OHE *Briefing*

The market for biosimilars: evolution and policy options

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Key Points

- Biopharmaceuticals are more complex agents than conventional chemical entities and therefore are more difficult to replicate on patent expiry. Off-patent versions of the originator product cannot rely on a simple demonstration of chemical comparability. They are best described as biosimilar.

- As a consequence biosimilar markets will evolve in a more complex way than traditional small molecule chemical generics markets.

- Regulators will need clinical trial evidence pre-launch of efficacy and safety, and clinicians will require post-launch "patient safety year" (PSY) evidence that biosimilars are in practice equivalent in effect and safety to originators.

- As a consequence generic companies may need commercial partners to enter biosimilar markets successfully and governments and other payers need to behave differently. Post patent expiry price cuts and/or the use of reference pricing will deter biosimilar entry and reduce long term savings.

- Governments and other payers should encourage pharmacovigilance and other outcomes studies that produce PSY data that will encourage interchangeability and greater price competition. Over time these markets can become biogeneric.

- Outcomes data will also help assess the value for money of second generation biopharmaceutical products as compared to the first generation originator and biosimilar products.

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EXECUTIVE SUMMARY

Defining biosimilars

Biologics or biopharmaceutical agents are medicines that originate from biotechnology processes. Examples of such agents include hormones e.g. insulin and growth hormone, other biological proteins such as erythropoietin (EPO) and monoclonal antibodies such as trastuzumab. Biopharmaceuticals are more complex agents than conventional chemical entities and therefore are more difficult to replicate on patent expiry.

The term "biosimilars" rather than "biogenerics" is therefore used by the European Medicines Evaluation Agency (EMEA) to refer to off-patent versions of innovators' biopharmaceutical products. These products are intended to be the same as the therapeutic protein product already on the market, i.e. off-patent versions of the originator product. However, as they cannot rely on a simple demonstration of chemical comparability, they are best described as *similar* and hence the term biosimilars.

A number of biologic products are now reaching the end of their patent life and there is an emerging debate about how the market should evolve and about the size of any potential savings for health care systems. The aim of this paper is to explore how off-patent entry into these markets may develop and, to the extent relevant, how these markets might differ from traditional chemical generics markets. Our focus is how ultimately payers may get value in such a market.

The potential for savings to health care systems

The emergence of biosimilars has been met with a very wide ranging set of predictions of potential cost savings to health care systems through price competition. In the US market these have ranged from cumulative savings of $3.6bn over the period of 2008-17 (Ahlstrom et al., 2007) to the Miller model which produces a $71bn savings estimate over an equivalent period (Miller and Houts, 2007).

The higher savings estimates assume that biosimilar markets will operate like markets for chemical generics with multiple entry and strong price competition within a relatively short period of time after the patent expiry. The typical equilibrium price of generics (discounting from pre-patent expiry innovator brand price) in the US market is at a price 80% below the pre-patent expiry price. The business model is low cost manufacture and either product "push" through distribution channels (with discounts) to pharmacists who can use generic substitution or discounts to large buyers who can shift pharmacist dispensing or clinician prescribing decisions.

We argue that biosimilars markets are quite different and payers have to adopt different policies to make savings over time.

The biosimilars regulatory environment

The biosimilars legislation in Europe is more advanced than in the US. The EMEA produced a guideline on similar biological medicinal products in 2005 (EMEA/CHMP, 2005) and approved their first biosimilar in 2006 (EMEA, 2006). A framework has been created for demonstrating similarity rather than identity for these biological products. The requirements for submission are set on a case-by-case basis depending on the existing knowledge of the reference biological medicinal product.

The encouragement of chemical generics across a range of European countries has made generic substitution a prominent policy issue. Substitutability and interchangeability are however different concepts. We use substitutability to refer to the

decision made at the pharmacy. The prescription has been written and the pharmacist makes a decision to substitute a generic version of the prescribed product if permitted by relevant national initiatives. We use interchangeability to refer to a clinical decision (at the formulary committee or at the clinician level made in relation to individual patients) to switch between products within a therapeutic area. At the regulatory and legislative level the trend is against both substitution and interchangeability in biologicals. Biosimilars are not treated as generics in the context of substitution policies. There are also concerns among clinicians about switching patients between biological products, although at the local level there have been examples of this happening – for example where hospitals have only purchased one type of EPO product through a tendering process. Anecdotal evidence suggests to date that this has not resulted in adverse consequences for patients.

Drivers of interchangeability of biosimilars and originator products

The only way to change the way substitutability and interchangeability of biologicals is handled is through the build-up of "patient safety years" (PSYs) data for biosimilars. Regulators will insist (at least initially) on pre-launch safety data obtained from clinical trials. But there will also be a need for post-launch data to provide clinicians with comfort as to the safety of interchanging products. Two or three years of good PSY data within the European market may change the nature of the interchangeabilty/substitutability debate. Clinicians will become more willing to interchange biosimilar and originator products. Governments will be more willing to consider substitution at the pharmacy level for non-hospital products. Regulators may reduce the clinical trial burden they impose on later biosimilar entrants. Positive PSY experience in Europe may also make it easier for biosimilars to penetrate the US market and indeed may impact on how regulation is implemented there. The potential strategic importance of European PSY data for the US market will influence the willingness of companies to invest in launching biosimilars in Europe.

Our expectation is that the market penetration achieved by biosimilars will initially (within the first couple of years) be low (perhaps less than 5% market share) due to the lack of safety data and clinical conservatism allied to this. As safety data are accumulated, more new patients will be commenced on biosimilars, leading to much greater penetration. However, there will be differences across therapy areas.

Differences in biosimilar markets across therapy areas

We examined three very different examples of biosimilar markets.

- In the EPO market there have already been a number of originator competitors. None of the products has been able to differentiate itself clearly. Two more products have recently been launched, and a number of biosimilars are expected in an already highly discounted market.

- The Granulocyte-Colony-Stimulating-Factor (GCSF) market currently consists of both first-generation and second-generation products. The ability of first-generation biosimilar products to compete with the originator first and second-generation products will depend both on PSY data and the perceived extent of differentiation and value for money of the second-generation product.

- In the growth hormone market medicines are predominantly prescribed for children. The product devices differ and it can need considerable training for a child to be comfortable in using them. Clinicians are therefore likely to be more conservative in this market with respect to interchangeability. They may restrict the use of biosimilars to new patients.

Within each of these markets there are important non-price aspects of competition such as home care and patient and clinician education. Greater price competition may erode the provision of these services.

Using market segmentation theory to understand biosimilars markets

We provide some theoretical underpinning for the statements we make. Our starting point is the Frank and Salkever (1997) model assessing the impact of generic entry. The authors argue that a market segments into two when a generic (in our case, a biosimilar) enters the market – the price-sensitive and the price-insensitive segment. For the price-insensitive segment, demand for the original product does not depend on the price of the competitor(s) – this segment can be referred to as the 'loyal' segment. On the other hand, in the price-sensitive segment all products compete.

Our model follows Frank and Salkever by combining market segmentation with linkage between the segments. The degree of product differentiation is linked to the generation of PSY data. The size of the "loyal" segment and the degree of price sensitivity are both impacted by PSY data. Thus accumulation of positive PSY data erodes (average weighted) price over time.

