosimilars substitution is not yet allowed in any European country and market share will need to be gained by costly marketing. Market research shows that only 8% of prescribing physicians has a positive attitude towards substitution of biosimilar mAbs, this is higher, 25%, for the simpler filgrastim biosimilars (BioTrends, 2012).

The decision on interchangeability and substitution lies with the national authority of the EU member states. The evaluation by the EMA does not include recommendations on interchangeability of biosimilars (EMA, 2012a). Interchangeability is a property of the biosimilar and is a prerequisite for substitution (Ebberts et al, 2012a). Substitution at the pharmacy level complicates the data gathering needed for the pharmacovigilance requirements (Mellstedt, 2013, Dörner, 2013).

The policy on biosimilar substitution varies widely between member states. Substitution rules are different for all European countries, a 2007 law prevents substitution in Spain (Misra, 2012) and so far no country adopted rules that favour biosimilars (Chu, Torstensson & Pugatch, 2010, Mellstedt, Niederwieser & Ludwig, 2008, European Commission, 2013). This is

illustrated below in figure 4 designed by H. Ebbers in May 2014 (Vulto, 2014) largely based on information from Niederwieser and Schmitz (2011, p.283).

Substitution / Prescribing policies in several EU countries (2014)



DIRECTIVE 2012/52/EU requires brand name prescribing for biologicals

Figure 4. Substitution / Prescribing policies in several EU countries, designed by H.Ebbers (Vulto, 2014), based on Niederwieser & Schmitz (2011,p.283).

Switching is prescribing or dispensing a biosimilar to a patient who was previously using the originator drug. To enable track and trace and prevent increased risk of immunogenicity repeated switching is not advised (Weise et al, 2012b). A company can only live up to its PASS requirements if accurate track and trace is facilitated, so an adverse event can be traced to the exact product causing it.

Without the possibility of substitution, biosimilars are a choice for new patients or for a one time switch for stable patients only. This market segmentation makes the size of the potential market for the biosimilar a fraction of the total market of the reference product, especially for those products used in long-term treatments (Rickwood & DiBiase, 2013).

Another consequence of the prohibition on substitution is that pharmacies will need to keep both biosimilar and reference products in stock, decreasing their buyer power for each.

5.6 Reach of innovator

As mentioned before the innovator company is likely to retaliate and has a better position to offer a differentiated product. Loyalty to the innovator company limits access to the distribution channels.

With the slow uptake of existing biosimilars and the difficulties in developing biosimilar mAbs the patent-cliff that innovator firms face will be much less sharp and acute for biologics than in the case of generic small molecule drug competition. Nevertheless with the high revenues of biologics threatened by biosimilar competition the innovator companies make great effort to fight off and delay this competition. The innovator firms protect their market share against biosimilar mAb competition not only by patent strategies but also through strong ties with physicians and patients and new or pseudo-new (“evergreening”) product development.

The innovator companies can use fears and doubts that already exist with clinicians to promote their product as better than any biosimilar. This is comparable to the disinformation campaigns about generic medicines (European Commission, 2009).

Innovative companies often have a long lasting relationship with the physicians, subsidising clinical research or practice support (e.g. nurses, home-care).

‘It may be difficult for some developers to find trial sites and specialists that are not already under contract or don’t have conflicts of interest from working with reference-product companies’

(Rader, 2013: p.20).

Patient associations often have strong ties with innovator companies that sponsor their meetings and promotional materials.

The incumbent might change the device, indication or route of administration to make their product more competitive (Lovenworth, 2012).

While many innovator companies started to develop biosimilars, Roche chooses not to; 'Roche is not interested in biosimilar compounds or compounds that do not have the potential to become first-in-class or best-in-class' (Roche, 2013).

Roche's strategy to counter biosimilar competition and loss of market share is to leverage its expertise in R&D with novel therapeutics, second-generation products, new devices and new formulations (Yang, 2010). Roche got FDA approval for a newer version of Rituxan[®], Gazyva[®] formerly known as GA101 (Garde, 2013). Businessweek already named GA101 the blockbuster drug for 2014 (Bloomberg, 2013). Roche has also developed subcutaneous versions of its blockbusters rituximab and trastuzumab. These subcutaneous versions have the practical advantage that they can be self-administered by the patient at home and do not require preparation in the pharmacy and hospital visits. Self-administration will possibly move these products from the inpatient to the outpatient market. The cost to third party healthcare payers and the revenues for pharma companies are very different between these markets (Vogler, 2013).

In many European hospitals, e.g. in The Netherlands and Belgium, the procurement of medication is done by a group of hospitals through extensive negotiation with the pharmaceutical industry. High rebates or interesting research sponsoring can be given if all medication is purchased from one company. This can make it difficult for a biosimilar developer who might not offer as complete a package and is not able to give the rebate (Lepage-Nefkens et al, 2013).

The extent of the rebates and other favourable agreements with hospital buying combinations is often unknown to the third party payer. For mAbs that are mainly used inside the hospital it may therefore be profitable for the hospital to procure the reference product, even if the biosimilar has a lower list and reimbursement price. Vogler et al (2013) found that high-cost cancer medication, like mAbs, are often not discounted, because many have no

therapeutic alternative and they are not likely to be continued for outpatient use. This can change when biosimilar mAbs enter the market offering a lower cost therapeutic alternative. Therefore the biosimilar mAb cannot rely only on price competition but will need to offer a differential advantage through marketing and service offerings (Bocquet et al, 2014).

In the naming debate the innovator companies generally plead for a unique INN for each biosimilar to ensure appropriate levels of patient safety (Lovenworth, 2012). The regulatory guidelines are not conclusive on the INN issue and of the currently marketed biosimilars some have a unique INN and others adopted that of the reference product (Lepage-Nefkens, 2013).

6. Removing the barriers

Many of the barriers mentioned above are more or less valid for all biosimilars, most of which have accordingly seen slow uptake in the European markets.

An exception is biosimilar filgrastim. The uptake of filgrastim in Europe now resembles that of generic drugs (Rickwood & Di Biase, 2013) and proves that market entry barriers can be overcome. However as with the regulatory process and the market dynamics for currently available biosimilars also the importance and strength of the different barriers has to be assessed on a case-by-case basis. Within the group of biosimilar mAbs, products of which the mode of action is better understood, the risk of immunogenicity is thought to be less, competition is high, and which are used in short term treatments are expected to be accepted by the market more easily and are expected to experience faster uptake than products for which the opposite is valid (Sheppard & Iervolino, 2012).

The year 2013 is seen as a turning point in the biosimilar development with the first biosimilar mAb approved and with a biosimilar filgrastim, Zarzio[®], out-performing the reference product in the EU (Rickwood & Di Biase, 2013).

6.1 Manufacturing Process

Technological advances have lead to more efficient cell-lines that produce more antibody while using more standardized, less expensive media and thus to create a higher yield at a lower cost (Gal, 2011).

The availability of single use technology lowers the requirements for technical facilities to manufacture a biosimilar mAb. Whitford (2012) describes the many advantages this technology brings to the development of biosimilars. Among these are cost and time savings for facility design, build and qualification. Further development cost and time savings can be realized through experience and outsourcing (Gal, 2011).

Governments, like that of the Republic of Korea and China, support the development of biosimilar manufacturing facilities in their country (Lovenworth, 2012, Bloomberg, 2013). Initial investment in a technically advanced production process will keep production costs low in the future and lead to a better competitive position when the biosimilar market becomes generic like with competition based on price.

With the ongoing technological advances in analysis and manufacturing, this barrier will decrease with time.

Manufacturing process

- Standardization, Outsourcing
- Use of flexible single use technologies
- Acquisition of biotechnological experience
- Government support

6.2 Regulatory process

The EMA guidelines are clearly a compromise between the different industry parties, innovator versus biosimilar, and the regulatory body.

