

Seminar Briefing 15

Biosimilar Competition: Lessons from Europe and Prospects for the US

Proceedings by Professor Henry Grabowski, Duke University

1. INTRODUCTION

In 2009, the Office of Health Economics (OHE) organised a conference on the economics of biosimilars (Mattison et al., 2010). At that time the US did not have an established regulatory pathway for biosimilars – it was in the making for a long time – and Europe just had the first EMA-approved biosimilars. Much of the discussion then was focused on theoretical models. My work with David Ridley and Kevin Schulman (Grabowski et al., 2007) looked at biosimilars from the cost side. Given the much higher cost of entry, competition was expected to evolve somewhat differently relative to chemical generics. The work by OHE (Chauhan et al., 2008) focused on how the sectors and the demand could be differentiated and segmented. Now, five years later, particularly in Europe we have a track record of biosimilar competition; albeit it is still evolving. The work presented here is work in progress.

The US is still in germination stage, but I think we will be seeing biosimilars in the US in the next few years. With this in mind, the structure of this Seminar Briefing is as follows. First, I review the European experience with biosimilars, including exploring how the market has evolved for two biologic

Table of Contents

1. INTRODUCTION	1
2. BIOSIMILARS APPROVED IN EUROPE	2
3. RESULTS: EVOLUTION OF MARKET SHARES OF BIOSIMILARS IN EUROPE	4
4. FURTHER RESEARCH ISSUES FROM A EUROPEAN PERSPECTIVE	10
5. KEY FACTORS DETERMINING HOW BIOSIMILAR COMPETITION EVOLVES	11
6. WHAT TYPE OF FIRMS ARE POTENTIAL ENTRANTS FOR BIOSIMILARS?	13
7. HOW IS THE US MARKET FOR BIOSIMILARS LIKELY TO EVOLVE?	14
7.1 Regulatory requirements to establish biosimilarity in the US	16
7.2 Biosimilars vs generics: nature of competition and incentives in the US	17
7.3 Case studies in the US – Omnitrope and Enoxaparin	19
7.4 Full BLAs vs biosimilar pathway	21
8. SUMMARY AND CONCLUSIONS	22
REFERENCES	24
GLOSSARY	25

products with biosimilars in five European countries. Based on this analysis, I highlight some key summary points and outline potential future research avenues. I then present an overview of the current state of affairs for the US biosimilars market, and consider some broad lessons for the US and how the US may evolve.

Pharmaceuticals are small molecules, whereas biologics are very large molecules. For instance, the complexity of two major products such as Herceptin (large molecule) and Lipitor (small molecule) is very different. The biologic space is often an injectable and infused product, whereas in pharmaceuticals it is usually an oral solid. Biologics, to the extent that they are injector-infused, are generally dispensed in clinics or hospitals. In the US that is usually a “medical benefit” – whereas an oral solid will be a “pharmacy benefit”. These have very different incentives and rules.

2. BIOSIMILARS APPROVED IN EUROPE

I will focus on what we have learned so far from Europe’s experience with biosimilars. Table 1 shows the approval dates for EMA-approved biosimilars in the area of human growth hormones, erythropoietins (EPOs) and granulocyte-colony-stimulating-factors (G-CSFs) (as of May 2013).

Table 1. Approval dates for EMA-approved biosimilars

Trade Name	Active Substance	Biosimilar Sponsor	Reference Product	Therapeutic Area	Approval Date
Omnitrope ®	somatropin	Sandoz	Genotropin®	Turner Syndrome, Pituitary Dwarfism, Prader-Willi Syndrome	April 12, 2006
Valtropin* ®	somatropin	BioPartners	Humatrope®	Turner Syndrome, Pituitary Dwarfism	April 24, 2006
Abseamed ®	epoetin alfa	Medice	Eprex®	Chronic Kidney Failure, Anemia, Cancer	Aug. 28, 2007
Binocrit ®	epoetin alfa	Sandoz	Eprex®	Chronic Kidney Failure, Anemia	Aug. 28, 2007
Epoetin alfa Hexal ®	epoetin alfa	Hexal	Eprex®	Chronic Kidney Failure, Anemia, Cancer	Aug. 28, 2007
Retacrit ®	epoetin zeta	Hospira	Eprex®	Anemia, Autologous Blood Transfusion, Cancer, Chronic Kidney Failure	Dec.18, 2007

Trade Name	Active Substance	Biosimilar Sponsor	Reference Product	Therapeutic Area	Approval Date
Silapo ®	epoetin zeta	Stada	Eprex ®	Anemia, Autologous Blood Transfusion, Cancer, Chronic Kidney Failure	Dec. 18, 2007
Biograstim ®	filgrastim	AbZ-Pharma	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Sept. 15, 2008
Ratiograstim ®	filgrastim	Ratiopharm	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Sept. 15, 2008
Tevagrastim ®	filgrastim	Teva	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Sept. 15, 2008
Filgrastim Hexal ®	filgrastim	Hexal	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Feb. 6, 2009
Filgrastim Zarzio ®	filgrastim	Sandoz	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Feb. 6, 2009
Nivestim ®	filgrastim	Sandoz	Neupogen ®	Cancer, Hematopoietic Stem Cell Transplantation, Neutropenia	Feb. 6, 2009

Source: EMA

Notes from the Editor: Since this seminar, EMA has approved one further biosimilar filgrastim (Grastofil® (Apotex) on October 18, 2013) and two biosimilars (Inflectra® (Hospira) and Remsima® (Celltrion) on September 10, 2013) for the reference product Remicade® (infiximab)

*Valtropin was withdrawn from the market by the manufacturer for commercial reasons.

Of all the biosimilars included in Table 1, the only overlap with the US is the first, Omnitrope. Omnitrope has been available in the US for a comparable period. The details of how Omnitrope was approved in the US are discussed in greater detail below.

My focus is on the G-CSFs and the EPO products in Europe. Biosimilars for these two products have been available since 2007/2008, with five or six products. Eprex (epoetin alfa) is the reference product for the EPOs and Neupogen (filgrastim) is the reference product for the G-CSFs. As discussed later, we also explore the impact on the evolution of the market of second generation versions of these two reference products. We have quarterly data over the period 2009 to 2011 for France, Germany, Italy, Sweden and the UK, from IMS.

Before discussing the results of the analysis of the evolution of the market for EPOs and G-CSFs, it is important to discuss the incentives to use biosimilars in different countries. Germany has had the greatest incentives to utilise biosimilars. It has a tradition of generic usage but in addition there are quotas for the Sickness Funds and for physicians for biosimilars that vary by region; these can be as high as 50 per cent. It has also instituted reference pricing for biosimilars. These are strong incentives. Most of the manufacturers of biosimilars come out of Germany and so biosimilars enjoy a fairly high reputation.

The UK and Sweden also have a strong tradition of generic usage (via physician and reimbursement incentives), which is one characteristic that might translate into receptivity to biosimilars. We included Sweden in our analysis because its health care system is highly decentralised to county councils, cost-effectiveness is used to determine access to medicines and prices for branded medicines tend to be high relative to other European countries. France and Italy provide very different regulatory systems, as does the UK.

It should be noted that regulations are evolving over time, so what is observed at one period may change over time.

3. RESULTS: EVOLUTION OF MARKET SHARES OF BIOSIMILARS IN EUROPE

The data sample contains a count of the biosimilars in each of the five countries, from first quarter of 2009 to the last quarter of 2011. Table 2 shows the count of biosimilars for EPOs and G-CSFs in the five countries, for selected quarters.

In the EPO area, the first products were approved by the EMA in the latter part of 2007. Germany and Sweden had biosimilars within that year, followed by the other countries in 2008 and 2009 (see column "biosimilar entry date" in Table 2).

Table 2. Count of biosimilars

Count of Biosimilars By Category and Country						
Category	Country	Biosimilar Entry Date	QTR 1 2009	QTR 4 2009	QTR 4 2010	QTR 4 2011
Erythropoietin	Germany	October-07	5	5	5	5
Erythropoietin	France	July-08	1	2	2	2
Erythropoietin	Italy	October-08	1	2	3	3
Erythropoietin	UK	May-09	0	2	2	2
Erythropoietin	Sweden	August-07	2	2	1	1
G-CSF	Germany	November-08	3	3	4	4
G-CSF	France	March-09	1	2	3	4
G-CSF	Italy	June-09	0	1	3	4
G-CSF	UK	October-08	1	3	5	5
G-CSF	Sweden	September-08	0	1	3	3

Source: IMS MIDAS data.

Biosimilar G-CSFs were approved in the latter part of 2008. Once again Germany and Sweden had the earliest launches (although this time there was biosimilar entry in the UK after Sweden but before Germany). By the first quarter of 2009 Germany had five separate products. They are not always separate companies but separate products, under different names. Similarly, Germany had a rapid introduction of G-CSF biosimilars. By the last quarter of 2011 five EPO and four G-CSF biosimilars were available.