This points to the need for theoretical development to take into account how the accumulation of PSYs could be modelled in a two-period model. If PSYs are linked to biosimilar sales then the biosimilar firm would choose prices taking account of the effect of current price on the future shift in demand as the stock of PSYs increases. In turn the originator company may be willing to lower its prices in response to a new entrant biosimilar company in order to reduce the ability of the entrant to gain market share and thereby generate PSY data. It may therefore make more sense for entrants to find non-price cutting routes to gaining market share and to generating PSY data. Of course, it may be very difficult to do this against an entrenched originator.

An illustrative view of how biosimilars markets may evolve

It therefore makes sense for biosimilar entrants to take a "follow on" rather than "biogeneric" approach to the market, i.e. not to compete solely on price. Most established generic companies are, however, not equipped to undertake a "follow-on" approach. We note however that potential biosimilar entrants are forming alliances with other companies to enable them to compete effectively in manufacturing and marketing skill with originator companies.

In this context the weighted average price (across the originator and biosimilar entrants) in biosimilars markets may evolve as follows, by way of comparison to a chemical generics market:

- A lower market price than current list price at time of biosimilar entry. This reflects the transaction prices in many biologic markets - mainly due to hospital discounts already in place. In addition originators may undertake further strategic discounting before biosimilars enter.

- Less rapid erosion towards the "equilibrium" price in the short term because of the need for post-launch PSY data to demonstrate practical "equivalence" before clinicians will use products interchangeably.

- A long term equilibrium price above the "pure" chemical generic level due to higher variable costs of manufacture for biologics as compared to chemical products and to higher fixed costs arising from clinical development costs pre-launch to meet licensing requirements and post-launch to generate PSY

data. However we expect equilibrium prices to be below those predicted by Grabowski et al, 2007 whose results assumed continuing high biosimilars entry costs and on-the-market costs. We expect these fixed costs to erode over time if PSY data reassure clinicians and regulators that biosimilar products are "equivalent" to the originator. We, in effect, reach a biogenerics market.

What should payers do to achieve value over time?

There are three options for intervention by government in biosimilars markets:

1. Substitutability rules, whereby governments permit pharmacists to substitute one biosimilar for another.

2. Direct price intervention to push down originator product prices. This could take the form of:
   a. inclusion into reference price systems with biosimilar entrants;
   b. a post-patent expiry price cut imposed on the innovator or a cut imposed on a biosimilar entrant.

3. Market support (e.g. investing in infrastructure for outcomes monitoring, and to facilitate pharmacovigilance work to collect PSY and other data to promote interchangeability) to create greater willingness of budget holders and clinicians to seek value for money by using biosimilar and originator products interchangeably.

We think it likely that governments and other payers will want to pursue Option 1 at a much later stage in the development of biosimilars when strong PSY data are available. It is, in any case, of limited value for products prescribed in a hospital setting.

Direct price intervention as per Option 2 is counterproductive. Reference pricing assumes a degree of interchangeability which is not likely to be reflected in clinicians' willingness to switch products. More fundamentally it will discourage biosimilar entry by reducing potential profits. Biosimilars manufacturers may not be able to recover development costs. Without this "follow on biologic" stage to biosimilar market development, the PSY data required to enable the market to evolve to a biogeneric market may never be collected. In our view it is not possible to "jump start" a biogenerics market by forcing down prices or by imposing substitutability. Governments may achieve a one-off cut, but they would put at risk the creation of a biogeneric market which would in time produce much greater savings.

Given the relatively efficient way in which the biosimilars markets are likely to evolve, we would recommend Option 3, with governments taking a more strategic approach. In particular, we would recommend a policy which supports and incentivises the generation of high quality and comprehensive outcomes data on the effectiveness and safety of biosimilars and originator products. Such studies could also explore the value for money of second-generation biotech products that are competing with the first-generation originator and biosimilar products. Government/industry collaboration to determine how to generate these safety and value for money data in biotech products would be helpful. Supporting market evolution in this way would better reward innovation by identifying when it benefits patients and payers and would also secure a path towards maximising price competition over time, enabling payers and patients to gain substantial savings from biologicals patent expiry.

1. INTRODUCTION

Biologics or biopharmaceutical agents are medicines that originate from biotechnology processes. Examples of such agents include hormones e.g. insulin and growth hormone; other biological proteins e.g. erythropoietin (EPO); and monoclonal antibodies such as trastuzumab. They contain proteins manufactured through techniques using recombinant DNA technology. They may go through a process of fermentation rather than of chemical synthesis. These different processes make biopharmaceuticals more complex agents than chemical entities.

Thus whilst small molecules can readily be replicated on patent expiry it is more difficult with biologics. For instance there is a debate over whether slightly different manufacturing processes may lead to heterogeneous proteins (Schellekens, 2004; Belsey et al., 2006). A slight change in manufacturing process for an originator EPO product led to a reduction in patients' red blood cells due to an increased immune response by the body, causing serious problems for some patients. This real-life example has highlighted the need for verification of the similarity of any copy biopharmaceutical product to the originator product. This issue is pressing as a number of first generation biologic products have now reached or are reaching the end of their patent lives. There is an emerging debate about how the post-patent market should evolve and the size of the potential savings for health care systems.

The term "biosimilars" is used by the EMEA to refer to off-patent versions of innovators' biopharmaceutical products (see for example EMEA/CHMP, 2005). These products are intended to be the same as the therapeutic protein product already on the market, i.e.

off-patent versions of the originator product. However, they are best described as similar and hence the term biosimilars rather than biogenerics. Although manufacturers of biosimilars refer to the innovator product in order to demonstrate quality, safety and efficacy, they cannot rely on a simple demonstration of chemical comparability to show equivalence. Additional clinical work is required to demonstrate efficacy and safety for the biosimilar product. The term biogeneric is sometimes used interchangeably with biosimilars. We use biogenerics to refer to a possible point in the development of a biologics off-patent market where the demonstration of equivalence *can* be done with very limited clinical work, if any, and the market can be considered as very close in characteristics to a standard chemical generic market. In other words, biosimilars markets *may* evolve into biogenerics markets. There is considerable debate about in what circumstances and how quickly that might happen.

The FDA has also used the term "follow-on protein products" to refer to biosimilars. This is confusing, as the term "follow-on" is more usually used in the context of an economic analysis to refer to innovative on-patent products entering a therapeutic area where there is already one product. The term "me-too" is also used in this context. We reserve the terms "follow-on" and "me-too" to refer to new differentiated innovative products entering an existing therapy area – for example offering greater effectiveness in some patient sub-groups or a different dosage regimen or delivery form that may have benefits for patients and/or for the health care system.

Biosimilar market dynamics are likely to develop differently from those of most small molecule chemical generic markets. There will be additional fixed costs due to the need for clinical trials to prove the efficacy as well as the safety profile of these products. The more complex manufacturing processes of biopharmaceuticals will also increase fixed costs. Allied to this, the regulatory framework for the approval of these medicines is in its infancy within Europe (each medicine will be analysed on a case-by-case basis) and, at the time of writing, no regulatory process has yet been established in the US despite discussions. Indeed only one biosimilar product has been licensed in the US and only then after the company took the FDA to court. The expectation is that Europe will see an earlier emergence of biosimilars markets because of the progress the EMEA is making and because of earlier patent expiries. We therefore concentrate on the position in Europe.

The emergence of biosimilars has been met with differences in view on potential cost savings to health care systems through price competition. The European Generic Medicines Association (EGA) produced a figure of €2bn per annum savings for payers from the introduction into Europe of biosimilars into the top six biopharmaceutical markets (European Generics Association, 2005).