Regulatory authorities need to ensure patient safety and encourage both competition and innovation in the biopharmaceutical industry (Blackstone & Fuhr, 2012). The EMA guideline is supportive of biosimilar development and it is up to the company developing the biosimilar to make most of the opportunities given to reduce the need for large and expensive clinical trials. The historical market approval of biosimilars shows the case-by-case approach and is not always consistent with the guidelines. An overview of currently available biosimilars shows that many did not meet all regulatory

requirements, but were given MA based on the combined data available and the intellectual judgement of the EMA (Schellekens & Moors, 2010).

The need for expensive clinical trials is debated, because of the availability of advanced analytical technologies (Schellekens & Moors, 2010).

Greater alignment between the organised medical community and the regulators can lead to greater trust in the regulatory process (Ebberts et al, 2012b). All stakeholders not just industry and regulatory, but also patient and physician organisations should be included. According to Weise et al (2012b) the Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) considers a more proactive approach to obtaining input from the medical community when further creating and updating the guidelines.

Contract research organisations (CRO) can help design both clinical trials and pharmacovigilance studies (Zuniga & Calvo, 2010b). This is a large opportunity for CRO's, because the clinical trial design for mAb biosimilars is very specific and many generic companies have no experience with clinical trials.

The EMA guidelines judge a biosimilar on its similarity and not on non-inferiority. It is possible that more advanced manufacturing techniques produce a drug based on a reference drug that has higher efficacy than its reference or is effective but has different properties that compromise biosimilarity. In both cases the biosimilar developer can choose to develop the product as stand-alone biologic (Declerck, 2013).

Profound knowledge of and experience with the regulatory requirements will help a company to adjust the biosimilar mAb development process to these requirements and overcome this barrier for the EMA regulatory pathway. The US FDA regulatory pathway has yet to prove sufficiently supportive of biosimilar mAb development. Real regulatory relief would come from a global mutual recognition of regulatory pathways. Payers, industry parties and regulatory bodies should concentrate their efforts on enabling global biosimilar development, with the end product being allegeable for approval worldwide. This would greatly decrease the cost of development and

increase the size of the potential market (Dalgaard, Evers & Santos da Silva, 2013).

Regulatory process

- First biosimilar mAb approval leads the way
- Alignment between regulators and medical profession and regulators worldwide

6.3 IP challenge

Innovator companies have protected their mAbs with several patents and will likely pursue infringement on these patents by biosimilar developers (Gal et al, 2011). The outcome of these patent disputes will provide jurisprudence for future cases. If the judge declares key patents as unenforceable or invalid this will greatly enlarge the opportunity to develop biosimilars using the production methods of the reference product. Which will lead to a decrease the number of differences that need to be explored in the comparability exercise demanded by regulation and therefore possibly decrease development time and clinical trial expenses.

“The path between avoiding infringement and creating satisfactory manufacturing performance can put a very high value in process adaptability” (Whitford, 2012).

The single use technology mentioned earlier can meet this demand for adaptability by providing highly flexible manufacturing solutions.

Patent laws are different around the world and impede global development of biosimilars. The market access of generic medicines is also, in a lesser way, hindered by originator patent strategies. Pay-for-delay cases and deregistration of market authorizations have occurred and delayed the entry of generic medicines, resulting in denial of cost savings to healthcare systems. These instances are investigated and prosecuted (Jessop, 2013). Increased awareness with the authorities and punishment of these cases might make companies less eager to use them in the future (Lovenworth, 2012).

Dylst, Vulto and Simoens (2012) provide a list of recommendations to enhance market access of generic medicines. Of these recommendations the following are equally applicable to biosimilars:

- Grant patents only for truly innovative medicines, thereby eliminating evergreening benefits.
- A unitary European Union (EU) patent.
- Unified patent litigation within the EU.

The main market entry barrier of the matter of composition patent cannot be removed and will determine the first possible date of market entry for the biosimilar mAb (Rader, 2013). Patents describing production processes, mAb applications and illegal patent strategies can and will be challenged (Gal et al, 2011). This will simplify production design and decrease the incumbent power over market entry of the biosimilar mAb.

IP challenge

- Removal of patents through litigation
- Punishment for illegal patent strategies
- Unified EU patent litigation

6.4 Lack of incentive

For several Central and Eastern European countries the relatively small price difference largely increases the access to biologic treatments that were too expensive before biosimilar introduction. This is illustrated by the almost 100% market share of biosimilar filgrastim in Romania, Hungary, Czech Republic and Slovakia (Ramachandra & Davies, 2013). Access to these markets increases the potential market size for biosimilar mAbs.

Reputation plays a role aside from price in reimbursement decisions, as high trust (innovator) company face fewer reimbursement restrictions (BioTrends, 2013). An unknown difference is likely between efficacy in a structured setting, as demonstrated to regulatory authorities, and efficacy in a real-world setting, as of interest for reimbursement authorities. This makes that a less expensive biosimilar is not necessarily more cost-effective than the reference drug (Simoens, Verbeken & Huys, 2011).

However research shows that the quality of biosimilars currently on the market is high, possibly higher than that of the reference drug (Schellekens & Moors, 2010, Gascón et al, 2013). Positive experience with available biosimilars (Vulto & Crow, 2012) is increasing confidence with payers and physicians and will positively influence uptake. Not all physicians are familiar with the concept of biosimilars neither are they confident about their safety and efficacy, but awareness has increased over the years (Noaiseh & Moreland, 2013, ASBM, 2014, BioTrends, 2012). Objective information provision about the characteristics of biosimilars is key in increasing physician acceptance (Lepage-Nefkens et al, 2013) and is undertaken by organisations like the Generics and Biosimilars Initiative (GaBI) and expert panels as described by Dörner et al (2013). Improved communication to physicians, payers and patients about the rigor of oversight for biosimilars will improve take up (Schneider et al, 2012). The positive experiences should strengthen reimbursement authorities, physicians and patients to have a positive attitude towards biosimilars and trust the EMA biosimilar pathway.

Towse and Mestre-Ferrandiz (2010) argue that a high discount strategy will not overcome the lack of physician confidence and might easily be countered by the originator company. They propose that the collection of what they call “Patient Safety Years” (PSY) data will lead to a shift from a large loyal market segment to a greater price-competitive segment.

The inclusion of a biosimilar in treatment guidelines, e.g. filgrastim biosimilars in European Organisation for Research and Treatment of Cancer (EORTC) guidelines (Aapro et al, 2010), will increase uptake and accumulation of PSY data.

The absence of demand-side policies for biosimilars in many EU member states restricts the potential price difference between originator and biosimilar (Simoens & Huys, 2013). Payers can increase market penetration through tenders, reference pricing or quota. From these the introduction of quota seems the most suited to biosimilars and has been implemented in Belgium (Declerck & Simoens, 2012) and also proven to be successful in

Germany (GaBI, 2013d). The rationale behind setting quota, that the prescription of biosimilar mAbs to a new patient or the one time switch for an existing patient is deemed safe, will need to be clearly communicated. This communication is best done through pharmacists and physicians, who can function as ambassadors for the cause. This communication will be a cause of increased uptake apart from the subsequent quota introduction (Lepage-Nefkens et al, 2013).

Third party payers cannot, with the growing pressure on healthcare budgets (Cornes 2012a), reasonably ignore the large absolute cost savings that biosimilars mAbs bring. If research can enlarge the knowledge on the immunogenicity risk and clarify what, if anything, exactly increases the risk for biosimilar mAbs, much uncertainty for the physicians will be taken away. The lack of incentive barrier will therefore become less high with the increase of experience and knowledge of biosimilars and the growing pressure on healthcare budgets.

Lack of incentive

- Large absolute savings due to high reference price
- Research confirms safety and efficacy biosimilars
- Quota

6.5 Impossibility of substitution

Haustein et al (2012) propose two possible ways to change the attitude towards biosimilar substitution. First the realization and publication of more head-to-head studies with the reference drug and second strict regulations on biosimilar exchange quota. More studies will lead to higher costs but publication of the comparative studies can more easily be realised. Information about biosimilars needs to be more transparent and better spread to all concerned. Members of the EMA Biosimilars Working Party (BMWP) have published a paper to promote that biosimilars can be considered therapeutic alternatives to the reference product (Weise et al, 2012b). Quota is mentioned in the previous paragraph as a suitable way to incentivise biosimilar uptake.