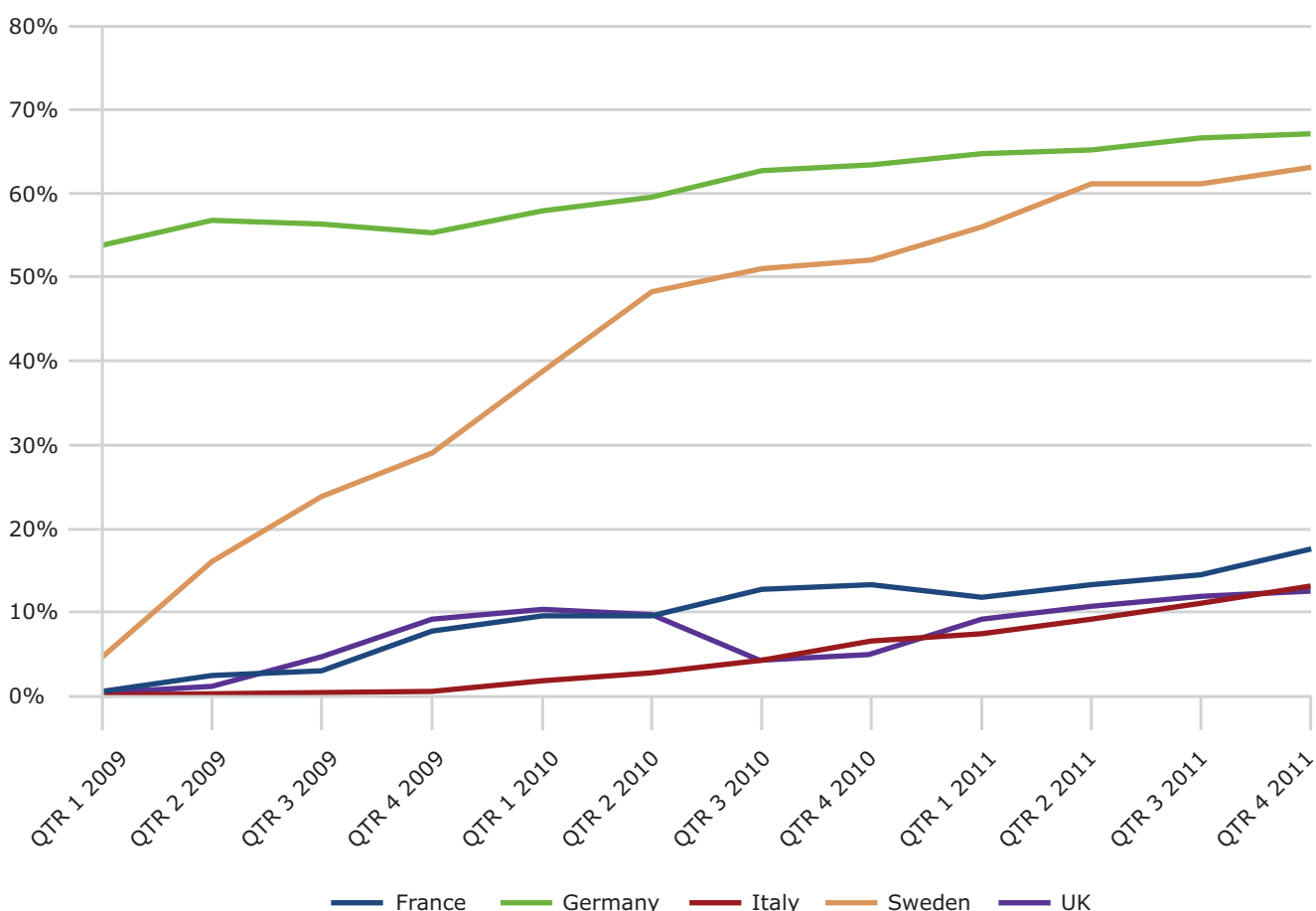
There is some variability between the EPO space and the G-CSF space. For example, by the end of 2011 in four countries there were more G-CSF biosimilars than EPO biosimilars (Germany being the exception). The variance in the number of biosimilars available across the five countries is lower for

the G-CSFs than for the EPOs. As discussed below, the share gained by the biosimilars in the G-CSF market tends to be higher than in the EPOs market.

Figure 1a looks at the evolution of biosimilar shares for the EPO market across the five countries. The audit data is collected in volume terms in what IMS refers to as “standard unit vials”. We converted this to defined daily doses (DDDs). First I look only at the Eprex market segment and then I will add Aranesp, the second generation product.

Biosimilars referenced to Eprex in Germany and Sweden had a market share in excess of 60 per cent by the fourth quarter in 2011, whereas the other three countries have epoetin biosimilar shares of less than 20 per cent. There is a contrast though in the evolution of the market share between Germany and Sweden. By early 2009, a little over a year after the first launch, biosimilars’ share of the market, in terms of daily doses, was close to 60 per cent in Germany. Sweden started close to zero in the beginning of our sample but the biosimilars’ share was around 60 per cent by the end of 2011. Shares in terms of revenues exhibit similar outcomes across these countries (Grabowski et al., 2014a).

Figure 1a. Biosimilar share of Epoetin (alfa and zeta) / Eprex market segment 2009-2011 (calculated in daily doses)



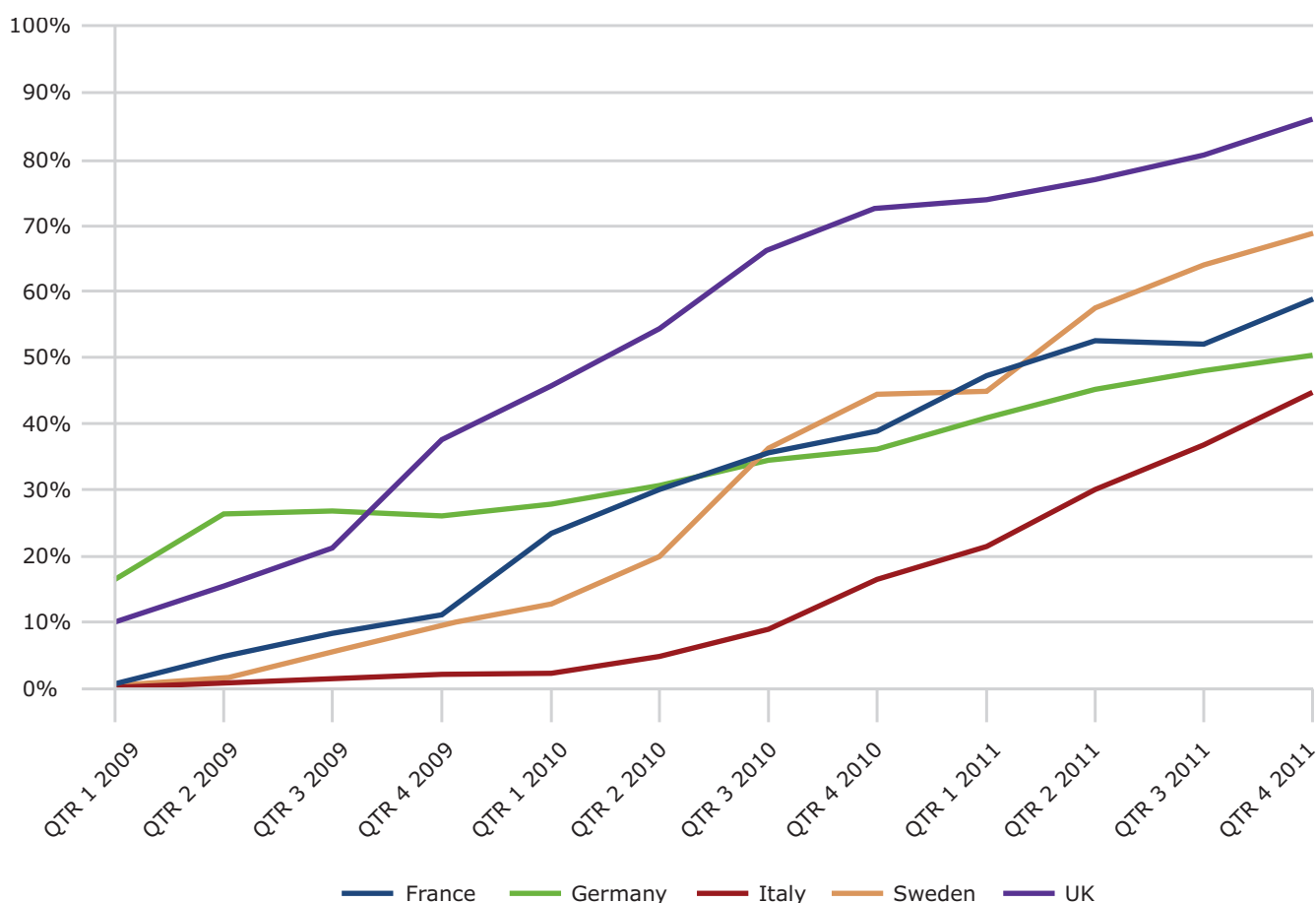
Source: IMS MIDAS data.

Note: The biosimilar products are Retacrit and Binocrit in France; Epoetin Alfa Hexal, Silapo, Abseamed, Retacrit, and Binocrit in Germany; Retacrit, Binocrit, and Abseamed in Italy; Retacrit and Binocrit in Sweden; and Retacrit and Binocrit in the UK.