The US market has been been the subject of a very wide range of estimates of potential cost savings. At the more conservative end, the Avalere Health Model predicted cumulative savings of $3.6bn over the period of 2008-17 (Ahlstrom et al., 2007). At the other extreme the Miller model estimated $71bn savings over an equivalent period (Miller and Houts, 2007). Somewhere in between is the Engell & Novitt projection of $14.4bn (excluding the EPO market) (Usdin, 2007).

Higher savings estimates assume that biosimilar markets will operate much like markets for small molecule chemical generic medicines. Here the costs of generic entry are low. This allows multiple entry and strong price competition within a relatively short period of time after the originator loses patent protection. The typical equilibrium level of price competition (discounting from pre-patent expiry innovator brand price) in a market such as the US is a price 80% below the pre-patent expiry molecule price. The business model is one of low cost manufacture and product "push" either through the distribution channels (with discounts) to pharmacists or discounts to large buyers who can shift pharmacist dispensing and/or clinician prescribing decisions.

Grabowski et al., 2007 suggest less entry into biosimilars markets than into standard generics markets and therefore more modest scope for savings. In this paper we seek to build on their approach. The paper is structured as follows:

- We begin by describing the current biosimilars environment particularly from a regulatory and pricing and reimbursement viewpoint.
- We construct a theoretical economic framework analysing the price competition between an originator and its biosimilar counterpart.
- We explore the different business models in the biosimilar market environment and indicate how we expect prices to develop over time.
- We discuss the public policy implications for regulators and payers seeking to address value for money and patient safety issues.

2. BIOPHARMACEUTICAL/ BIOSIMILARS ENVIRONMENT

2.1 Substitutability and Interchangeability

2.1.1 Substitutability/interchangeability of biosimilars – current state of play in Europe

Biosimilars legislation in Europe is far more advanced than that in the US. The European Medicines Evaluation Agency (EMEA) produced a guideline on similar biological medicinal products in 2005 (EMEA/CHMP, 2005) and approved its first biosimilar in 2006 (EMEA, 2006). The guideline asks for a full quality dossier in which comparable clinical quality, efficacy and safety profiles have to be demonstrated, i.e. a framework has been created for demonstrating similarity rather than identity for these biological products. The requirements for submission are set on a case-by-case basis depending on the product and on the existing knowledge of the reference biological medicinal product. Therefore the hurdles for demonstrating bioequivalence for a biosimilar/biogeneric approval are substantially higher than the data required for small molecule chemical generics. A product may require substantial clinical development work before approval. The EMEA has stated that "biologics are not necessarily interchangeable".

At an international level, the World Health Organisation is in the process of reviewing the INN nomenclature system given the increasing complexity of biological products. There is debate over whether biosimilars should have a unique INN to distinguish them from the originator product (WHO, 2006). Non-glycosylated biologics (i.e. less complex biopharmaceutical products) are likely to be treated like standard chemical generics. The review has been put in place to look at the more complex molecules. A paper from the EU pharmaceutical and biotech trade associations argued a unique INN would be a good way of ensuring that adverse events could be traced back to the relevant biosimilar product. Many substitution rules require products to share the same INN number so this issue has direct implications for pharmacy level substitutability of biosimilars.

2.1.2 Current policies in Europe on generics at the payer, prescriber and pharmacy level

Substitutability and interchangeability are different. Substitutability is typically used to refer to the decision made at the pharmacy level, where a prescription has already been written and the pharmacist makes a decision to substitute if permitted by relevant national initiatives. Interchangeability usually refers to the clinical decisions relating to individual patients at the formulary committee or at the clinician level.

The policy on substitution for chemical generics in the five major European markets is as follows:

- In France, authorisation to prescribe under International Non-proprietary Name (INN) was granted in 2001. Doctors made a commitment to prescribe generics under INN. Generic substitution at pharmacy level has been allowed and encouraged. Generic medicines deemed substitutable are included in a generic group ("groupe générique" or "Répertoire des génériques"). Note, however, that substitution can be prohibited by the prescriber.

- Generic substitution has been allowed in Germany since 1999. Indeed, a pharmacist can substitute every prescribed item for other products containing an identical active substance.

- In Italy generic reference pricing has been implemented since 2001 and a pharmacist can substitute a cheaper equivalent drug for the prescribed medicine, unless prohibited by a physician.

- In Spain generic reference pricing has been implemented since 2000, with changes instituted since the July 2006 Medicines Act. The reference price system now applies to all presentations of medicines with the same active ingredient and administration route – hence pharmacists are now forced to substitute to the cheapest product and even under price parity a generic product should be dispensed.

- The UK is the only one of the main five European countries not to allow generic substitution at the pharmacy level. However generic prescribing is very high with most prescribing undertaken on INN and there is a competitive generics market.

There are therefore two different models. In the UK the model is based more on interchangeability. The clinician makes the decision to prescribe by INN and the pharmacist in the community will dispense a generic if one is available, but no substitution can occur at pharmacy level if a clinician has decided to prescribe by brand.

In other European countries a traditional generic substitution model is in place whereby pharmacists can directly substitute a cheaper generic unless the physician prohibits. There are varying incentives to substitute both at the pharmacist level at the clinician level.

2.1.3 What are the current models of substitution for biosimilars?

France has taken a precautionary stance in this area by prohibiting substitution of a biologic/biopharmaceutical through law, i.e. biological products cannot be listed in a generic group where generic substitution applies. Biosimilars are not considered as generic medicines due to the differences in the manufacturing processes and cannot meet the criteria for bioequivalence of chemical molecules. Given this guidance, biological products would not be substitutable at pharmacy level, and biosimilars would in principle have to follow the same pathway for authorisation as originators. Given the explicit legislation against substitution due to safety issues it may be less likely that clinicians will regard biologicals and biosimilars as interchangeable when making a prescribing decision.

In Germany it is our understanding that the current legal framework does not allow substitution of biologics with biosimilars unless there is permission from the prescribing physician. The current regulations governing generic substitution at the pharmacy level do not include biosimilars.

In the UK, pharmacists are not allowed generic substitution, and the UK government has not put forward an official stance on substitutability/ interchangeability with regard to biosimilars.

In Italy, there has been no official statement from either Farmindustria (the branded pharmaceutical trade association) or the Italian Medicines Agency (AIFA) regarding biosimilars. It seems that Italy's stance is to defer to EMEA guidance on a case-by-case basis.
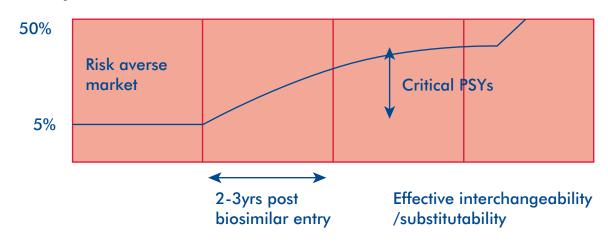
In Spain in September 2007 a new Ministerial Order was approved by the Department of Health, replacing an earlier one that defined a list of products where substitution was not allowed at pharmacy level unless authorised by prescriber because they were deemed to be of "narrow therapeutic range". In this piece of legislation, biological medicines (including insulin, vaccines and biotechnology medicines) have been included. Thus, biotechnology products (including biosimilars) cannot be substituted in Spain without prior authorisation from the prescribing doctor.