Chu, Torstensson and Pugatch (2010) emphasise the risks of switching biologics and recommend the involvement and agreement of both physician and patient in a decision to switch. With 72% of physicians considering their role “critical” or “very important” in deciding whether a patient should receive a reference product or a biosimilar (ASBM, 2014) automatic substitution at pharmacy level certainly seems a bridge too far.

To change national laws regarding biosimilar substitution the biosimilar developer will need a powerful lobby with lawmakers. This lobby is more likely to be successful in those countries that have biosimilar industries and when supported by healthcare associations.

Norway tried to add biosimilar filgrastim to the list of products that are available for substitution, but was prevented to do so by a court ruling, prompted by a lawsuit submitted by innovator company Amgen (Ellery & Hansen, 2012).

For now it seems that switching will be limited to new patients, making this barrier most relevant for those biosimilar mAbs with indications for long-term chronic use like rheumatoid arthritis (RA).

Impossibility of substitution

- Information gathering and dispersion on clinical comparison between biosimilar and reference
- lobby with lawmakers

6.6 Reach of innovator

With many brand manufacturers also producing biosimilars, it is no longer in their interest to campaign against the concept of biosimilars.

The innovator might no longer be opposed to the concept of biosimilars but will still have a competitive advantage over other biosimilar developers and defend its own reference product against biosimilar competition.

Even biotech giant Amgen, an innovator company that has experience in biotechnology and is under commercial pressure from biosimilar filgrastim in Europe, has plans to develop biosimilar mAbs (GaBI, 2012). Amgen motivates its decision by stating that the high barriers to market entry can be attractive for those companies who do have the capabilities to overcome

these barriers (Ellery & Hansen, 2012). Biosimilar mAbs that are developed by innovator companies can benefit from the company's network and reputation. The strong ties that originator companies have with physicians through supporting investigator initiated trials can be challenged when the biosimilar developer has enough credibility, product and resources to facilitate these trials. Data from these trials then add to the PSY data. Biosimilars may be positioned as late-entrant branded products rather than generics (Narayanan, 2010). The biosimilar developers will need to develop strategies to differentiate products on the basis of branding and corporate identity by providing services linked to the brand identity (Ellery & Hansen, 2012). Biosimilar developer Hospira puts effort into converting key stakeholders, e.g. physicians and patient groups, into advocates as it sees this as one of the critical success factors expected to drive biosimilar mAb adoption (Ramachandra & Davies, 2013). At the same time EMA works on providing objective scientific information to the medical community to clarify some common misconceptions about biosimilars (Weise et al, 2012b). Hospira continues to invest in commercialization efforts for its existing biosimilar brands, with full colour advertisement campaigns (Ramachandra & Davies, 2013). In an interview with Life Science Leader magazine the president of Merck BioVentures says: "Biosimilars can provide added value through improved delivery devices, training and education and patient support services" (Mintz, 2011). An optimized formulation and packaging variants and sizes are other ways a biosimilar developer can positively differentiate its biosimilar (Sheppard, 2011).

The competitive threat of novel therapeutics is somewhat contained by health economic policies that set incremental cost effectiveness ratio (ICER) thresholds. The ICER threshold uses the cost of a quality-adjusted life year (QALY) to decide on reimbursement (Cornes, 2012a, Garrison, 2013). For example the biosimilar filgrastim is compared to the successor of filgrastim, pegfilgrastim in ICER analysis and preferred because of its lower price (Declerck & Simoens, 2012). When biosimilars can be proven to have real-world efficacy equal to that of the reference product the ICER will be lower

for biosimilars and a cost-minimisation analysis is sufficient (Declerck & Simoens, 2012). Economic pressure can result in lower ICER threshold limits and therefore new therapies will have to prove highly efficacious or cannot ask a premium price when a biosimilar is used as comparator in the analysis (Lovenworth, 2012).

However with the long development time and slow market uptake the risk remains that an innovative treatment replaces the need for the biosimilar mAb before it has become profitable.

This reach of innovator barrier will become less relevant when biosimilar mAbs are more accepted as therapeutic alternatives, but will never cease to exist.

Reach of innovator

- Innovator companies also develop biosimilars
- Differentiation through branding and services
- High ICER thresholds for new therapies

7. Impact of barrier removal

Only two barriers can effectively be removed by advancements in technology, knowledge growth, information dispersion and tougher health economic measures. The removal of the manufacturing process and lack of incentive barriers will ease new entry and enlarge market potential for the biosimilar mAb industry in Europe.

It is not expected that laws on biosimilar substitution, the regulatory pathway for approval or the patent strategies and reach of innovator companies will change in a way that they will no longer represent a barrier to market entry or success. Therefore only a limited number of the companies currently developing biosimilar mAbs will actually have the capabilities and resources to proceed through to market launch (Ramachandra & Davies, 2013).

Choosing an appropriate business model, through exploiting economies of learning from earlier biosimilars, pre- and post-launch stakeholder management and effective branding and go-to market strategies will help overcome the remaining barriers mentioned above (Sheppard, 2013).

The barrier removal as described, benefits companies with a strategic, resource and capability fit to biosimilar mAb development. Companies that do not have this fit will need to form alliances with other companies to overcome the remaining barriers.

Scannel et al (2012) describe the difficulties of new drug design. The successful launch of biosimilars can provide the industry with a source of revenue that will enable them to compensate for the lack of success in developing new drugs. With less barriers to market entry, more biosimilars can be successfully developed and real competition will lead to lower prices (Bocquet et al, 2014). Over time this price erosion might make the market less attractive for innovator firms, who will return their focus to innovation and possibly sell of their biosimilar assets. With increased competition of biosimilars, the pharmaceutical industry will need to focus even more on new drugs, increasing innovation. The market entry of biosimilars and subsequent lower cost of medication put a higher pressure on the cost effectiveness of a new intervention when evaluated by calculating the ICER (Simoens, 2009). However if an innovator company can demand a low price for a more efficacious comparable drug this would end biosimilar competition and once again put the innovator company in a monopoly position (Lovenworth, 2012). Future competitors on the market will be biobetters and new me-too/same-indication innovator products (Rader, 2013, Declerck, 2013).

Successful biosimilar market entry will lead to greater revenue for biosimilar developers and related industries, like contract research organisations that assist in clinical trial and PASS design. With the EU being the first to adopt a regulatory pathway for biosimilar mAbs, EU based companies are likely to benefit more, but for all companies the real gain will come when regulatory pathways are globally aligned (Milmo, 2012).

Forecasts are undecided on whether the biosimilar market will stay brand-like or become generic-like (Gal et al, 2011). The impact of barrier removal will be that the biosimilar market will become generic-like faster and only the first few biosimilars that obtain MA can demand prices close to the price of the reference product. While these first movers will be able to demand a higher

price, they will also have higher cost for marketing and possible patent disputes. Innovator companies have a chance to be successful as first movers and should try to achieve pay back while the market is still brand-like. However the financial impact of biosimilar development is unlikely to be transformative (Gal et al, 2011). In the end, the biosimilars market will show similar dynamics to the current generics market where sales are entirely price-driven and no longer brand-driven (Calo & Martínez, 2012). In a generic-like market innovator companies lose their brand advantage and a cost leadership strategy becomes more important. The cost of manufacturing has decreased, but the requirement of clinical studies and PASS for MA will keep the cost of biosimilar development and prices relatively high (Calo & Martínez, 2012, Declerck & Simoens, 2012).

For the biosimilar company several scenarios have to be considered, but it is highly unlikely that this can be a lucrative market for all. When market entry barriers remain high only few biosimilar mAbs will reach the market and the companies involved will need to invest in marketing, but can ask a relatively high price. When market entry barriers fall many biosimilar mAbs will enter the market and fierce competition combined with policy interventions can lead to price erosion and only low cost companies will be successful.