Of the five countries, Germany and Sweden have a large market penetration for EPO biosimilars. The other three countries show a more mixed evolution but EPO biosimilars represent a much smaller share of the market. It is somewhat surprising that the UK and France were so low. Later I will discuss why that might be so.

The filgrastim/Neupogen market behaves differently to the EPO market. In particular, there is a more rapid and extensive market penetration for biosimilars than in the case of Eprex. This greater acceptance of filgrastim biosimilars in the G-CSF market appears to reflect both medical considerations and reimbursement policies (Grabowski et al., 2014a; 2014b). For instance, it has been argued that biosimilars penetration has been higher for the G-CSFs as the impact of treatment is more readily apparent and therefore any concerns over efficacy can be immediately addressed (IMS, 2011). Figure 2a shows the biosimilars' share of the filgrastim-Neupogen market segment in volume terms.

Figure 2a. Biosimilar share of Filgrastim/Neupogen market segment, 2009-2011 (calculated in daily doses)



Source: IMS MIDAS data.

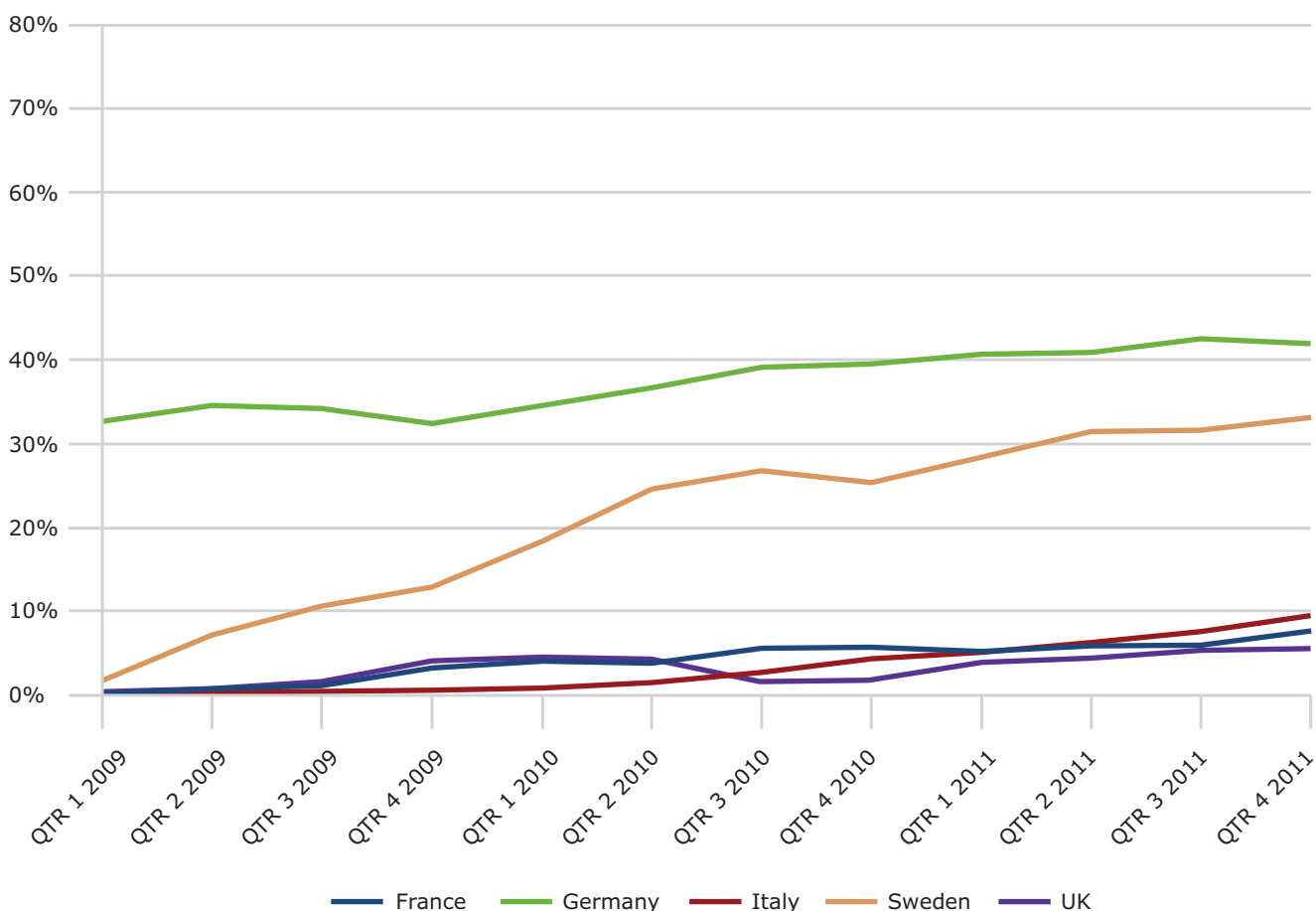
Note: The biosimilar products are Zarzio, Tevagrastim, Ratiograstim, and Nivestim in France; Filgrastim-Hexal, Ratiograstim, and Nivestim in Germany; Zarzio, Tevagrastim, Ratiograstim, and Nivestim in Italy; Zarzio, Ratiograstim, and Nivestim in Sweden; and Zarzio, Ratiograstim, Nivestim, Filgrastim, Teva, Tevagrastim, and Filgrastim Sandoz in the UK.

Biosimilars attained shares of between 45 per cent (Italy) and 87 per cent (the UK) by the end of 2011. A very similar picture emerges based on revenue shares (Grabowski et al., 2014a).

In both the EPO and the G-CSF markets, the reference product and its biosimilars compete with a second generation product. These second generation products are longer-lasting, so patients require substantially fewer infusions over a course of treatment. Aranesp and Neulasta are the second generation products in the EPO and GCS-F market respectively. In both markets, they were introduced prior to biosimilar entry.

A very different picture emerges when the second generation products are considered. Broadly speaking, shares of the biosimilars are substantially smaller in terms of this broader market segment when compared to the market segment without the second generation products (Figures 1a and 2a above). This reflects the fact that the second -generation products have the largest overall share in most countries. Figure 1b replicates Figure 1a, but includes Aranesp.

Figure 1b. Biosimilar share of Epoetin (alfa and zeta) / Eprex/Aranesp market segment 2009-2011



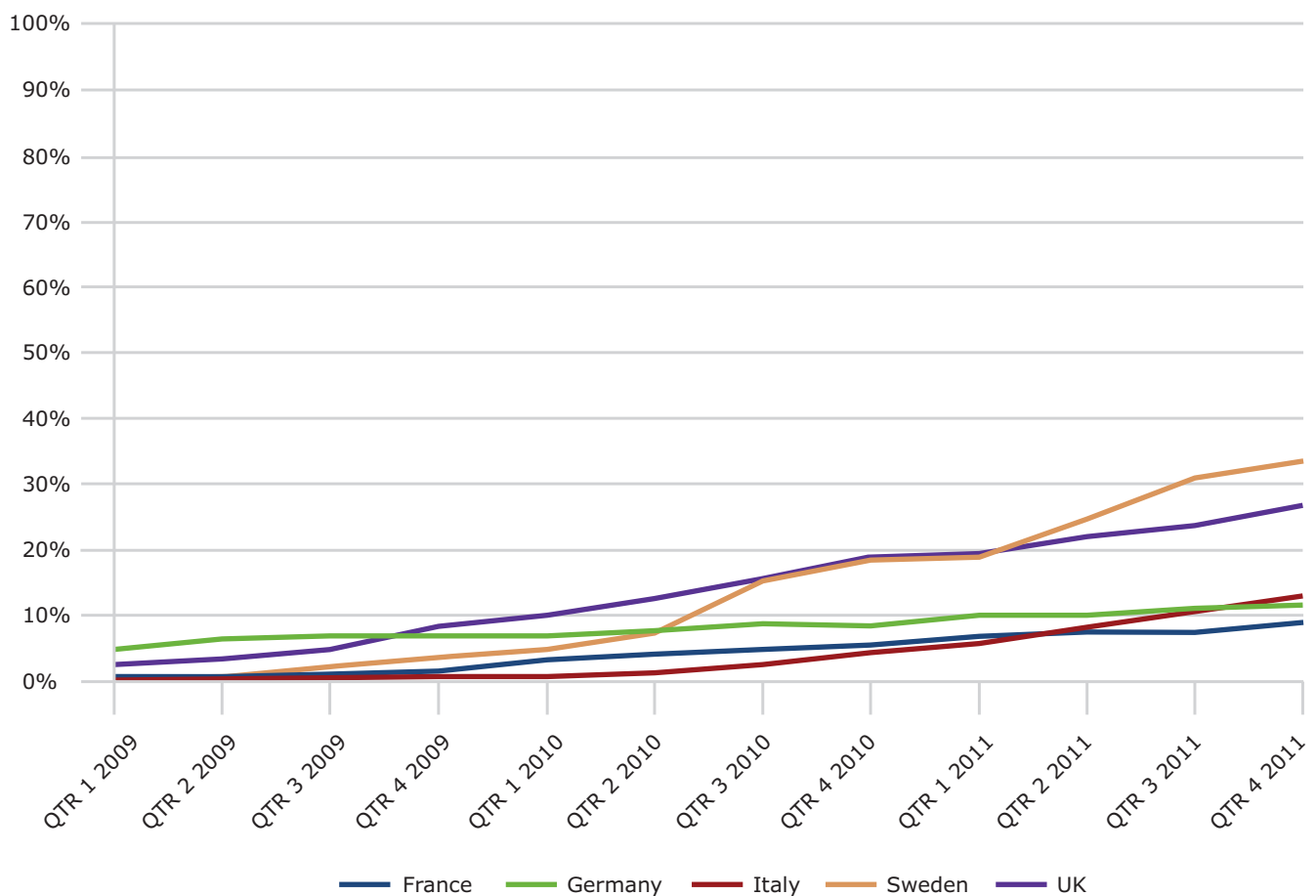
Source: IMS MIDAS data.