2.1.4 How may the status quo change?

At the regulatory and legislative level the trend is currently against substitution and interchangeability in the biologicals arena. At the local level, however, for example in UK hospitals, there have been examples of substitution. In some tendering processes hospitals only purchase one type of competing originator EPO product. This forces clinicians to substitute the drugs of patients who come in on a different brand with the hospital product choice. Anecdotal evidence within nephrology units suggests this has not, to date, resulted in any adverse consequences for patients.

Our view is that the only way that there will be change in the way that the substitutability and interchangeability of biologicals is handled is through the build-up of "patient safety years" (PSYs) data for biosimilar products. Regulators will initially insist on extensive pre-launch data being obtained from clinical trials to establish the safety, quality and efficacy of the biosimilar product in its own right. But there will also be a need for post-launch PSY data to provide clinicians with comfort on interchangeability between the biosimilar and the originator product, i.e. on the safety of interchanging products. This will be independent of (but could incorporate) any pharmacovigilance requirements for the biosimilar imposed by the regulator as part of the approval package. Two or three years of good safety data within the European market may change the nature of the interchangeabilty/substitutability debate. Clinicians are likely to become more willing to use biosimilar and originator products interchangeably. Governments are likely to be more willing to consider permitting substitution at the pharmacy level and regulators may reduce the clinical trial burden they impose on later biosimilar entrants. Positive European PSY experience may also make it easier for biosimilars to penetrate the US market (i.e. companies might be able to use European data to persuade US clinicians of the benefits of using products interchangeably) and indeed may impact on how regulation is implemented there. The potential strategic importance of European PSY data for the US market will influence the willingness of companies to invest in launching biosimilars in European markets.

Our expectation is that the penetration achieved by biosimilars will initially be low (i.e. below 5% market share) due to clinical conservatism reflecting the lack of cumulative safety data on the products and data on their interchangeability. As PSY data are accumulated, more new patients will be commenced on biosimilars. The critical point may be in two to three years after entry when enough data may have been accumulated to encourage clinicians to opt for "automatic" interchangeability in some markets, leading to much greater biosimilar penetration and potentially to a process that leads to pharmacy substitution becoming acceptable policy. We summarise our view in Figure 1.

Figure 1: Strategic overview of patient safety data

Market penetration

2.2   The Market Environment

2.2.1   Demand-side features

Hospitals

The specialist nature of biopharmaceuticals means the majority of prescribing occurs within hospitals although there are variations between European markets. Recent years have seen more use of tenders and the formation of large hospital buyer groups - particularly in the UK. However, there is still considerable variation, even within European markets using tenders, in the extent of buyer power. The market is thus segmented. Part of the market has a high elasticity of demand, with large buyer groups able to obtain large discounts (sometimes as high as 60-70%) where originator biopharmaceutical products currently compete and where clinicians are prepared to use these products interchangeably. Other buyers have a more inelastic demand due to clinical conservatism, i.e. clinicians are reluctant to change from the products they are currently prescribing despite price discount incentives. Hence there is heterogeneity and as a result different levels of price pressure in different markets.

There can be tension within a hospital tendering process. The purchasing pharmacist may be willing to substitute and therefore favour a tender based on price rather than on the service levels. Clinicians may be more conservative and less likely to interchange products based on a lower price. The outcome of the tendering process may depend on which of these groups holds the balance of power. This may further add to the segmentation of the market. The example within a hospital where only one EPO product is tendered for and doctors are required to interchange products could happen in other markets when biosimilar products enter.

Tendering is designed to promote competition but it also raises barriers to entry. Companies need good market intelligence to compete effectively in the tendering process, i.e. to win tenders and to do so without underpricing. It will take time for new entrants to identify different segments of the market, and to gather enough information to assess which accounts to target. The process of winning tenders requires considerable know-how and investment in account management resources, taking time as well as resources.

Retail sector

If primary care physicians do prescribe biopharmaceuticals it is often under the direction of specialists or at the initiation of a specialist. Primary care clinicians are therefore likely to avoid switching specialist treatments if they and their patients are familiar with a certain medicine and it is working. Hence demand is relatively inelastic. In this environment, generalist clinicians are unlikely to rapidly adopt biosimilars unless there is substantial outside pressure to do so.

Germany is one biologicals market with a strong retail element. We might expect generalist physicians in primary care not to have the specialist knowledge of those in secondary care and as a consequence demand for biologics in Germany is likely to be inelastic under the influence of clinical conservatism. We can already see payer concerns about the knowledge of generalists in other areas such as oncology where sickness funds request a second opinion before reimbursing their patients for particular drugs.

Some companies have attempted to implement strategies to circumvent the high discounts within hospital accounts. One of particular note is a strategy that Shire has attempted for a "follow on" originator

biopharmaceutical product within the UK market with a 20% discounted list price aimed at local payers – the Primary Care Trusts (PCTs). By offering a discount for primary care prescriptions the company was hoping to get PCTs to influence the hospital choice of product without having to offer substantial discounts in the hospital sector. However these kinds of strategies are only likely to work if primary care prescribing is the more important market.

In a number of European markets there are also trends to greater regionalisation. For instance in Italy regions now have more financial independence. In Spain, policy around pharmaceuticals is regionalised – especially in terms of prescribers' incentives. The shift of power to the regions may mean regional influence over procurement of specialist medicines which may lead to greater efforts to exert buyer power.

2.2.2. Current level of non-price competition

There appears to be a consensus between companies and clinicians at the moment that given the complicated administration of a number of biologic products, service provision and support is an important value-added part of the package for these products. It is therefore an area where companies compete. Services offered include inventory support, education/support for the patient (e.g. home care) and education for clinicians. Companies also seek to involve the patients of key customers in trials. Combinations of additional services will be customised for different market segments via direct marketing to the account holders. Marketing expenses, particularly those directed at account holders in the form of additional services, can be high. This will make it difficult for biosimilar companies to enter and compete.

Biosimilar companies may of course choose not to provide the same standards of service and support as the current competitors in the market place. They may decide to compete primarily on price. Originator companies may then withdraw value-added services as part of tender negotiations in order to institute greater discounts to try to win accounts. It will then become much clearer the extent to which these services are of real value to clinicians.

2.2.3 Product differentiation

Pricing will be affected by the scope for discounting (in relation to costs) and by demand-side preferences for different product attributes and for value-added services. Product markets may vary in a number of important ways with respect to the importance of these. We illustrate with three different therapeutic examples.

EPO market

Erythropoietin or EPO is a hormone produced by the kidney to regulate red blood cell production. It is licensed for the treatment of anaemia in renal disease and for cancer-induced anaemia. In the EPO market there are high price elasticities of demand due to the already established branded price competition between originator products within the market. There may however be segments of the market where demand is more elastic than others.

Amgen originally developed epoetin alfa (known as Epogen) in partnership with Johnson and Johnson, who were then granted a licence to market it as Procrit in the US. Eprex (which has the same biomolecule as Epogen/Procrit) is manufactured independently by Johnson and Johnson for the European market. Roche market an epoetin beta product, Neorecormen. In 2001 Amgen launched a second generation EPO in Europe – darbepoietin alfa (Aranesp) which has longer activity in the body.

In September 2006, NICE published clinical guidelines on anaemia management in people with chronic kidney disease in the UK. Its evaluation of the EPO class of products concluded that all three products (Eprex, Neorecormen and Aranesp) are equally effective and therefore no specific recommendation was given on which product to use. Choice of EPO type product in chronic kidney disease was recommended based on patient status, route of administration and local availability. Only one economic evaluation was found in chronic kidney disease but NICE concluded it was methodologically flawed, hence no evidence statement was put forward in the NICE clinical guidelines (NICE, 2006).