For healthcare payers, the biosimilar mAbs provide some relief. Most relief will come when the biosimilar market develops into a generic-like market. But it is unlikely that innovator companies will continue to develop biosimilars once the market has become generic-like. When they stop developing biosimilars innovator companies can once again put up a lobby against biosimilars and therefore reinforce the “reach of innovator” barrier.

Continued growth is foreseen for biosimilars in developing non-saturated markets (Sheppard, 2011), mainly Central and Eastern Europe.

7.1 The case of biosimilar trastuzumab

Not only do the biosimilar mAbs differ from the currently available biosimilars they are a heterogeneous group themselves. As can be seen in the overview in appendix 1 the same reference product can be applied in

immune diseases and cancer. The biosimilar mAb developer faces different attitudes in the different physician groups (BioTrends, 2012). Further differences are in the innovator company they will be competing against and the new therapies for the same indications that enter the market.

Biosimilar trastuzumab is chosen to illustrate what the impact of barrier removal is for one specific biosimilar mAb.

Trastuzumab is currently marketed in Europe as Herceptin® by Roche. Global sales for Herceptin® totalled US\$ 6.3 billion (4.5 billion euro) in 2012 (La Merie, 2013). It is registered for the indication cancer, and mainly used to treat breast cancer. Oncologists are significantly more aware of biosimilars than physicians from other specialities (BioTrends, 2012), increasing the chance of fast uptake of biosimilars with cancer indications over those targeting different indications. However trastuzumab does not have a direct clinical effect that can be measured in the short term and MA for a biosimilar trastuzumab will likely be granted on the basis of surrogate endpoints rather than PFS/DFS or OS data. This complicates the design of phase III clinical trials. This will influence physician acceptance and therefore add strength to the lack of incentive barrier. It might also be of importance to the strength of the impossibility of substitution barrier, as it will be more difficult to prove interchangeability. The legislation on substitution can allow or prohibit biosimilar as a concept but also concern specific products.

Several companies are far advanced in developing a biosimilar trastuzumab, see appendix 1. The patent for trastuzumab in large EU markets expires in 2015 and only in 2019 in the US, see figure 1 (GaBI, 2013a). Roche has decided not to pursue its patent in India, opening this less regulated market to many copies (GaBI, 2013e). On January 15th 2014 Celltrion gained approval for biosimilar trastuzumab in South Korea (GaBI, 2014a). As mentioned before the Korean regulatory pathway is based on the EMA pathway. MA in Korea is a good indication that this biosimilar trastuzumab can also gain MA in the EU. Thereby Celltrion has overcome the manufacturing process barrier and the regulatory process barrier. Part of the IP challenge barrier will be specific to the EU and introduction of the product

on the European market could possibly lead to patent disputes over composition and application patents.

Rovira et al (2013) found that on average biosimilar competition starts three years after patent expiry. This would mean that Herceptin® can expect biosimilar competition to start in 2017. A newer version and enhanced version of trastuzumab would have to be significantly more efficacious to compare favourably in an ICER analysis with biosimilar trastuzumab and form a competitive threat. Roche has recently marketed two successors for Herceptin®, Perjeta®, a newer mAb, in 2012 and Kadcyla® an antibody-drug conjugate combining trastuzumab with emtansine in 2013 (Yang, 2010). Both have seen fast market uptake (Weintraub, 2014) and especially Kadcyla® seems to be a competitive threat to future biosimilar trastuzumab products, because of its positive results in phase III clinical trials EMILIA and TH3RESA (Goodman, 2013). The introduction of better innovative therapies may turn trastuzumab into a good enough therapy. A strong patient advocacy demanding the best treatment can put pressure on payers to reimburse these innovations and decrease the market potential for biosimilar trastuzumab. On the way to market success for its biosimilar trastuzumab Celltrion will face a strong reach of innovator barrier by opposing Roche. Assuming that because barriers to market entry in general cannot be completely removed, only seven of the 18 biosimilar trastuzumab developers from the overview in appendix 1, succeed in launching their product on the European market, this would equal the number of biosimilar filgrastim products currently available (Declerck & Simoens, 2012). This number of competitors is also consistent with the view of Sanford Bernstein Research, who believe large markets to eventually have around five biosimilar competitors, not one or two (Gal, 2011). The price of the reference product will go down, either through direct lower pricing or because of increased discounts and rebates, due to the loss of monopoly (Vogler et al, 2013). The increase of discounts and rebates does not directly benefit the healthcare system third party payer, but might lead to a better access of the medication within the hospital or investment by the hospital in other areas, resulting in

overall healthcare benefits. The access to treatment with trastuzumab increases as clinicians can treat more patients with the same budget. Demand-side policies will be needed to promote the use of biosimilar trastuzumab. More patients treated with biosimilar trastuzumab would result in more knowledge about the product through accumulation of PSY data. When these data show equal efficacy and safety in patients of the biosimilar trastuzumab to the reference product, and this information is effectively communicated, it will help to lower the lack of incentive and reach of innovator barriers.

The case of biosimilar trastuzumab continues in paragraph 8.1 with a calculation of potential cost savings.

8. Assessment of economic consequences

The current situation with high growth in biologics use is unsustainable for payers (Sheppard, 2013, Cornes, 2012a). Healthcare finance reforms have an impact on economic evaluations of drugs and put further pressure on drug prices. There is a need for biosimilar competition to drive drug prices down, but this competition needs to be sustainable in the long run in order to achieve lasting cost savings.

Biosimilar mAbs create an opportunity for cost containment (Haustein et al, 2012) and are needed to make treatment with biologics affordable and increase access to this treatment. As a consequence of lower prices, treatment plans can become more progressive with use of the biologic not just in secondary prevention or most serious cases but also in primary prevention and less serious cases (Lapadula & Ferraccioli, 2012).

When the barriers to market entry are overcome, next is the shape of the adoption curve, where biosimilar mAbs might profit from the slow adoption and knowledge gained with earlier biosimilars. Gal et al (2011) predict the current flattish, elongated adoption (S) curve to become sharper in future launches. The development of market share is associated with the lack of incentives, substitution rules and innovator reach. Government interventions

will be needed to give the biosimilars a chance to obtain market share (Lepage-Nefkens, 2013).

Haustein et al (2012) calculated that the development of market share and the time to market entry after patent expiration have a huge impact on the level of savings. Slow uptake and substitution restricted to new patients make that significant cost savings can only be achieved many years after biosimilar mAbs enter the market (Haustein et al, 2012).

Market entry of biosimilars will lead to a lower reimbursement price and further savings will come from a price reduction of the originator drug (Haustein et al, 2012). It is expected that the price of biosimilar mAbs will be around 20% lower than the reference product, this is a similar discount as is seen with the currently available biosimilars. A greater price reduction to the level of 80% as is seen for generic drugs is not likely because of the higher cost and longer time of development, the costly regulatory requirements and the price regulations by national governments (Declerck & Simoens, 2012). Prices for biologics, biosimilar and innovator, are expected to remain higher than for small-molecule drugs because of the higher marginal cost (Garrison, 2013).

Simoens (2011) describes the difficulty with assessing cost-effectiveness of biosimilars and suggests that the cost-effectiveness of a biosimilar changes when data on effectiveness in a real-world setting and long-term safety data become available. If both effectiveness and safety compare favourably or non-inferior to the reference product this will increase the pressure on the price. With multiple biosimilars on the market price erosion similar to that for generic drugs can follow. Rader (2013) predicts many companies adding biosimilars to round out their portfolios resulting in a generic like market, with as much as a dozen biosimilars on the market for one reference product after patent expiry. When the biosimilar market becomes generic-like, the same policies as used for generics can be applied to biosimilars. Dylst, Vulto and Simoens (2014) describe demand and supply side policies that influence generic market share in Spain. They recommend electronic prescribing systems and enforcement of INN prescription to increase the efficiency of

health care with regards to pharmaceuticals. While electronic prescribing systems will help to choose the least expensive alternative, INN prescription might not be appropriate for biosimilars because it would complicate accurate pharmacovigilance (Zuñiga & Calvo, 2010a, Gascón et al, 2013).