Note: The biosimilar products are Retacrit and Binocrit in France, Epoetin Alfa Hexal, Silapo, Abseamed, Retacrit, and Binocrit in Germany; Retacrit, Binocrit, and Abseamed in Italy; Retacrit and Binocrit in Sweden; and Retacrit and Binocrit in the UK.

In the Eprex/Aranesp market, biosimilars have the highest share in Germany, at around 40 percent of the total market in volume terms. The biosimilars' share in Sweden is second highest, reaching nearly 30 per cent by the fourth quarter of 2011. In all the other countries, biosimilars' shares are less than 10 per cent. The shares of Aranesp, the longer-lasting second generation product, generally approach or exceed 50 per cent in a majority of these countries.

Figure 2b looks at the Filgrastim/Neupogen/Neulasta Market Segment (in volume terms).

Figure 2b. Biosimilar share of Filgrastim/Neupogen/Neulasta market segment 2009-2011 (calculated in daily doses)



Source: IMS MIDAS data.

Note: The biosimilar products are Zarzio, Tevagrastim, Ratiograstim, and Nivestim in France; Filgrastim-Hexal, Ratiograstim, Biograstim and Nivestim in Germany; Zarzio, Tevagrastim, Ratiograstim, and Nivestim in Italy; Zarzio, Ratiograstim, and Nivestim in Sweden; and Zarzio, Ratiograstim, Nivestim Filgrastim Teva, Tevagrastim, and Filgrastim Sandoz in the UK.

The highest penetration rate for Neupogen's biosimilars is around 35 per cent, in Sweden, by the end of 2011, followed by the UK. In the remaining three countries, the shares are less than 20 per cent. The share of the second generation product is relatively high in these countries; Neulasta had shares between 50 per cent and 80 per cent across the five countries in the fourth quarter of 2011.

Though this is still a work in progress, I can highlight two main findings. First, the market experience varies greatly across product classes and countries – mainly due to differences across countries in reimbursement practices and incentives as well as variations in medical practices. This is particularly clear with the EPOs.

Second, the second generation products (Neulasta and Aranesp) tend to be dominant across almost all countries because patient utilisation had shifted in that direction, prior to biosimilar entry. I think there is a broader lesson about the size of cost savings that might result from the use of biosimilars in these two areas. To the extent that biosimilars are focused on a product that has been improved with a new generation product, with longer intellectual property protection, savings will be lower.

Second generation products tend to be more expensive on a cost per vial basis versus the reference product, but not necessarily on a cost per daily dose since they require substantially fewer doses per course of treatment. They often also provide quality advantages and cost savings not just in the pharmacy sector but more broadly in other parts of the health sector, such as physician visits and physician utilisation. The implication is that potential cost savings from biosimilar products have been moderated.

This dynamic competition through market entry has implications for the next wave of future biological medicines losing patent protection over the coming years. These include monoclonal antibodies and the interferon products. We already see development of next generation products in many of these sectors. For instance, Biogen is developing the PEGylated version of its interferon beta product for multiple sclerosis; Roche is developing subcutaneous injections for Herceptin and Rituxan and there are other approaches that provide for possible next generation products, including some of the cancer products.

4. FURTHER RESEARCH ISSUES FROM A EUROPEAN PERSPECTIVE

Based on our research to date, there are few issues that merit further investigation. First, the degree of price competition we could expect from biosimilars and whether the price of the reference product will change after biosimilar entry? The theoretical analysis published few years back [see for instance, Grabowski et al. (2007) and Chauhan et al. (2008)] postulated that the biosimilar market was going to be more like brand-to-brand competition, rather than behaving like a standard chemical generic market. This means that the expected level of price competition from biosimilars would be lower than with a chemical generic.

We see a general pattern where price discounts from biosimilars are around 25 to 30 per cent relative to the reference product price, which is consistent with the literature. However, we also see some bizarre patterns in some countries for limited time periods, where biosimilars prices were higher than the reference brand price. This might be due to IMS data not picking up discounts or rebates in the supply chain and/or to payers. IMS data are based on invoice prices, and hence does not take into account where prices are subsequently discounted. For instance, manufacturers

can offer discounts to pharmacies and/or hospitals based on volume usage. Rovira et al. (2011) also highlight the issue about discounts, for both the reference product and biosimilars, relative to invoice prices. It would be useful to capture rebates in those countries where rebating is stronger, especially when there are tenders. IMS will not report sales at the tender price.

The second issue to explore is what would be the response from the reference product after biosimilar entry. On the one hand, the reference brand might at least respond selectively to its best customers by decreasing the price after a biosimilar enters the market. On the other hand, and given automatic substitution laws and the speed by which generics can gain market share in the US (and in other countries), the off-patented brands often choose not to respond strategically by competing on price. In the US, for instance, off-patent brands tend not to compete on price except through authorised generics, when there are one or two first filing generics that have exclusivity rights for limited periods. With biosimilars, to the extent it is more like brand-to-brand competition, one would expect the reference brand to compete on price only in certain sectors and with certain customers. How prices of the reference product react to biosimilar entry is still a very interesting issue to explore.

Third, there is a hint in our data – which do not cover a long enough period – that in some countries biosimilars have expanded demand in daily doses and access. That is an interesting issue to pursue from a lot of different angles. Biosimilars might lead to an increase in access and increased demand. But from a payer's point of view trying to achieve savings, this will depend how prices of biosimilars and the reference product change.

This last point links to the general issue of cost savings to payers and patients. Most of my earlier work exploring the biosimilars market was on innovation, incentives and exclusivities, but it is interesting to look at what are the cost savings to date and how are they likely to play out. Particularly in the US, where we have a lot of products in the pipeline, how much is the cost saving going to be as a result of biosimilars? Is it going to be equivalent to what the Congressional Budget Office postulated (US\$25 billion savings over ten years after the law's passage) (CBO, 2008), less or more? This issue is discussed further in the concluding section.

5. KEY FACTORS DETERMINING HOW BIOSIMILAR COMPETITION EVOLVES

When thinking how the market for biosimilars is going to evolve in the US (and generally), the factors economists think about are:

- What is the market size and commercial opportunity?
- What barriers to entry are associated with patent and exclusivity provisions?
- What are the regulatory standards going to be that the FDA is going to impose for biosimilarity?

- Will companies decide just to do biosimilarity alone or will they try to do interchangeability?
- Will the biosimilar pathway be used rather than using a full Biologic License Application (BLA)? For instance, in October 2010 Teva filed for approval of its filgrastim product (Neutroval) using the full BLA with supporting clinical data, and not the abbreviated BCPA route.

As already mentioned, biosimilar markets are not going to be generic markets driven by price, bioequivalence and automatic substitution; hence the actions of physicians, insurers and patients are going to be very important in this market and will evolve over time. The introduction of next generation products is also going to weigh in very heavily, as we have seen in Europe and as I think we will see in the US.

Table 3 shows some of the outstanding market opportunities for future biosimilars.

Table 3. US sales of leading biological products and earliest reported years of patent expiry

Drug	Product Type	Company	2011 US sales (\$ mil)	Earliest Reported Year of Key Patent Expiry
Humira® (Adalimumab)	Monoclonal antibody	Abbott	\$3,531	2016
Enbrel® (Etanercept)	Monoclonal antibody	Amgen	\$3,507	(1)
Remicade® (Infliximab)	Monoclonal antibody	J&J	\$3,474	2018
Neulasta® (Pegfilgrastim)	G-CSF	Amgen	\$3,316	2015
Rituxan® (Rituximab)	Monoclonal antibody	Biogen	\$3,005	2016-2018
Epogen/Procrit® (Epoetin alpha)	Erythropoetin	Amgen and J&J	\$2,854	2013
Avastin® (Bevacizumab)	Monoclonal antibody	Genentech	\$2,662	2019
Lucentis® (Ranibizumab)	Monoclonal antibody	Genentech	\$1,767	2019
Herceptin® (Trastuzumab)	Monoclonal antibody	Genentech	\$1,656	2019
Avonex® (Interferon beta-1a)	Interferon	BiogenIdec	\$1,558	2013

Drug	Product Type	Company	2011 US sales (\$ mil)	Earliest Reported Year of Key Patent Expiry
Rebif[®] (Interferon beta-1a)	Interferon	Merck	\$1,056	2013
Aranesp[®] (Darbepoetin)	Erythropoetin	Amgen	\$986	2024
Neupogen[®] (Filgrastim)	G-CSF	Amgen	\$945	2013

Source: IMS Health; Epogen, Procrit and Aranesp are based on 10-K SEC filings given extensive rebates provided to dialysis centres and hospitals are not captured in the IMS audits.