According to NICE the three products cannot be differentiated on safety grounds either. It found the type and frequency of adverse events was similar for all three medicines, i.e. all were associated with increased risk of thromboembolic complications such as deep vein thromboembolisms and pulmonary emboli.

There have been attempts to clinically differentiate by the newer brands into the market. The newest product, Aranesp, seeks clinical differentiation on dosing frequency. A second, pegylated, long-acting agent, Mircera was launched by Roche in 2007. It remains to be seen whether it can differentiate itself. Long acting agents may increase convenience to the patient, by decreasing the burden of painful injections, and may also reduce the need for professionals' time. However, there is little evidence to date of market acceptance of the reality and value of these characteristics, and more pragmatic studies may be needed to demonstrate any practical benefits of such attributes.

Table 1 shows the current brands on the EPO market and future launches. Two products are due to be launched in 2011 which are likely to have mechanisms of action different from those currently on the market. However it is too early to be able to gauge their likely relative clinical effect. The 2007 launch of a follow-on originator product, Dynepo, by Shire, is discussed below. Table 1 does not include biosimilars, but a number of biosimilars were authorised in 2007 – from Sandoz (with Medice and Hexal also licensed to sell versions of the same product), Hospira and Stada.

Dynepo is the fourth "first generation" EPO product, an epoetin delta. It is an interesting case study as the pricing strategies employed could be similar to those which biosimilars companies may use. Dynepo has been shown to be clinically similar to both epoetin alfa and epoetin beta in the EMEA evaluation, but there is purported advantage in terms of adverse effects. In the UK Shire (the marketing company) felt it could not compete on hospital discounts so launched with a 20% discounted list price in a bid to attract PCTs as commissioners of care to persuade hospitals to use their product. In Germany the current EPO products are all in the same reference group for reimbursement. If a product prices itself at a 30% discount to the reference price then patient co-payment will be avoided, and so Dynepo launched at a 30% discount. Shire's product entry highlights the different strategies that biosimilars entrants could also try and employ to gain some market share.

GCSF market

In the GCSF market there are slightly different market dynamics and there may be greater product differentiation within the market at present. There are three products currently on the market. The two first generation products Neupogen (filgrastim) and Granocyte had respectively 55% and 16% of prescribing share within Europe, based on a 2007 published audit, with the rest attributed to a second generation product Neulasta.

Neulasta enables GCSF to be administered by a single injection, and therefore could avoid the risk of less than optimal dosing that occurs with the market leader Neupogen, as well as improving patient compliance and convenience. Phase III trials showed that the optimal dosing schedule for Neupogen was for it to be used for 10-14 days post completion of chemotherapy cycle, but recent evidence shows that on average the duration is only 5.3 to 7 days in Europe (Holmes et al., 2002a; Holmes et al., 2002b; Green et al., 2003). Clinicians have not been convinced that a shorter duration regimen gives patients suboptimal outcomes despite studies showing that shorter durations of Neupogen treatment do result in a higher incidence of febrile neutropenia. This makes it harder for Neulasta to differentiate itself on

Table 1: Current and pipeline originator products for the EPO market

Brand Name	Company	Type of Product	(Expected) Launch Date
Epogen/Procrit/ Eprex	J&J/Amgen	Epoetin Alfa	Launched in 1987 in US markets
Neo-Recormen	Roche	Epoetin Beta	Approved in EU in 1997
Aranesp	Amgen	Darbepoetin Alfa – second wave product – prolonged activity due to change in glycosylation	Marketed since 2001 in EU for renal anaemia
Dynepo	Shire	Epoetin delta –produced in human cell lines	2007
Mircera	Roche	Continuous erythropoietin receptor activator –modified human erythropoietin and then pegylated	2007
Hematide	Affymax	Synthetic peptide-based erythropoesis stimulating agent	2011
FG2216	Fibrogen	HIF Enzyme inhibitor – oral administered product	2011

Source: Porges et al. (2006)

administration frequency as compared to Neupogen. As we noted in the case of Aranesp, many clinicians will remain unconvinced of the benefits of a second generation biopharmaceutical in the absence of relevant evidence from routine clinical practice.

There do not appear to be any new originator products due to be launched into this market, but there are several biosimilar versions of the first generation products due to be launched. In February 2008 the EMEA approved biosimilar versions of filgrastim for Teva, CT Arzneimittel and Ratiopharm.

Growth hormone market
The demand for growth hormone in Europe is inelastic. Most of the patients prescribed growth hormone are children. Caution around biosimilar safety profiles will make clinicians conservative in most markets but this aspect may be even more prominent where prescribing in children takes the majority share. In addition to any differences in the dosing and bioavailability of biosimilars there may be differences between the devices available. It can take a significant period of time for a child to be trained on a particular device. Most clinicians are unlikely to feel that a change is warranted, even if there is a major cost discrepancy between the currently prescribed product and the alternative, when a child is already well-maintained on a particular growth hormone product. It is unlikely therefore that switching products will occur with great frequency in the growth hormone market and with a low number of new patients each year, the market for biosimilars is likely to take time to develop.

The growth hormone market was the first to see the launch of a biosimilar – Omnitrope. As our analysis suggests might be the case, it has had difficulty gaining market share with a market share well below 5%. This suggests that the levels of price discounting discussed in Grabowski et al. (2007), around 30%, may not in some markets lead to sufficient penetration of the market to justify investment in clinical trials.

Clinicians and patients can be highly influential in the substitutability debate. Following the launch of the biosimilar Omnitrope in Germany, patient groups and medical societies published position statements discouraging doctors from prescribing it, particularly discouraging switching patients to the biosimilar. At present there is no pressure from the sickness funds to prescribe Omnitrope. If price differences increase this may become more of an issue, although doctors will still have clinical responsibility for the prescription.

2.3   Conclusions

In this section we have set out the current environment within European biosimilars/biopharmaceuticals markets:

- A regulatory framework has been set up by the EMEA to look at similar biologicals on a case by case basis. Comparable clinical quality, efficacy and safety profiles have to be demonstrated, thereby acknowledging the importance of patient safety and the need for substantial testing prior to approval.

- Given the EMEA framework, the individual European countries have been precautionary in their stance with regards to the substitutability or interchangeability of biosimilars for the originators products. There will only be a change in regulation and clinicians' conservatism more generally through accumulation of PSY data post-launch. It will probably require two or three years' cumulative PSY data for the environment to change.

- In most European markets, prescribing of biopharmaceuticals is specialist and hospital led. There has been some consolidation of hospital buyer groups but across Europe there is considerable variation in bargaining power leading to market segmentation. Research has shown that purchasing pharmacists are much more price-sensitive and willing to substitute than their medical colleagues.

- Services including home care and education for clinicians and patients are currently important non-price aspects of company support packages. There is a general expectation from clinicians that these services will be provided. Price competition may result in them being dropped to enable companies to offer larger price discounts.

- We explored three very different examples of biosimilar markets:

  - In the EPO market there are already a number of originator competitors and none of the products has been able to differentiate itself clearly. Two more products have recently been launched, and a number of biosimilars have also been licensed in an already highly discounted market. Thus, innovative pricing strategies by the new entrants might be expected.

- The GCSF market currently consists of two first-generation products and a second-generation one. Biosimilar products have recently been licensed. If the second generation product can differentiate itself then biosimilars may compete only with the first generation products.