High uptake of biosimilars in Eastern European countries expands the market and gives these countries, e.g. Romania and Czech Republic, an opportunity to improve healthcare to bring it closer to Western European standards (Gal et al, 2011).

In Europe 4% of total healthcare expenditure are cancer related costs of which 30% is drugs (Luengo-Fernandez et al, 2013). Medication is only part of the cost of disease treatment. In cancer treatment however the introduction of monoclonal antibodies is described to have increased the cost of medication five hundred-fold (Cornes, 2012a). Even a 20% reduction in price results in substantial savings, this will also happen if the originator lowers its price and accepts a smaller profit on its mAbs. Haustein et al (2012) predict biosimilars to provide an accumulated cost savings of 11 to 33 billion euro between 2007 and 2020 in eight major EU countries. This estimation is largely based on the imminent market entry of biosimilar mAbs. Facilitated by the economic crisis and the consequential pressure on the healthcare budget (Rickwood, Kleinrock & Nunez, 2013) as well as the growing knowledge about and trust in biosimilars the higher estimates for 2020 are more likely to come true, compared to the estimates made in 2007 for savings in 2011 (Sheppard, 2013).

8.1 The case of biosimilar trastuzumab continued

An estimation of potential cost savings for biosimilar trastuzumab will be based on the data available for biosimilar filgrastim, approved by the EMA in 2009. Filgrastim is a biologic used in the treatment of neutropenia, a lack of certain white blood cells after chemotherapy (Aapro, Cornes & Abraham, 2011). It is therefore comparable to trastuzumab in that it is also used in cancer and therefore prescribed by the same group of physicians and not for long-term chronic treatment, even though filgrastim is used as acute

treatment and trastuzumab can be given as adjuvant or follow up therapy in consecutive treatment cycles (Genentech, 2014).

Sheppard and Iervolino (2012) place filgrastim and trastuzumab on opposite sites of the continuum between a commodity and a differentiated market. The commodity market is price-driven and highly competitive, while the differentiated market is characterised by limited competition and requires a greater marketing effort. The larger mAb structure and associated unclear mechanism of action and immunogenic risk position trastuzumab at the differentiated market site. Part of the measures available or in development that are proposed above to alleviate entry barriers, address these issues and propose advanced technologies that will clarify structural and pharmacodynamic uncertainties of mAbs.

Considering that experience with and knowledge of biosimilar mAbs will grow with time and lead to faster market uptake it is reasonable to extrapolate data for biosimilar filgrastim that was on the market for four years in 2013 to the situation for biosimilar trastuzumab in 2020.

Biosimilar filgrastim was found to be cost-efficient relative to its reference drug Neupogen[®] (Aapro, Cornes & Abraham, 2011). Annual savings in 2011 resulting from the use of biosimilar filgrastim rather than reference product amounted to 85 million euro across 17 EU countries (Gascón et al, 2013). Hausteine et al (2012) calculated the expected savings based on three scenarios of which two, 'slow growth' and 'fast growth', are based on the German generics market and the third, 'EPO', is based on the market uptake of EPO biosimilars. They have calculated a cost savings of between 5.5% and 15.3% for biosimilar filgrastim towards the expected cost volume in 2020.

Currently trastuzumab marketed as Herceptin[®] costs 2400 euro per month of treatment. Annual global sales for trastuzumab amounted to 4.5 billion euro in 2012 (LaMerie, 2013). The overall share of biologics sales for Europe is 21.6% (Rickwood & DiBiase, 2013), this would mean 1 billion euro for trastuzumab sales in the EU. Assuming that trastuzumab sales follow the forecasted biologic market growth and no biosimilar enters the market, they

will reach 6.7 billion euro by 2020. This translates into 1.4 billion euro for sales in Europe, assuming that the share of biologics sales for Europe will not change significantly. Based on the savings calculated for filgrastim, biosimilar trastuzumab can provide a cost saving in 2020 of 80 to 221 million euro in Europe. In 2009 the average spent on drugs for breast cancer treatment was 3.07 billion euro and made up 46% of total health care cost for breast cancer (Luengo-Fernandez et al, 2013). The introduction of biosimilar trastuzumab can lower the total health care cost for breast cancer or make payment of more advanced therapies, like Kadcyla[®], possible.

9. Discussion

Patent expiration of biotechnology drugs presents a possibility for other companies to develop generic versions of these biologics. Due to the differences between biologics and small molecule drugs, as presented in table 1, a new regulatory pathway and guidelines have been developed to ensure safety and efficacy of similar biologics. Innovator companies will defend their multibillion-dollar market share against the competition of these similar biologics. All this results in market dynamics that are still in full development, but differ from the small molecule generics market. This research aimed to determine the barriers for successful market entry, how these barriers could be removed and what the economic and other consequences of this removal might be.

A more accurate answer to the research question about the economic consequences will only be possible after biosimilar mAbs have actually entered the European market. Research into the subject of biosimilar mAbs is limited by the fact that they are novel products and most literature is trying to predict the future of biosimilar mAbs, but with so many uncertainties it is hard to assess the value of these predictions. In addition, as is the case with generic drugs, large differences in markets exist within Europe as a consequence of national and in some cases even regional health care policies. In this research project much of the analysis was based on data obtained with the currently available biosimilars. The principle of biosimilarity

is the same for all biosimilars. Even though the currently available biosimilars represent a diverse group they overall have a more simple structure, an understood mechanism of action (namely substituting an endogenous hormone or growth factor) and a lower risk of immunogenicity than biosimilar mAbs. It is therefore debatable to what extent data can be extrapolated to future market potential for biosimilar mAbs. Payers will be more eager to prefer a biosimilar mAb because even a small percentage discount on the high price results in a large cost saving, this is different from the earlier biosimilars for less expensive biologics.

An obstacle to transparency in the research data is the incorrect use of the term biosimilar. This complicated the gathering of information for the overview of biosimilar mAbs in development as presented in appendix 1 and the assessment of the potential number of future competitors. It is possible that a portion of the companies listed in the overview state on their website that they are developing biosimilar mAbs while they never intend to file for MA with the EMA but focus on market entry in less regulated markets.

Greater access to company data is needed to identify all identical biosimilar mAbs listed, as some may now be mentioned multiple times due to the small number of manufacturers and many partnerships in biosimilar mAb development. The long list of biosimilar mAbs in development shows the interest of companies in this market. However the fact that no biosimilar mAb has yet reached the major European markets is proof of the existence of effective market entry barriers. The clear identification of barriers to market entry helps to form strategies to overcome these barriers. It is important to overcome these barriers to achieve a positive return on investment. Many companies or alliance of companies have invested heavily in biosimilar mAb development and even though it is foreseen that only a few of these will actually be able to market a biosimilar mAb successfully, the others need to understand when to halt their effort and stop investing. Profound knowledge of the entry barriers will give companies insight in the capabilities needed to become successful and also the potential size of this success; they can therefore make a more informed choice about continuing their biosimilar mAb

development process. Furthermore this research identifies stakeholders, who play varying roles in potential biosimilar mAb success and need to be managed accordingly. Innovator companies can use the knowledge on market entry barriers and stakeholder roles in their biologics' life cycle planning and to put up an effective defence against biosimilar competition. Healthcare policy makers have to decide on interventions that will either facilitate or block biosimilar market uptake and can to some extent build on experience with the generic drug market.

The EMA regulation is demanding but at the same time accommodating to the development of biosimilars. Physician acceptance is likely to increase with time and experience and through objective information provision. A significant increase in biosimilar mAb uptake would come if national laws in EU countries are adapted to allow for substitution when safety data collected from the use of biosimilars show no added safety risks.