Note:

- 1. Enbrel's patent expiration was widely reported as 2012, but based on November 2011 issued patent, Amgen now claims protection until 2028.*
- 2. Other top selling biologic drugs including the insulin products Humalog, Novolog and Lantus, may lose protection from key patents by 2016, but were approved through NDAs and are eligible for approval under an abbreviated pathway through the Hatch-Waxman process.*

Table 3 reports 2011 sales in the US for some of the leading biological products. The patent expiration data come from company filings and from security analysts; but there is some uncertainty about this. The three largest biological products in the US now have sales of over \$3.5 billion each. They are all the tumour necrosis factor (TNF) inhibitors used for rheumatoid arthritis, Crohn's disease, other autoimmune diseases and psoriasis. Just those three products represent more than a \$10 billion market, and it has been growing rapidly. These are followed by the G-CSFs and EPOs but there are also a number of monoclonal antibody cancer drugs, drugs for macular degeneration and other drugs for autoimmune diseases like multiple sclerosis. The markets are growing, particularly markets involving the monoclonal antibodies. The EPO market in the US has been shrinking in value because of dosage changes. First generation Neupogen has been declining, and being replaced by Neulasta.

In any case, development costs for biosimilars are much greater than generics. Even for the ones that are less complex, that are already available in Europe, development costs are in the region of tens of millions of dollars. For monoclonal bodies and interferons, these costs will be possibly in the \$100 million plus region and take more than five years (Grabowski et al., 2014b). These compare to a generic cost of entry of between \$1 million to \$5 million and a time span of two to three years (see for instance, IMS (2011)). While the prize can be very large, the cost of entry is also very large.

The interesting thing for both Europe and the US is that these monoclonal antibodies are more complex, harder to produce and costlier - but have a huge commercial opportunity.

6. WHAT TYPE OF FIRMS ARE POTENTIAL ENTRANTS FOR BIOSIMILARS?

For chemical compounds, there tends to be two different types of companies, with some blurring in the middle. On the one hand, there are the established innovative companies with the following business model: very high costs to develop new products; long exclusivity periods; and relatively high prices to follow on generic products. In the other extreme, we have the generic firms that are introducing low price alternatives with first mover advantages being very important. There are obviously generic firms that have branded products and branded companies that have generics but there are still separate company divisions and very different business models.

There are a number of prominent generic firms, such as Teva and Sandoz, announcing an interest in biosimilars, as are global research-intensive biopharmaceutical firms, such as Merck, Pfizer, Amgen and Biogen. There are also many partnerships being formed on a global basis between specialty pharma and biotech firms to take advantage of relevant expertise at different stages of development, manufacturing and marketing. There are alternative characterisations and scenarios of the market and companies are thinking about biosimilars. Even many companies that have produced products in this space are seeing an opportunity to enter as a biosimilar or as a therapeutic alternative in other parts of the biological space.

7. HOW IS THE US MARKET FOR BIOSIMILARS LIKELY TO EVOLVE?

In the US, the Public Health Service Act (PHS Act) was modified to create an abbreviated approval pathway by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) for products that are confirmed to be “biosimilar” to or “interchangeable” with an FDA-licensed biologic. Under this Act, if a product is highly similar to an existing approved biologic then it is considered as a biosimilar. It allows only minor differences in clinically inactive components in terms of safety, purity and potency. This took effect in March 2010. The BPCI Act, after much deliberation and debate, became law as part of the Patient Protection and Affordable Care Act (PPAC Act). This is important because such legislation in the US is generally designed to be “revenue neutral”. This means that any new expense is to be offset either by equivalent savings or by additional sources of revenue, usually over a time frame of five to ten years.

A lot of the debate in the US was initially about the science required to set up the regulatory pathway. The FDA led this strand of work. The law itself says that biosimilars must be highly similar to the reference product, notwithstanding minor differences. The FDA has the discretion to use structural characterisations to determine how similar a biosimilar has to be to the reference product. There are potentially two routes forward. On the one hand, the approval process for biosimilars could be similar to the one used for chemical generics i.e. there is an abbreviated approval based on demonstrating that the generic drug is pharmaceutically equivalent (that is, it contains the same active ingredient in the same purity, strength, dosage form and route of administration) and bioequivalent (that is, it is absorbed into the body at a similar rate and extent) to the original drug. On the other hand, and

more likely for the foreseeable future, structural characterisations can be used to govern the type of animal studies and clinical trial studies required to show that the potency, purity and safety of the biosimilar is close enough to use this abbreviated pathway. Below I discuss how this characterisation might impact the economics of biosimilars, as the extent of the evidence required by the FDA to gain approval will ultimately affect the degree of competition (price and quality) among biosimilars.

In the US we have a second step that is part of the law. The FDA can approve a product as interchangeable to another product, which then would set up the likelihood that products could be automatically substituted (i.e. the pharmacist could substitute the reference product with a biosimilar without the consent of the physician). It should be noted, however, that individual States can weigh in on that with their own laws. Interchangeability requires showing the biosimilar as interchangeable with the reference product – entailing that (1) the biosimilar will produce the same clinical result as the reference product in any given patient, and (2) the risk in terms of safety or diminished efficacy of alternating or switching between use of the biosimilar product and the reference product is not greater than the risk of using the reference product without such alternation or switch (or in other words, if a prescription is renewed with the reference brand and it were switched to a biosimilar then it would be producing the same outcome).

There are four other key provisions of the Act. First, exclusivity, which was the second major part of the debate. The law has the same broad objective as earlier laws on generic competition: the government aims to produce price competition but maintain incentives for innovation. The law provides for 12 years of exclusivity for the originator's biologic product plus the potential for six months more of paediatric exclusivity. A firm can file an abbreviated biosimilar pathway after four years but the biosimilars cannot be approved until 12 years after the original product was approved.

Second, the anti-evergreening provisions in the US are different from the European "8 + 2 + 1". In the US there is no additional exclusivity for a new indication, formulation or delivery system.

Third, next generation products have a potentially interesting hurdle. Manufacturers have to demonstrate to the FDA that the next generation product embodies a change in safety, purity or potency to gain a new 12-year exclusivity period. That is one area within intellectual property where the FDA has to make a judgment about whether there is enough of a change with the next generation product to award a new 12-year exclusivity or whether the product comes under the umbrella of the original 12-year exclusivity.

Fourth, patent provisions for biologics. It is important to understand how the exclusivity period for biologics differs from the chemical products. The chemical generics process in the US is regulated by the 1984 The Drug Price Competition and Patent Term Restoration Act that came to be known as the "Hatch-Waxman Act". Branded pharmaceutical companies are required to list patents involving composition of matter (substance), formulation, and method of use in the FDA Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book. When applying to enter the market with a generic form of a reference product, the generic company files an Abbreviated New Drug Application (ANDA) and certifies against patents listed in the Orange Book. The certification states that either (a) the FDA should approve of its generic version after the date

the last patent expires (a "Paragraph III" filing) or (b) that its generic product does not infringe on the listed patents or that those patents are not enforceable (a "Paragraph IV" filing). If the generic company files an ANDA with a Paragraph IV certification, then the branded company is notified. After the notice, the branded company has 45 days to file a patent infringement action against the generic company. After the suit has been filed, the FDA cannot approve of the application until the generic company successfully defends the suit or until 30 months, whichever comes first.

In relation to patent provisions for biologics, perhaps because it was thought the Hatch-Waxman Act had too much litigation with Paragraph IV filings and rights – the first generic filer that either settled or won a patent case is awarded a 180-day exclusivity and this became very important to the generic business model – there is none of that for biosimilars. Instead of having an Orange Book listing of patents, a 30-month stay on litigation or 180 day exclusivity for the first generic filer, the Law requires a private information-exchange between the biosimilar firm and the firm whose product they are referencing. It is a very elaborate exchange that has created some issues. I will come back to this at the end of this paper.

7.1 Regulatory requirements to establish biosimilarity in the US

The FDA has issued some guidelines on the regulatory requirements to establish biosimilarity. They are not nearly as clear as the EMA's. The FDA has said that it will consider the totality of the evidence. In terms of products already in Europe, the FDA is willing to take a bridge product approach or bridging studies i.e. the FDA will accept studies using a foreign competitor product accompanied by bridging studies referencing the US product. This possibility would reduce significantly entry costs for biosimilars for the US. For more complex biologics (such as monoclonal antibodies, interferons and TNF-inhibitors), they are likely to require very extensive clinical trial data. In its documents the FDA holds out the promise that science will evolve and eventually it will be able to use analytical characterisations rather than rely heavily on clinical trial testing. It sees a long-term future that could resemble a "generics-like" market. For the foreseeable future I think the FDA is moving very cautiously. It is meeting individually with firms. Many firms have expressed uncertainty about what to do, particularly when they are considering developing biosimilars for complex monoclonal antibodies.