- The growth hormone market differs from the previous two as medicines are predominantly prescribed for children. The devices differ and it needs considerable training for a child to be comfortable in using them. Clinicians are therefore likely to be more conservative in this market with regards to interchangeability. Not surprisingly, although this market saw the launch of the first biosimilar (Omnitrope), it has very low market share.

3. AN ECONOMIC FRAMEWORK FOR ANALYSING BIOSIMILARS

The role of this section is to provide some theoretical underpinning for the statements made throughout the paper about the evolution of prices. We briefly summarise the existing literature and then introduce our approach to modelling the market for biosimilars. As highlighted, the key variable is the accumulation of PSYs which impacts on prices. For a more technical description of the model, see Annex 1.

3.1 The Grabowski et al. Model

There is only one paper in the economics literature which models biosimilars markets. Grabowski et al. (2007) characterise the market for biosimilars as monopolistic competition. Monopolistic competition in general assumes there are a large number of sellers. Products are differentiated although they are close substitutes of one another. Entry and exit of firms is costless, i.e. there are no irrecoverable sunk costs. Grabowski et al. argue this model is suitable as an approximation to represent the biosimilars market. They are interested in modelling how costs of entry relative to market size affect the number of entrants and in turn how this entry affects the equilibrium of biosimilar price relative to the pre-entry originator price. They do not model any strategic behaviour on the part of the originator. Within this framework, they find the equilibrium number of firms by setting profits equal to zero – assuming all firms are identical and products are homogenous. In their model, the equilibrium number of entrants decreases as fixed costs and marginal costs for biosimilars increase. In other words the more clinical development work needed and the

more complex is manufacturing, the fewer entrants there will be, with less scope for price discounts.

While this model allows for interesting comparative statics, it does not take into account some of the factors likely to be driving competition between the originator and biosimilar products. In particular, we argue that: (i) competition (at least in the short run) is oligopolistic, i.e. it is competition between a few entrants, rather than between many; (ii) products are differentiated; and (iii) the market is segmented according to different own-price and cross-price elasticities of demand. The following section sets out our theoretical framework and focuses on some of the more interesting implications in terms of what drives the equilibrium. Annex 1 contains technical details of the Grabowski et al. model as well as of our approach.

3.2 Our Proposed Theoretical Model

Our starting point is the model developed by Frank and Salkever (1997) to assess the impact of generic entry[1]. These authors argue that a market segments into two when a generic (in our case, a biosimilar) enters the market – the price-sensitive and the price-insensitive segment. For the price-insensitive segment, demand for the original product does not depend on the price of the competitor(s) – this segment can be referred to as the "loyal" segment. On the other hand, in the price-sensitive segment all products compete. Frank and Salkever also assume there is a competitive fringe producing the homogeneous generic drug. We modify this model in a number of ways.

First, we assume that there is one biosimilar product rather than a competitive fringe (although there is still an originator product). Thus, we have a duopolistic market. Second, we assume both products are differentiated in the price-sensitive segment, where the originator and the biosimilar compete. Two market segments for the originator product arise from two types of patients: the "loyal" segment places a very large weight on safety and therefore will "never" use the biosimilar version of the product, while the other segment (price sensitive) is less risk averse. Third, firms choose prices simultaneously to maximise profits.

As we indicate in Section 2, market segmentation based on product differentiation is key. Our model represents the degree of product differentiation between the originator and the biosimilar product at two levels:

- There is a level of differentiation which means that in the loyal segment the originator enjoys a de facto monopoly situation.

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[1] This model was later adapted by Mestre-Ferrandiz (1999) to assess the incentives of originator firms to produce their own generic version.

- within the price sensitive segment, both products compete – but (at least initially) consumers treat the products as heterogeneous.

The key feature of our model is that it follows Frank and Salkever by combining market segmentation with linkage between the segments. Note, however, there are a number of ways of linking the two market segments. We follow Frank and Salkever by assuming the originator company can charge only one price for its product in both segments. This implies the price charged by the originator company will affect the demand for its product in both segments – which in turn also affects the demand for the biosimilar product in the price competitive segment.

The more important linkage we want to explore is how the accumulation of PSYs will affect the relevant model parameters which in turn will affect equilibrium prices. In particular, we want to identify what set of assumptions gives us the time path we illustrate later (see Figure 4). PSY data are expected to provide evidence that the biosimilar is comparable to the originator product and hence clinicians can use the products interchangeably. In terms of our theoretical model, that could imply a number of scenarios in terms of how parameters change, as illustrated in Annex 1. The most likely in practice is that the accumulation of PSYs leads to a reduction in the degree of differentiation between the originator and the biosimilar product. This reduces the size of the "loyal" market for the originator and increases the market share of the biosimilar product in the price-competitive segment at given prices. This is in turn likely to encourage the originator to cut price or see an erosion of its market – until eventually it has only the (now small) "loyal" market left – at which point it may increase price as in conventional chemical generic markets, leaving the vast majority of the market to the biosimilar.

In order for the biosimilar company to generate this PSY data, its product needs to gain some market share, i.e. it needs to be sold and consumed to generate real life data, or be used in studies of interchangeability. This requires an investment in generating clinical evidence and/or price cuts to win market share. Our current model assumes that the degree of product differentiation is exogenous and companies cannot affect it – however, this variable could be made endogenous, and dependent on the biosimilar's post-launch clinical study investment and its market share. Assuming still that the originator company could not price discriminate across segments (i.e. it could only charge one price) an additional link between the two segments would thus be the (endogenous) degree of product differentiation. It might make biosimilar entrant strategies of large price discounts to win market share attractive. Originators will be reluctant to match these discounts if they have also to offer them to their (intra-marginal) loyal customer base. However, there is a problem for the biosimilar entrant with a high discount strategy. Lack of perceived similarity means price discounts may not be sufficient to generate customers, and very high discounts risk undermining the market. Moreover it will be very difficult to raise prices once interchangeability is demonstrated. Thus large discounts may be self-defeating for the biosimilar entrant. They may not achieve market share because PSY data are not there, thus requiring investment in the collection of PSY data that the price discounts have made it harder to recover.

Another possibility for future theoretical development to take into account how the accumulation of PSYs could be modelled might be to construct a two period model, where the demand in period 2 for the biosimilar depends on sales in period 1. The underlying assumption here is that if the size of the market for the biosimilar depends on the stock of PSYs (which is technically the integral of the rate of sales over time) the biosimilar firm's decision is to choose prices now and in the future, taking account of the effect of current price on current profit and future profit via the future shift in demand as the stock of PSYs increases. Of course the originator could seek to pre-empt the ability of the biosimilar entrant to generate PSYs from sales by cutting its price.

As noted we have not modelled the possibility for the originator to price discriminate between the two segments, i.e. charging a different price in the loyal and in the price sensitive segments. This is clearly a characteristic of some European hospital sector markets and may be becoming possible in both the UK and German primary care markets. As our model stands, it would imply the link between the two segments disappears, as the originator will charge the high monopoly price in the loyal segment and the lower standard duopoly price with heterogeneous products in the competitive segment. We can replace this linkage with one based on product differentiation as noted above. If the size of the loyal segment is formally dependent on the degree of product differentiation in the price sensitive segment; then for example, as more PSY data is generated, the lower is the size of the loyal segment.