The experience with and efficacy and safety data from copies of mAbs marketed outside the EU will increase knowledge about the field of biosimilar mAbs (Mellstedt, 2013). On the other hand these copies or biogenerics, which are marketed in unregulated markets, mainly in Asia can also impact the image of biosimilars in a negative way. They have not passed a similarity assessment and can have different pharmaceutical activity from the originator. If use of a specific biogeneric proves to be safe and efficacious, then it may be concluded that for such a molecule the development parameters are less critical. This can benefit biosimilar acceptance. However if a large-scale adverse event, comparable to the red cell aplasia case with Eprex[®] a decade ago, happens with one of these biogenerics it will have a negative effect on the image of the biosimilar (Blackstone & Fuhr, 2008). This negative effect will likely be of more impact than any potential positive effect, because it adds to the uncertainty and fear that is already present.

It came as rather unexpected that many originator companies started the development of biosimilar mAbs. As a result it is likely that the "big pharma" lobby against biosimilars will become less fierce. At least in the short term all companies developing biosimilar mAbs should focus their lobby capacity on

achieving policy interventions that stimulate biosimilar mAb market uptake. It is understandable that innovator companies might not be as aggressive as others in this lobby, because for them the protection of their innovations is more valuable and they will likely no longer participate in the biosimilar market once this becomes more generic-like.

Policy interventions can reduce the time to market and help the biosimilar mAb to reach a large enough market share before the particular mAb becomes out-dated by new innovative products.

The healthcare payer will look for high discounts for biosimilars, but should be aware that price erosion will lead to less investment in biosimilar development with the ultimate consequence of a dry biosimilar pipeline.

Challenges are cost of development and limited accessible market size.

Opportunities are increase in market size through improved access for lower income countries and use of biotechnology know how to create innovative drugs.

Throughout this thesis it is assumed that health economics play a large role in the assessment of new drugs and reimbursement decisions, leading to access of biologics to patient groups and that this will remain even when the economic crisis in the EU is over.

The calculation of cost savings achieved by the market entry of biosimilar trastuzumab would undoubtedly be more accurate had more recent and specific data on price, cost volume and expected volume growth been accessible. A further distinction between different European countries would then also have been possible and would have provided additional insight. As illustrated in figure 5, within Europe the individual countries differ in their market uptake pattern for biosimilars (Rickwood & DiBiase, 2013).

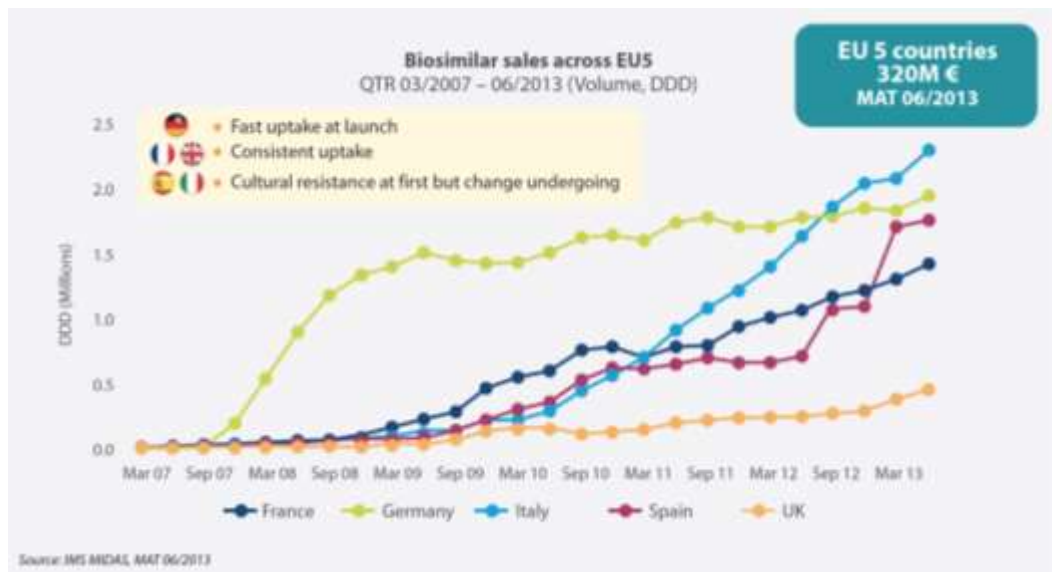


Figure 5. Uptake of biosimilars in five European countries (Rickwood & DiBiase, 2013 p.10)

The cost savings for trastuzumab were now calculated from sales figures. Sales figures differ from cost when reimbursement prices do not match list prices and due to rebates and discounts given in hospitals. The use of list price does not accommodate for the discounts and rebate packages that hospital procurement organisations are often able to negotiate (Vogler, 2013). However since these discounts are not always passed on to the third party payer, the list price would have been the most objective value to use here in calculations for cost savings (Walsh, 2013). In the analysis the payer perspective was chosen over the societal, provider and patient perspective (Garrison, 2013). When assuming all other costs are equal the probability of biosimilar use for those patients that currently have no access to trastuzumab is ignored. The economic benefit of increased patient access to treatment with trastuzumab as a result of the lower price of the biosimilar can be substantial when this treatment leads to a decrease in sickness and related productivity loss.

Economic studies calculating the ICER per QALY gained for mAb treatment in rheumatoid arthritis (RA) suggest that the use of mAb should not be restricted to the most severe cases (Lapadula & Ferracioli, 2012). With the introduction of biosimilar mAbs for RA the cost of medication will go down allowing for a greater part of the patient population than just the severe cases

to be treated. This will be of benefit to the national economy as these patients can be more productive and will have less disease related complications.

The innovation in medicine is eagerly pursued, not in the least part due to the decreasing and limited profit opportunities in the generics and biosimilars market. This innovation can be incremental with small changes to existing treatments, e.g. antibody-drug conjugates, or radical, as it was when the monoclonal antibodies were first introduced. A radical innovation that is more cost effective than the use of monoclonal antibodies discussed in this thesis, will largely affect the potential benefits for biosimilar mAbs.

A potential failure of biosimilar mAbs to become successful would not only impact the biosimilar developer but also related industries, e.g. CRO and analytical services, who have recently targeted their effort and expertise to supporting biosimilar mAb development

Many of the companies currently developing biosimilar mAbs are thought to terminate at least part of these programs for different reasons. These companies may very well benefit from their efforts towards biosimilar mAb development. With less money available for R&D of innovative drugs and the little scientific added value of the clinical trials needed for MA, the development of biosimilars can be said to counter innovation. However biosimilars do contribute to innovation in production processes and analytical procedures (Lepage-Nefkens et al, 2013). The different approach needed for biosimilar development (Calo & Martínez, 2012) means a break from the traditional way of drug development. This break from tradition can open the way for more innovation in the company (Tidd, 2006). The next paradigm shift in medical treatment is thought to bring personalised therapeutics to the mass market (FierceBiotech, 2014).

10. Conclusion

The main barriers to market entry for biosimilar mAbs in Europe are the manufacturing process and the regulatory process. These barriers can be overcome by a combination of resources and capabilities, as is proven by the

market entry of biosimilar infliximab. The barriers to subsequent market success are the IP challenge, the lack of incentive for stakeholders in the market, the impossibility of substitution and the reach of the innovator. It is in the interest of both the companies developing biosimilars and the healthcare payers that biosimilar mAbs can obtain market approval and significant market share. Allowing substitution for biosimilars for all patients currently using reference products would have the biggest impact, but this is not foreseen in the near future due to safety issues. Biosimilar developers can increase market share with marketing strategies that are focused on diversifying their product through branding and service offerings. All parties should make an effort to better involve physicians in the regulatory process and to increase the knowledge diffusion on biosimilars. Long-term mechanisms to enhance biosimilar market access are changes in patent law and global alignment of biosimilar approval regulations. Important factors are competitive threat from radical innovations and government interventions to stimulate biosimilar market uptake.