The FDA has not even put forward the regulatory requirements to establish interchangeability. It has indicated that it views it as a two-step process, where manufacturers first introduce their product as a biosimilar and then need to show in patients that it can be interchangeable. It is likely to require crossover studies, where patients are shifted from the reference product to the biosimilar over time and the outcomes are compared. These are difficult trials for which to recruit patients, and costly for companies to perform. As a consequence, few if any biosimilar products are likely to be rated as interchangeable in the foreseeable future. Should technological advances permit it, the FDA may be willing to accept a biosimilar as interchangeable with the reference product, based on a structural analysis.

From the perspective of a firm producing biosimilars, showing interchangeability might pay off for the

first firm to show it. However, in a world in which products may be already established as biosimilar it may not be that attractive as an alternative. Thus, many firms may choose to submit applications on biosimilars as therapeutic alternatives rather than therapeutic equivalents. The optimal decision will depend on the science, as argued before. There may be a future in which interchangeability can be shown through analytical characterisation; this will change the economics, as it will be less costly to show interchangeability. However, for the foreseeable future, the economics of the biosimilars market will be very similar to what we were speculating on five years ago with theoretical models i.e. not pure generics-style models.

7.2 Biosimilars vs generics: nature of competition and incentives in the US

In the small molecule space in the US, everything is driven by price: there is price competition and it is driven by bioequivalence and substitution – automatic substitution in many cases. There is a very rapid erosion of shares when there are multiple entrants; there may be a period when there is 180-day exclusivity with one or two competitors but when everybody enters for big selling products prices decline within a matter of months. Generics capture most of the market and there is no role for marketing either by the generics or by the brand products.

Looking at the biologic space and how it is likely to be characterised, there are much higher barriers to entry and many fewer entrants; competition can be differentiated and it will not be price alone in many cases that determines market shares; quality and delivery system will have an impact. If products are not interchangeable by the FDA they will not be subject to automatic substitution and they will not be in the same J-Code for Medicare reimbursement. Price declines will be less significant and marketing as well as patient support will have a greater role. Table 4 summarises the key differences between the nature of generic and biosimilar competition respectively.

Table 4. Nature of generic/biosimilar competition

Pharmaceuticals	Biologics
Low barriers to entry due to low manufacturing and R&D costs; multiple generic entrants	Higher barriers to entry; lower number of entrants expected
Price competition	Differentiated competition: price and quality
Automatic substitution; rapid loss in market share	No automatic substitution; market share loss expected to be less significant
Rapid price decline; generic price approaches marginal cost	Price decline expected to be less significant
No role for marketing after generic entry	More significant role of marketing for both biologic and biosimilar

So what are the incentives for insurers to encourage generic/biosimilar use? For small molecules, there are very strong incentives across the board for Medicare and private plans in the US with formularies, and pharmacy and physician incentives.

In Medicaid, the maximum allowable cost programme is essentially a reference pricing programme, which means that Medicaid will only pay for the lowest generally available product. In hospital-based insurance there is a bundled fixed payment by diagnostic related group (DRG). There are strong incentives in both sectors, therefore, to use generics, and erosion comes very quickly.

Most biologics are reimbursed by Medicare Part B, when dispensed by a physician in a clinical setting and thus Medicare Part B is the primary payer. Congress anticipated that if the biosimilars were not in the same J-Code for reimbursement as the reference product (and thus would not be rated as interchangeable), the doctors, to the extent it is a physician-dispensed product, might use the more expensive product – which would naturally be the reference product. The Affordable Care Act mitigated this by mandating that Medicare Part B payment for a biosimilar be based on the sum of its own average selling price plus six per cent of the average selling price of the reference product. Hence, the law will give physicians the same reimbursement, net of product costs, whether they dispense the biosimilar or the reference product.

On the other hand, given the familiarity, experience and confidence in the reference product, more needs to be done to encourage the use of biosimilars. I think the Medicare Payment Advisory Commission (MedPAC) (an independent Congressional agency established to advise the US Congress on issues affecting the Medicare program) and others realised this, and so they are considering if and how the reference product and biosimilars can be deemed as close therapeutic alternatives and hence new patients can start with the biosimilar, rather than the reference product. In which case, there may be very strong incentives to use products that are similar. All of that is evolving. In the short run there probably would not be strong incentives for biosimilars, at least not like the formularies and the physician incentives that exist for small molecules.

Within Medicaid, I think the States are so hard pressed for money that they will encourage biosimilars, not by a maximum allowable cost programme but by other mechanisms: prior authorisation and various regulatory mechanisms. In hospital products, because there are bundled payments, there will be strong incentives to use biosimilars. If the Pharmacy and Therapeutics (P&T) Committee says that the outcomes are similar, they will gravitate to the least expensive product. That will be governed by contracts and other things and the reference brand product will have a strong incentive to compete for some of that business.

Table 5. compares the insurer incentives for generic/biosimilar use.

Table 5. Insurer incentives for generic/biosimilar use

	Small Molecule Brand/Generic	Biologics/ Biosimilars
Medicare/ Private Plans	Strong: Formularies, pharmacy and physician incentives	Mixed but evolving
Medicaid	Strong: Maximum Allowable Cost Program	States likely to encourage biosimilars
Hospital-based Insurance	Strong: DRGs and bundled fixed payments	Strongest economic incentives to utilize biosimilars

Looking at patient and physician perspectives, there could be a lot of influences depending on the nature of the disease. Several issues come into play: Is this a product for cancer? Is it a product for a life-threatening disease or illness? Should physicians be more cautious particularly about switching the patient? Is it a product that is not for a life-threatening, disabling illness?

In relation to short-term versus maintenance therapy, to the extent that there is a lot of turnover, new patients may receive biosimilars if there is an economic incentive, but it would be difficult, I think, to shift existing patients.

It is not something we have researched a lot but it is likely that certain specialists have more brand persistence and loyalty than others. Doctors treating rheumatoid arthritis may have very different loyalties and experience in preference to, for example, allergists. That is an area worth exploring.

The size of the co-pay differentials to patients will be important. Under the previous medical benefit these have not been large. It will be interesting to see how that will evolve for physician-dispensed products.

7.3 Case studies in the US – Omnitrope and Enoxaparin

There are two interesting case studies in the US of biosimilar type competition – one is a biologic type product (Omnitrope, a human growth hormone) while the other used the more traditional generics route (m-enoxaparin sodium - enoxaparin). Omnitrope was approved in the US as a non-interchangeable biosimilar to Genotropin under 505(b)2 pathway in 2006 and was launched on the market in January 2007. Novartis/Sandoz introduced Omnitrope into a market already mature and very competitive. Six products were already in the market, differentiated by price and delivery systems.

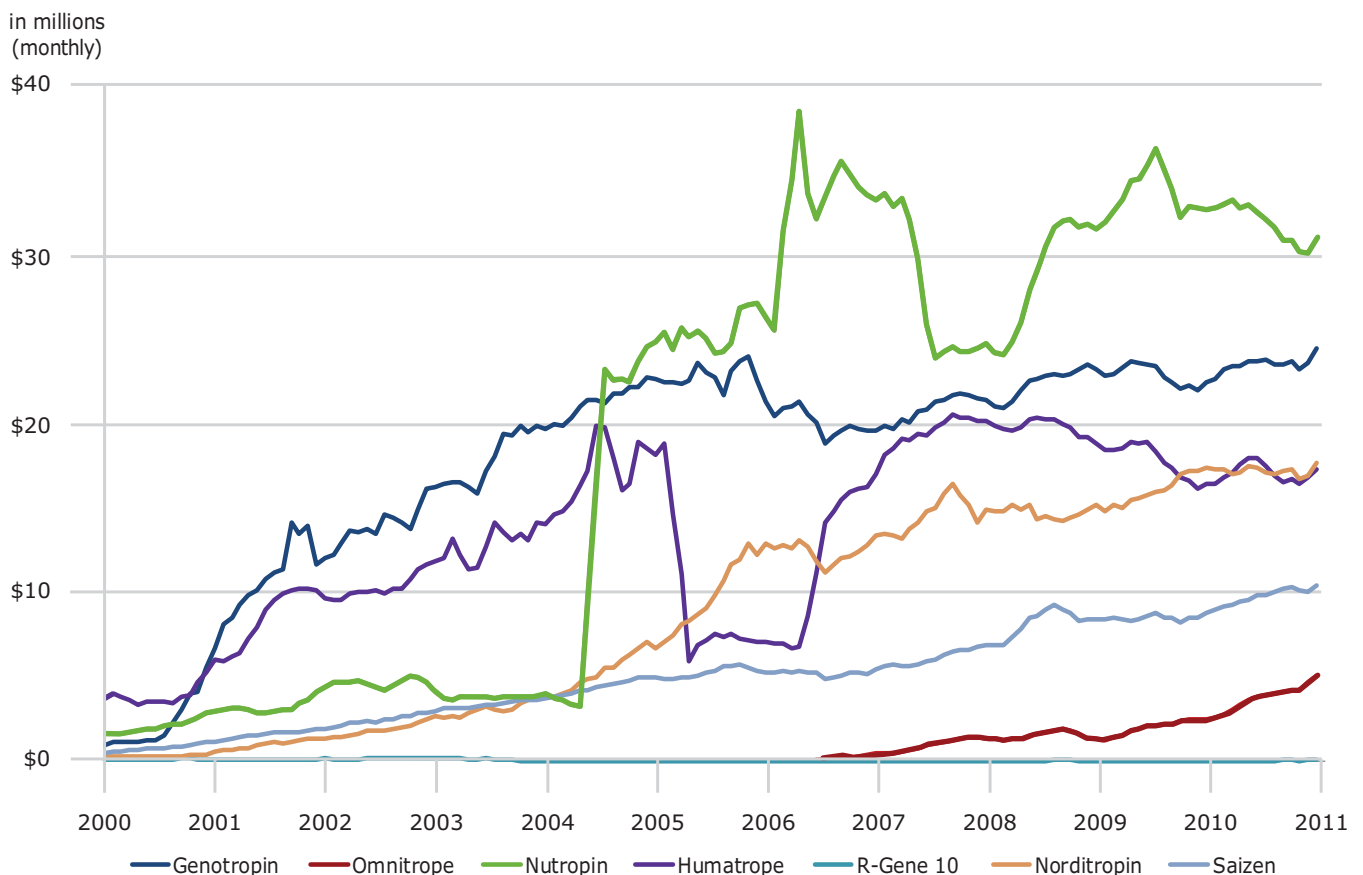
The other case that is very interesting, and more recent, was for a much bigger market: low weight heparin products. Lovenox[®] is the market leader. Enoxaparin is a product that was meant to have