Making the degree of product differentiation endogenous by linking it to the generation of PSY data through market share gain and/or linking the segments according to the degree of product differentiation are not mutually exclusive. Both are likely to produce results showing that the originator company may be willing to accept a lower price in order to reduce the ability of the entrant to gain market share and so to generate PSY data. In other words heavy discounting by a biosimilar entrant is likely to be matched in key market segments by the

originator, reducing the benefits to the entrant of doing this. It is likely therefore to make more sense for entrants to find non-price cutting routes to gaining market share and to generating PSY data.

We can also relax our duopoly assumption. As more biosimilar companies enter the market the likelihood of price competition increases. Where prices end up depends on the number of entrants and the underlying cost structure. Here the Grabowski et al. model is helpful. The higher are fixed costs (of pre-entry development work and post entry PSY data collection) then the fewer companies will enter – with a higher long run equilibrium price and a longer time path to get there. If, as we expect, PSYs are seen as therapeutic agent or therapy class related then there are public good characteristics to PSY generation by early entrants - it reduces the cost burden on later entrants. This will increase the room in the market for viable entrants, reduce the equilibrium price and speed up the process of getting there.

These additions to our model merit further research, but are beyond the scope of this paper. The main purpose of our theoretical framework presented here is to provide the next step in thinking about biosimilars markets.

4. DYNAMIC MODELLING OF BIOSIMILARS

Both the Grabowski et al. model and our proposed theoretical framework are "comparative static" models. They do not take into account explicitly the interaction between the competitors. In this section we consider product attributes as dependent in part upon firm strategy. We use a simple business model taxonomy to show how the market might evolve over time.

4.1 Taxonomy of Business Models

We have two types of biosimilar business model. We summarise them in Table 2. The principal difference between these models is the degree of investment in product development and in marketing know-how required in the "follow on" model versus winning share through price discounting in the "biogeneric" model.

Most established generic companies are not equipped to undertake a "follow-on" approach to the market. We can note that potential biosimilar entrants are forming alliances with other companies to enable them to compete effectively with the originator companies in manufacturing and marketing skill. In Table 3, we illustrate some of the alliances being formed to enter the EPO and GCSF markets.

The principal point is that none of the "1st wave" of biosimilar companies will be in the position of having to follow a "biogenerics" business model. Competing through account management and sales and marketing investment is a realistic and likely prospect. Indeed, these biosimilar companies have other marketing alliances:

- Ratiopharm with Ribosepharm, a dedicated oncology generics company with a specialist sales force);

- Sandoz can draw upon the marketing know-how of Novartis;

- Stada has placed its biosimilars group within its specialist pharma division – giving a signal as to the business model it expects to deploy.

Table 2: Taxonomy of biosimilar business models

Business Model	Description
"Follow on": To position the biosimilar as both: • a follow-on (me-too) biologic (FOB) with attributes which merit starting new patients on the treatment; • a product that it is both safe and of value to switch patients to, from the originator's product	Invest in new device/formulations if rational/feasible Invest in sales and marketing and account management skills Rigorous attempt to price discriminate. Consider impact of own pricing behaviour on market price dynamics. Invest in generating patient safety years data
"Biogeneric": To position the biosimilar as a biogeneric offering the same benefits at lower cost than the innovator's product	Low cost model (low price and push through distribution channels with discounts) Minimal sales and marketing

Table 3: Alliances among biosimilar entrants in the EPO and G-CSF markets

Market	Biosimilar entrant	Manufacturing partner	Marketing partner
EPO	Biogenerix Stada Sandoz Pliva	Norbitec Merckle	Hospira Ratiopharm
GCSF	Biogenerix Sandoz Stada Pliva	Merckle Hospira	Ratiopharm Norbitec

It would be rational for biosimilar companies to follow the originators in adopting different models for different market segments according to their price elasticity of demand and sales and marketing accessibility. Price elasticity of demand of all parts of the market will change over time, so the business model mix of the market will vary over time. A particular threshold in our analysis is the point at which enough PSY data have been collated for the market to begin to accept bioequivalence and interchange or substitute more freely. As safety data build up with biosimilar products and as the prices of originator products continue to fall, so the price elasticity of demand in the market will increase and prices will approach marginal cost – in effect approaching a de facto "biogenerics" business model.

4.2 Price Trajectories

As we noted earlier, the literature can be divided into those predicting large price discounts and the Grabowski et al. (2007) view that cost-of-entry limits will lead to lower discounts in equilibrium.

Our analysis suggests:

(i) There is a lower starting price, i.e. there will be a lower market price at the time of biosimilar entry than is assumed in the modelling to date.

Published studies have used list prices. In practice in many European markets there is already competition between brands which has led to price discounting to hospitals below list prices, particularly within the more price sensitive markets where consolidation has led to the formation of large hospital buyer groups. (As we noted, in most European markets biopharmaceuticals are specialist secondary care products). These effects are leading to a systematic downward price trend. By the time of biosimilar entry, prices will be even lower than now.

(ii) Less rapid price erosion because of the lack of evidence to support interchangeability or substitutability and a limited number of entrants.

We do not subscribe to the view of an immediate "biogeneric" business model with high rates of price elasticity of demand. Our analysis suggests there is low price elasticity in the market place. This is due to lack of evidence to support the safety and efficacy of interchanging biosimilar with originator products. There may also be significant non-price elements of a service package that are valued by clinicians.

There will be strategic investment value for biosimilar companies post-entry from generating PSY data and from learning how to compete. This differs from the assumptions of the Grabowski et al. analysis, which argues that the clinical work required to generate patient safety data creates a one-off barrier to entry. Our analysis suggests that this clinical work is necessary not only to obtain regulatory approval but also to ensure these products ultimately generate significant market share. Investment post-launch with a "follow-on biologic" approach on the part of biosimilar entrants (marketing investment, high service levels and supply of product differentiation where possible) will be more successful than "biogeneric" business models. Until enough time has elapsed for PSY data to be collected post launch to establish the safety of biosimilars, companies are likely to find it more profitable to follow a strategy that allows them to differentiate their product from those already on the market.

Price erosion is therefore slower in our analysis but starting from a lower base. If a company were to implement a "biogenerics" strategy in the short run, then it is unlikely this company will gain any significant market share as clinical conservatism would prevail - the lower price would not overcome clinician patient safety concerns. This situation will only change once adequate positive PSY data are collected by the first biosimilar entrants and this is communicated to clinicians to encourage interchangeability.

(iii) A long term equilibrium price that is above the competitive chemical generics level.

Much of the literature seems to assume not only a rapid realisation of savings, as per highly competitive conventional product generics markets, but that end prices are discounted by 70-80% of current levels. This only truly reflects experience in the US and UK generics markets for high value markets. The Grabowski et al. model, by contrast, predicts more modest equilibrium price discount levels of nearer to 40-50%, based on limited generic entry due to high fixed costs. Prices come down to costs, but it takes longer due to limited entry (as a result of high entry costs) and costs are high compared to standard chemical generics markets because of high entry costs.

In our analysis, a price equilibrium near to long run marginal cost could prevail, but a pure "biogenerics" model is unlikely until regulators and/or payers are in a position to introduce equivalence and substitutability into the system. We calculate that it may take between two to three years post-entry of biosimilars to generate sufficient PSYs for regulators to review their policies on biosimilars. If this does occur then the regulatory barriers described by Grabowski et al. (2007) may be reduced. This in turn would mean that later biosimilar entrants may not need to invest so heavily in trials to prove safety and/or bioequivalence, reducing their fixed costs. Hybrid models would then become more prominent and eventually a "biogenerics" low cost model which has minimal sales and marketing

expenditure and a focus on price competition strategies would prevail. Where biosimilars are more successful in taking market share, patient data and reputation for quality might help to overcome clinical conservatism at a faster rate, introducing scope for earlier market (as opposed to regulatory) interchangeability and substitutability.