Key stakeholders, in particular the innovator companies and the health care payers, determine the strength of the remaining barriers to market success. The possibility to overcome these barriers to success needs to be addressed case by case, depending on the relevant patents, the innovator company concerned and the physician and patient groups. Biosimilar trastuzumab faces a strong defence strategy of the innovator company Roche, who has developed both a new, more convenient, route of administration for the reference product and two innovative successor products that will compete for market share with the biosimilar. Patient groups might advocate receiving these newer treatments and rejecting treatment with a cheaper biosimilar trastuzumab.

On the other hand biosimilar trastuzumab will be applied in cancer and this is an indication where costs have been rising above budgets. Therefore health care payers will welcome a less expensive treatment alternative and should employ the appropriate policies to increase its market uptake. From all prescribing physicians, oncologists are least reluctant to prescribe biosimilars

to their patients for the currently available biosimilars and possibly for biosimilar mAbs. Based on the market uptake of and savings achieved with biosimilar filgrastim the market entry of biosimilar trastuzumab will lead to cost savings between 80 and 221 million euro. These savings can be used to pay for more advanced treatment or to cover costs elsewhere in the health care system.

11. Recent developments and suggestions for further research

France recently changed its legislation so that biosimilar substitution of first prescription is now allowed (GaBI, 2014b). This restricted allowance of substitution will not increase market uptake hugely as it does not allow for switching. Instead this law tends to stigmatise biosimilars and may actually limit the market potential for biosimilars in France (DiBiase, 2014).

Norway and Poland have allowed biosimilar infliximab on the market and added it to the reimbursement list with a 39% and 32% discount compared to the reference product respectively. In Norway biosimilar infliximab experienced fast market uptake through a national tender (Benassi, 2014). The Norwegian government wants to further increase uptake by funding a head-to-head study of biosimilar infliximab versus the reference product to help convince physicians to prescribe the biosimilar. This is probably not the best move to make as it justifies doubts to the EMA approval and if the study has a negative outcome for the biosimilar can discredit all other and future biosimilars (King, 2014).

In January 2014 Biocon introduced biosimilar trastuzumab in India at a 25% discount from the reference product and with some storage and vial size advantage over the reference product. Biocon has a global partnership with Mylan and all trials for the biosimilar trastuzumab followed international regulatory and quality guidelines, this is an indication of the intent to market the product globally (Biocon, 2014). Roche is defending against this move and has sued Biocon and Mylan and won, so that they can't claim their products are biosimilar (GaBI, 2014c). In the UK on April 10th 2014 Hospira

succeeded in having two patents on Herceptin[®] declared invalid, which helps pave the way for their biosimilar trastuzumab (Hirschler, 2014).

The United States is by far the biggest market for biologics and its market entry issues are different from the EU (Gal et al, 2011, Lepage-Nefkens et al, 2013) and make for an interesting research subject. Part of the investment in biosimilar mAb development currently come from private equity (Hollamby, 2013), additional research can focus on the sustainability of this resource for biosimilar development. Further research should be done into the knowledge of biosimilars mAbs with national health authorities deciding on reimbursement and demand side policies. This would clarify the precise obstacles for biosimilars mAb with these authorities. Another interesting subject for further research is the potential that similar biologics available in semi- and unregulated markets have to obtain market approval in regulated markets.

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Appendix 1: see overview of biosimilar mAb development on next two pages

Inventory of imminent antibody biosimilars

Generic name	expiration EU	Indication	Reference	Company	Developer	Code-name	Marketer	EMA-filing	Status	Development phase
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Synthon / Watson (Actavis)	ABP 980	Amgen	n/a	dec-13	Phase III
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Celtrion/Nippon Kayaku	CT-P6	Hospira	n/a	dec-13	Phase III, Korea, Romania
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Emcure India		Roche	n/a	apr-12	ww sales 5 billion\$ (2011), deal that allows emcure to produce Roche's product for Indian market
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Pfizer	PF-05280014	Pfizer	n/a	nov-13	Phase I completed, Phase III is planned
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Biocon India	Bmab-200	Biocon India/Mylan	n/a	aug-13	Phase III in India completed (Aug2013)
trastuzumab	aug-15	breast cancer	Herceptin	Roche	PlantForm			n/a	apr-13	clinical trials scheduled for 2014
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Blocad	BCD-022		n/a	jan-13	Phase III, Russia, India, Belarus
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Gedeon Richter		STADA		apr-13	?
trastuzumab	aug-15	breast cancer	Herceptin	Roche	BioXpress				apr-13	in development
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Hanwha Chemical	HD-201	Merck		mar-12	Phase I
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Oncobiologics				nov-13	preclinical
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Viropro				nov-13	
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Curaxys					production
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Cipla					
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Nichi-Iko Pharmaceutical					
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Nacto/Mabxience					
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Dong-A/Meiji Seika Pharma	DA-3111			dec-13	preclinical
trastuzumab	aug-15	breast cancer	Herceptin	Roche	Mabxience		Natco Pharma		oct-11	Natco purchases compound to test and market in Asia
etanercept	feb-15	arthritis	Enbrel	Amgen	Celtrion		Hospira	n/a	dec-11	clin trials in Korea
etanercept	feb-15	arthritis	Enbrel	Amgen	Hanwha	HD203		n/a	apr-13	dec 2012 merck terminated MK 8953 now called HD203 Phase II completed in Korea
etanercept	feb-15	arthritis	Enbrel	Amgen	Samsung	SB4	Samsung	n/a	jun-13	Phase III started June 2013 (n=500)
etanercept	feb-15	arthritis	Enbrel	Amgen	Sandoz	GP2015	Sandoz	n/a	sep-13	Phase III started June 2013 (n=ca.400)
etanercept	feb-15	arthritis	Enbrel	Amgen	Viropro			n/a	nov-13	not disclosed
etanercept	feb-15	arthritis	Enbrel	Amgen	Shanghai CP Goujian Pharmaceutical	Etacept	Cipla	n/a	apr-13	launched in India at 30% discount on originator price
etanercept	feb-15	arthritis	Enbrel	Amgen	BIOXpress Therapeutics			n/a		
etanercept	feb-15	arthritis	Enbrel	Amgen	Avesthagen	Avent		n/a	apr-13	preclinical
etanercept	feb-15	arthritis	Enbrel	Amgen	LG Life sciences	LBEC0101		n/a	apr-13	Phase I completed in Korea
etanercept	feb-15	arthritis	Enbrel	Amgen	Mycenax Biotech	TuNEX		n/a	apr-13	Phase III, Japan, Korea
etanercept	feb-15	arthritis	Enbrel	Amgen	Protalix	PRX-106		n/a	apr-13	preclinical
etanercept	feb-15	arthritis	Enbrel	Amgen	Shanghai CP Goujian Pharmaceutical	Etanar, Yisaipu		n/a	apr-13	Colombia, China
etanercept	feb-15	arthritis	Enbrel	Amgen	Coherus Biosciences		Baxter	n/a	sep-13	collaboration
etanercept	feb-15	arthritis	Enbrel	Amgen	Biocon		Mylan	n/a		
etanercept	feb-15	arthritis	Enbrel	Amgen	zenotech			n/a	nov-13	Phase III
etanercept	feb-15	arthritis	Enbrel	Amgen	intas			n/a	nov-13	Phase III
etanercept	feb-15	arthritis	Enbrel	Amgen	Mabxience		Natco Pharma		oct-11	Natco purchases compound to test and market in Asia
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Celtrion	CT-P13(Remsuma)	Hospira	apr-12	apr-12	
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Nichi-Iko Japan	NI-074	Nichi Iko, Sanofi	n/a	may-13	Phase III planned for June 2013
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Mitsubishi Tanabe Pharma	TA-650	Mitsubishi Tanabe Pharma	n/a	sep-12	Multiple trials
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Samsung	BS2	Samsung	n/a	sep-12	Phase III (Sept 2013); n = 586
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Pfizer		Pfizer	n/a	nov-13	in trial in 2014
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	BioXpress			n/a	apr-13	in development
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Amgen			n/a	apr-13	in development
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Episun	BOW-015		n/a	sep-13	Phase III
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Viropro			n/a	nov-13	
infliximab	feb-15	rheumatology	Remicade	J&J/Pfizer	Curaxys			n/a	nov-13	production