a technology that was able to characterise this complex polysaccharide. It is a product derived from pig intestines. The manufacturer of enoxaparin was able to characterise it to the satisfaction of the FDA. It was treated essentially as a generic product under the ANDA process and did not require any additional clinical trials. This means enoxaparin was approved, in July 2010, with bioequivalent rating to the reference product Lovenox.

Figure 3. shows sales of human growth hormones in the US between 2000 and 2011.

The bottom curve in Figure 3 (in red) is Omnitrope, which had a low share in terms of dollar sales. Sales for Omnitrope start in 2007. It was reported to have had a wholesale cost that was 30-40 per cent less than that of Genotropin (Grabowski et al., 2014b). By November 2012, there were indications that its share had come up significantly, close to 20 per cent when measured in extended units, but it stayed low for many years compared to all the other products available (Grabowski et al., 2014b). It was referenced to Genotropin. I think this market reflects its differentiated characteristics related to multiple dimensions, including price, promotion and the delivery devices. Growth hormones can usually be delivered in two forms: with a syringe injection process or with an injection pen. Initially Omnitrope was not differentiated as was not available in more sophisticated delivery devices that used pens. That has changed over time. The product was marketed more as a generic product initially but is now competing more in a differentiated type situation, by focusing on support services and obtaining FDA approval for pen delivery system; Omnitrope has since increased its market share. In this non-interchangeable world there exists a non interchangeable biosimilar, in a very mature market with lots of product differentiation, getting very low penetration until recently. Even now the market is split among many products and there is lots of rebating and price competition going on in this market as well as product differentiation.

Figure 3. Human growth hormone sales in the US (2000–2011)



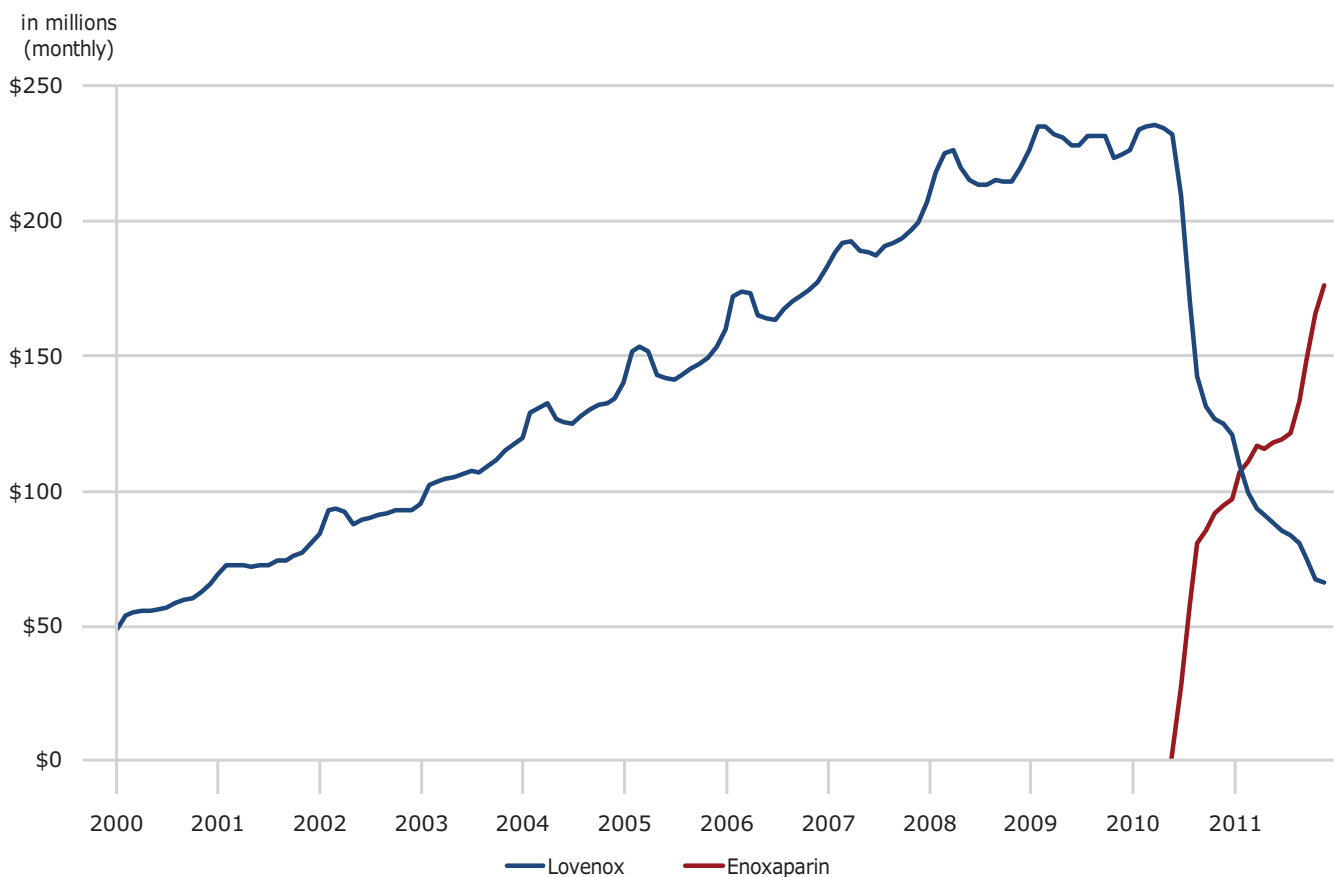
Source: Authors' analysis of data from IMS Health.

Note: To correct for IMS Health's induced data fluctuations, monthly sales volume is a three-month moving average of reported sales.

Figure 4. shows the sales evolution for Lovenox and Enoxaparin in the US.

Enoxaparin was an interchangeable bioequivalent to Lovenox coming through the end of the patent pathway – and it is different from Europe: at least initially the EMA is treating low weight heparin as a biologic that requires a biosimilar pathway. In the US the FDA determined that the technology and characterisation was sufficient to allow it to compete as a so-called generic. This allowed pharmacists to substitute it for Lovenox. Lovenox hit the patent cliff after the introduction of enoxaparin in the fourth quarter of 2010, resulting from automatic pharmacy substitution and managed care formulary incentives to use enoxaparin. Enoxaparin has taken over most of the market and captured more than half of the market in its first year.

Figure 4. Sales of Lovenox and Enoxaparin in the US market (2000 – 2011)



Source: Authors' analysis of data from IMS Health.

Note: To correct for IMS Health's induced data fluctuations, monthly sales volume is a three-month moving average of reported sales.

The degree of price competition in this market has become even more extreme, with the entry of a second authorised generic by Sanofi. This product is used both in the retail and the hospital sector. Initially, I think Sanofi retained most of the hospital sector because of contracts and the way it competes, and lost most of the retail sector. Over time this market displays very much a generic pattern.

7.4 Full BLAs vs biosimilar pathway

It is very interesting on a number of dimensions in the US to examine the differences between the BLA pathway and a biosimilar pathway. The only biosimilar-type product approved to date by the FDA since the BPCI Act was passed is Teva's tbo-filgrastim, and that was under a full BLA. It is mainly a product that was available in Europe and it used a lot of the same clinical trial data to get into the US. Teva was applying for this even before the Act was passed.

Then there are other products where companies may have negotiated a pathway with the FDA but nobody has filed a biosimilar pathway. Several companies have talked about the advantages of perhaps going through the full BLA route if the FDA allows it on a cost-effective basis (sometimes referred to as a "skinny" BLA application by biosimilar firms.)

The FDA does not seem thrilled with the “skinny BLA” approach. However, it has the advantage to companies of avoiding all this patent identification and exchange well before entering the market and, down the road, delays associated with the 12-year exclusivity provision.