Generic name	expiration EU	Indication	Reference	Company	Developer	Code-name	Marketer	EMA-filing	Status	Development phase										
rituximab	nov-13	oncology / arthritis	Mabthera	Roche	dr Reddy's Laboratory	Redtux				Bolivia, Chile, India and Peru										
rituximab	nov-13	oncology / arthritis	Mabthera	Roche	Celltrion	CT-P10	Hospira	n/a	nov-13	Phase I RA, lymphoma2012Phase III planned for 2H13										
rituximab	nov-13	oncology / arthritis	Mabthera	Roche	Sandoz	GP2013	Sandoz	n/a	apr-13	phase III RA and nH lymphoma, phase III adv. foll. lymphoma										
rituximab	nov-13	arthritis	Mabthera	Roche	Lonza	TL011	Teva	n/a	apr-13	Phase III halted, input from regulators needed										
rituximab	nov-13	arthritis	Mabthera	Roche	Merck Bioventures	MK8808	MSD	n/a	apr-13	Phase I, Belarus										
rituximab	nov-13	arthritis; lymphoma	Mabthera	Roche	Boehringer Ingelheim	BI695500	Boehringer I	n/a	oct-13	Phase III RA started, Phase II Lymphoma										
rituximab	nov-13	arthritis	Mabthera	Roche	Pfizer	PF-05280586	Pfizer	na	nov-13	Phase II RA recruiting										
rituximab	nov-13	?	Mabthera	Roche	Biocad	BCD-020	??	na	oct-13	Phase III RA completed Oct2013										
rituximab	nov-13	arthritis	Mabthera	Roche	Samsung Biologicals	SAIT101	Quintiles	na	nov-13	Phase III halted due to uncertainty over biosimilar regulation in the US										
rituximab	nov-13	?	Mabthera	Roche	Gedeon Richter		STADA		apr-13											
rituximab	nov-13	?	Mabthera	Roche	Viropro		Spectrum		nov-13	Phase III										
rituximab	nov-13	?	Mabthera	Roche	iBio				apr-13	announcement of rituximab production in nontransgenic green plants in 2011										
rituximab	nov-13	?	Mabthera	Roche	Amgen				apr-13	in development										
rituximab	nov-13	?	Mabthera	Roche	BioXpress				apr-13	in development										
rituximab	nov-13	?	Mabthera	Roche	Probiomed		Kikuzubam		apr-13	Bolivia, Chile, Mexico and Peru										
rituximab	nov-13	?	Mabthera	Roche	Roche				apr-13	In March Severin Schwan, CEO, was quoted, biosimilar launch pushed back from 2016 to end of decade										
rituximab	nov-13	lymphoma	Mabthera	Roche	Emcore		Roche		apr-12	deal that allows emcore to produce Roche's product for Indian market										
rituximab	nov-13	lymphoma	Mabthera	Roche	Oncobiologics				nov-13	Preclinical										
rituximab	nov-13	arthritis	Mabthera	Roche	Zydus Cadila				nov-13	Phase III, India										
rituximab	nov-13	lymphoma	Mabthera	Roche	Viropro		Intas		nov-13	Phase III, India										
rituximab	nov-13	?	Mabthera	Roche	Curaxys				nov-13	production										
rituximab	nov-13	oncology	Mabthera	Roche	Mabxience		Natco Pharma		oct-11	Natco purchases compound to test and market in Asia										
adalimumab	apr-18	arthritis	Humira	AbbVie	Boehringer Ingelheim	BI695501	Boehringer I	n/a	oct-12	Phase I completed (New Zealand)										
adalimumab	apr-18	arthritis	Humira	AbbVie	Pfizer		Pfizer	n/a	nov-13	Phase I to start 2014										
adalimumab	apr-18	arthritis	Humira	AbbVie	Biocon		mylan			Preclinical										
adalimumab	apr-18	arthritis	Humira	AbbVie	AET BioTech and BioXpress		AET BioTech	n/a	apr-13											
adalimumab	apr-18	arthritis	Humira	AbbVie	Amgen		Amgen	n/a	apr-13	in development										
adalimumab	apr-18	arthritis	Humira	AbbVie	Fujfilm and Kyowa Hakko Kirin	FKB327		n/a	apr-13	Phase I in UK										
adalimumab	apr-18	arthritis	Humira	AbbVie	Oncobiologics			n/a	nov-13	Preclinical										
adalimumab	apr-18	arthritis	Humira	AbbVie	Zydus Cadila			n/a	nov-13	Phase III										
bevacizumab	jan-22		Avastin	Roche	Pfizer		Pfizer	n/a	nov-13	Phase I to start Q1/2014										
bevacizumab	jan-22		Avastin	Roche	Biocad	BCD-021			nov-13	Phase III										
bevacizumab	jan-22		Avastin	Roche	Actavis		Amgen		apr-13	in development										
bevacizumab	jan-22		Avastin	Roche	Biocon	Bmab100	Mylan			Preclinical										
bevacizumab	jan-22		Avastin	Roche	Fujfilm and Kyowa Hakko Kirin				apr-13											
bevacizumab	jan-22		Avastin	Roche	BioXpress				apr-13											
bevacizumab	jan-22		Avastin	Roche	Boehringer Ingelheim	BI695502			nov-13	Phase I completed										
bevacizumab	jan-22		Avastin	Roche	Oncobiologics				nov-13	Preclinical										
bevacizumab	jan-22		Avastin	Roche	Viropro				nov-13	sequence determined open to discuss partner possibilities										
bevacizumab	jan-22		Avastin	Roche	Mabxience		Natco Pharma		oct-11	Natco purchases compound to test and market in Asia										
cetuximab	jun-14		Erbix	BMS	Actavis		Amgen													
cetuximab	jun-14		Erbix	BMS	Oncobiologics				nov-13	Preclinical										
abctimab			ReoPro	Eli Lilly	Reliance Life Sciences	R-TPR-019			nov-13	Phase III, India										
??					Zhejiang Huahai Pharmaceutical					strategic partner with oncobiologics										
??					Samsung Biologics		Biogen Idec		dec-11											
??					Momenta		Baxter		dec-11	agreement for the development of six biosimilars, 3 mAbs M923, M834 and M511										
??					Biocon (cancelled?)		Pfizer		dec-11											
??					Stada		??		dec-11											
??					Cipla		??		dec-11											
??					GE Healthcare		??		dec-11											
??					Biocon		Mylan		apr-11	5 mAbs contract										
??					Epirus				sep-13	4 mAbs in preclinical development BOW030, BOW040, BOW050, BOW060										
??					Gene Techno Science				nov-13	5 mAbs in development GND-001, GND-002, GND-003, GND-004, GND-005										
??					Glenmark															
Sources:	Company websites www.biosimilars.com (29/12/2011) Nature Biotechnology, April 2012 http://apps.who.int/trialsearch																			
	https://www.clinicaltrialsregister.eu http://www.biocentury.com http://igabionline.net http://clinicaltrials.gov																			

Appendix 2: List of experts consulted for their opinion on the subject of research in alphabetical order

J. Bos	Director MS Ventures, Merck Serono
S. DiBiase	Consultant Thought Leadership, IMS Health
S. Simoens	Professor of Clinical Pharmacology and Pharmacotherapy at Research Centre for Pharmaceutical Care and Pharmacoeconomics, Faculty of Pharmaceutical Sciences, Katholieke Universiteit Leuven, Leuven, Belgium.
A. Vulto	Professor of Hospital Pharmacy at Erasmus University Medical Center, Rotterdam, The Netherlands.