Whether a firm elects to file a full BLA or take the biosimilar approach will depend on the expected regulatory requirements in each case. Generally, the full BLA strategy could be attractive in classes with an easy to prove endpoint and a single indication, as well as when companies are developing a next generation product when they would not be trying to be a me-too type product but offer some kind of an advance over the existing products in the market (sometimes referred to as “biobetters”). Under such circumstances, sponsors would not be constrained by the requirements of biosimilarity. Using the full BLA, however, would delay the development and entry of cost-saving biosimilars.

The FDA has expressed a willingness to consider extrapolation of a biosimilar’s data filing for one indication to its filing for another approved indication if the same mechanism of action is involved (similar to what the EMA already has); for such circumstances, the full BLA is less likely to be used, as well as when the sponsor wishes to seek interchangeability.

It could very well be that the market will gravitate in the US and perhaps worldwide to a biobetter strategy and the biosimilar strategy may be more prevalent in developing markets. That is just speculation but it is one way that this market could evolve.

8. SUMMARY AND CONCLUSIONS

To summarise, biosimilars have huge commercial opportunities, particularly as we look at the next wave. The biologic space is the “sweet spot” for many innovative companies - about half of the products in the pipeline are biologics. Cancer products, in particular, have a huge number of products in the pipeline.

Biosimilars have large commercial opportunities but they face large regulatory hurdles, particularly as we move down the road to the more complex products. From the models that we derived, competition is likely to be confined to a few entrants and more resemble brand-to-brand competition (which is based on differences in quality, price and promotion). It is still an operative model but I do not know whether it will evolve beyond that over the long run. If the science advances so that analytical characterisations can be used to obtain biosimilar interchangeability, then I think we will move more towards a generic type world.

On the costs savings, the CBO works with ten-year windows for Congress and it pushed for \$25 billion savings over ten years after the law’s passage (CBO, 2008). The \$25 billion sounds a lot but it is less than one per cent of the total healthcare savings over ten years. That was a bit of a shock to Congress which felt that there would be much larger cost savings over the initial ten-years. Other parties, such as Express Scripts, a pharmacy benefit management firm, put forward projected savings over ten years of \$100 billion.

As I look at the situation and do some research I think we will be hard pressed even to achieve \$25 million in savings by 2020 because the FDA is moving fairly slowly. The CBO thought that within a year of the law being passed there would be filings and that within a few years, particularly for products like EPO and filgrastim, we would have products in the market; but we do not. As we look down the road to the more complex products, they are going to be coming into the market more slowly than envisioned by the FDA. We may still have savings, but they could be south of \$25 billion by 2020. After that there may be a dramatic increase. Particularly as science advances and as these products become more important in the market, insurers will find a way to encourage them and physicians will become more experienced in them, but I think the short-term horizon is for even less than what the CBO envisioned.

REFERENCES

- Congressional Budget Office (CBO), 2008. Cost estimate: S.1695 Biologics Price Competition and Innovation Act of 2007. Available at: <http://www.cbo.gov/sites/default/files/cbofiles/ftpdocs/94xx/doc9496/s1695.pdf> [Accessed 20 August 2014].
- Chauhan, D., Towse, A. and Mestre-Ferrandiz, J., 2008. The market for biosimilars: evolution and policy options. *Briefing*. (45). London: Office of Health Economics.
- Grabowski HG, Guha, R. and Salgado, M., 2014a. Biosimilar competition: lessons from Europe. *Nature Reviews Drug Discovery*, 13, pp 99-100.
- Grabowski, H.G., Guha, R. and Salgado, M., 2014b. Regulatory and cost barriers are likely to limit biosimilar development and expected savings in the near future. *Health Affairs*, 33(6), pp.1048-1057.
- Grabowski, H.G., Ridley, D.B. and Schulman, K.A., 2007. Entry and competition in generic biologicals. *Managerial and Decision Economics*, 28(4-5), pp.439-451.
- IMS, 2011. *Shaping the biosimilars opportunity: a global perspective on the evolving biosimilars landscape*. London: IMS Health.
- Mattison, N., Mestre-Ferrandiz, J. and Towse, A., 2010. eds. *Biosimilars: how much entry and price competition will result?* London: Office of Health Economics.
- Mestre-Ferrandiz, J. and Towse, A., 2014. *What is the role of HTA for biosimilars?* Briefing. London: Office of Health Economics.
- Rovira, J., Espin, J., Garcia L. and Olry de Labry, A., 2011. *The impact of biosimilars' entry in the EU market*. Report prepared for the EC (DG Enterprise and Industry. Available at http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_market_012011_en.pdf [Accessed 17 June 2014].

GLOSSARY

Abbreviated New Drug Application (ANDA): the process used by the Food and Drug Administration (FDA) to review and ultimately approve a generic drug product.

Biosimilar: 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.

Biologic License Application (BLA): a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (in the US). The BLA will contain specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product. If the information provided meets FDA requirements, the application is approved and a license is issued allowing the firm to market the product. For more information, see: <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#B>.

Biotherapeutic medicines: medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances produced by living organisms (such as cells, viruses and bacteria). They are larger and more complex than chemically-synthesised medicines and their characteristics and properties are typically dependent on the manufacturing process itself. Biotherapeutic medicines can also be referred to as biologics, biological medicines and biopharmaceuticals.

EPOs: erythropoietins. Hormone produced by the kidney to regulate red blood cell production. They are used for treatment of anaemia associated with chronic kidney disease, cancer and reduction of transfusion requirements in adult patients receiving chemotherapy.

European "8 + 2 + 1" rule: refers to the rules in Europe that determine exclusivity. During the first eight years from the grant of the innovator company's marketing authorisation, data exclusivity applies. This is the period of time during which a company cannot cross-refer to the data in support of another marketing authorisation. After the eight years have expired a generic company can make use of the pre-clinical and clinical trial data of the originator in their regulatory applications, but still cannot market their product. After a period of 10 years from the grant of the innovator company's marketing authorisation, the generic company can market their product, unless the innovator product qualifies for a further (maximum of) one year of exclusivity. This additional one year may be obtained in a number of circumstances, such as where the innovator company is granted a marketing authorisation (but during the first eight years) for a significant new indication for the relevant medicinal product. In such a situation the generic company can only market their product after 11 years from the grant of the innovator company's marketing authorisation. Thus, the "2+1" refer to market exclusivity. In practical terms, this means that a generic application for marketing authorisation can be submitted after Year 8, but that the product cannot be marketed until after Year 10 or 11.

"Evergreening": not a formal concept of patent law; it usually refers to the different ways in which pharmaceutical patent owners use the law and related regulatory processes to extend their high rent-earning intellectual property rights, particularly over highly profitable (either in total sales volume or price per unit) drugs.

GCS-F: granulocyte-colony-stimulating-factor. Filgrastim used to reduce the risk of infection in patients with some tumours, who are receiving strong chemotherapy that may cause severe neutropenia with fever.

Somatropin: growth hormones used for children and adults.

PEGylation: a process of attaching the strands of the polymer PEG to molecules most typically peptides, proteins and antibody fragments, that can help to meet the challenges of improving the safety and efficiency of many therapeutics.

Reimbursement codes in the US: a component of the Centres for Medicare and Medicaid Services (CMS) Healthcare Common Procedure Coding System (HCPCS) and the American Medical Association (AMA) Current Procedural Terminology (CPT®) coding systems. These codes provide a uniform language for healthcare professionals, including physicians, physician assistants and nurse practitioners, to bill their services to payers. They include drugs/products that are utilised in the physician's office, clinic or home health agency. J-Codes in particular relate to permanent codes used to report injectable drugs that ordinarily cannot be self-administered; chemotherapy, immunosuppressive drugs and inhalation solutions as well as some orally administered drugs.

Reference product/medicine: the originator biologic. Biosimilars use this reference product in their regulatory submission. The reference product for the EPOs is Eprex. The reference product for the GCS-Fs is Neupogen.

Second generation products: longer-lasting products, so patients do not have to take them as frequently as the reference product and its biosimilars as they require substantially fewer infusions over a course of treatment. Aranesp and Neulasta are the second generation products in the EPO and GCS-F market respectively. In both markets, they were introduced prior to biosimilar entry.

Tenders: Tenders can take place at hospital level, where a hospital groups a number of medicines and then purchases one product, usually the one offering the lowest price. In our case, a tender can group the reference product and its biosimilars together and the hospital will purchase the cheapest one.

About the Office of Health Economics

Founded in 1962, the OHE's terms of reference are to:

- commission and undertake research on the economics of health and health care
- collect and analyse health and health care data for the UK and other countries
- disseminate the results of this work and stimulate discussion of them and their policy implications.

The OHE's work is supported by research grants and consultancy revenues from a wide range of UK and international sources.

The views expressed in this publication are those of the author and do not necessarily represent those of the OHE.

Acknowledgments

This is joint work with Rahul Guha and Maria Salgado, Cornerstone Research. Cornerstone Research obtained data from IMS Health.

Two papers, partly based on the results presented at this lunchtime seminar, were published in Nature Review Drug Discovery and Health Affairs in February and June 2014 respectively (Grabowski et al., 2014a; 2014b).