We therefore expect equilibrium prices to be lower than the level described by Grabowski et al. (2007) as the level of expected clinical development requirements pre- and post-launch (and hence fixed costs) will be reduced by licensing bodies and clinicians as PSY data reduce (we assume) concern around the safety of biosimilars. However there will still be a greater barrier than in the chemical generics market as some clinical development activity pre- and post-launch will be required and/or expected. Manufacturing costs are also likely to be a higher share of list price than is the case for chemical entities. These two factors mean that the equilibrium price is unlikely to be as low as that described in the cost-saving literature based on the experience of chemical generics.

Figure 4 below summarises our analysis of how biosimilars markets might play out according to our analysis. It shows:
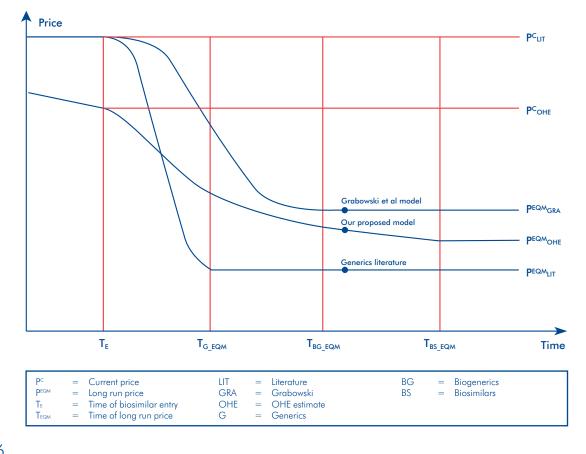
Figure 4: Summary of findings on price discounting: price trajectories

P^C	=	Current price	LIT	=	Literature	BG	=	Biogenerics
P^{EQM}	=	Long run price	GRA	=	Grabowski	BS	=	Biosimilars
T_E	=	Time of biosimilar entry	OHE	=	OHE estimate			
T_{EQM}	=	Time of long run price	G	=	Generics			

- A lower starting price. Use of list prices as a basis for current prices is not reflective of transaction prices in many markets due to the higher hospital discounts in place in practice.

- Lower market price at time of biosimilar entry based both on a lower starting price and expectations of further discounting before biosimilars enter.

- Less rapid erosion towards the "equilibrium" price in the short term because of the need for post-launch PSY data before clinicians will use products interchangeably.

- A long term equilibrium price sitting in between those associated with two camps, i.e. below the Grabowski et al. assumptions but above the "pure" chemical generic level. It cannot reach that which might be expected in the chemical generics market due to higher variable costs of manufacture and higher fixed costs arising from development.

5.   WHAT SHOULD PAYERS DO?

There are three options for intervention by government in biosimilars markets:

1. Substitutability rules to drive price competition, whereby governments permit pharmacists to substitute one biosimilar for another.

2. Direct price intervention to push down originator product prices. This could take the form of:
   a. inclusion into reference price systems;
   b. a post-patent expiry price cut imposed on the innovator or a cut imposed on a biosimilar entrant.

3. Market support to encourage competitive entry (e.g. investing in infrastructure for outcomes monitoring, and to facilitate pharmacovigilance work including studies on interchangeability).

Our analysis suggests that the risks to patient safety associated with Option 1, which involves jumping ahead of the regulatory position on bioequivalence and of clinical acceptance of biosimilar interchangeability, are not warranted. Nor do we think it likely that governments or other payers will want to pursue this option until a much later stage in the development of biosimilars when substantial supportive PSY data are available. Moreover, it would hinder the collection of PSY data as biosimilar

entrants would be forced to adopt a low cost "biogeneric" strategy to compete on price at the pharmacy level.

Direct price intervention as per Option 2 is potentially counterproductive for the following reasons:

- In the case of reference pricing it assumes a degree of interchangeability (i.e. patients can switch to the lower priced product) that is not likely to be reflected in clinicians' willingness to switch patients given safety concerns.

- More fundamentally it will discourage biosimilar entry by reducing potential profits. This is particularly important given the need for new entrants to invest to meet regulatory hurdles, to collect post-launch patient safety data and to market to clinicians. Without this "follow on biologic" stage to biosimilar market development, the PSY data required to enable the market to evolve to a biogeneric market may never be collected.

We recommend Option 3, with governments taking a more strategic approach, through supporting market evolution. Grabowski et al. (2007) hypothesised that incentives for entry could be created by push mechanisms to reduce costs through grants for research and by easing regulations, or by pull mechanisms to raise revenues (such as the US 180-day exclusivity period for the first chemical generic entrant). Our analysis supports their view that it is important to encourage the entry of biosimilars. We believe, however, that market support policies that facilitate post-launch PSY data collection and better outcomes data more generally would be more appropriate.

In particular, we would recommend a policy which supports and incentivises the generation of high quality PSY data. Such studies could also explore the value for money of second-generation biotech products that are competing with the first generation originator and biosimilar products. Government/industry collaboration to determine how to generate this PSY and value for money data in biotech products would be helpful. Supporting market evolution in this way would both better reward innovation that benefits patients and secure a path towards achieving price competition over time so enabling payers and patients to gain substantial savings from biopharmaceutical patent expiry. In our view it is not possible to "jump start" a biogenerics market by forcing down prices or by imposing substitutability. Either of these approaches is likely to set back the evolution of efficient biosimilars markets.

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ANNEX 1 COMPARISON OF (THEORETICAL) MODELS OF MARKETS FOR BIOSIMILARS. OUR APPROACH

This Annex introduces a model that provides theoretical underpinning for the time path of prices outlined in the paper. The key variable is the accumulation of patient safety years (PSYs) data. We focus on how the key parameters of our model (market size, demand responsiveness and degree of substitutability) might be affected by PSYs. This, in turn, enables us to analyse the effect of PSYs on prices.

There is only one biosimilars market model in the economics literature, Grabowski et al. (2007). They characterise the biosimilars market as monopolistic competition. Their rationale is that there are significant entry costs into the market. They model how entry costs affect equilibrium generic prices relative to the pre-entry monopoly price.

They use an inverse demand curve:

$$p = a - bQ,$$

where p is the price and Q is the sum of the output produced by N identical firms. The cost function for firm *i* is:

$$C (q_i) = mq_i + F$$

Where *m* is the constant marginal cost and F is the fixed cost.

They solve for the symmetric equilibrium values for q_i. As the authors assume a monopolistic competition scenario, they solve for the equilibrium number of firms (N*) by setting profits equal to zero. They find that the equilibrium number of firms decreases as fixed costs and marginal costs rise. Moreover, as marginal costs rise, the relative gap between generic and branded prices narrows.

Our starting point is the model by Frank and Salkever (1997) assessing the impact of generic entry[2]. They argue that the market segments into two when a generic (in our case, a biosimilar) enters the market – the price sensitive and the price insensitive segment. For the price insensitive segment, demand for the original product does not depend on the price of the competitor(s) – this segment can be referred to as the "loyal" segment. On the other hand, in the price sensitive segment all products compete. The originator sets the same price in both markets. They also assume a competitive fringe producing the homogeneous generic drug.

We depart from this model, and the Grabowski et al. model in two ways.

First, we assume there is one biosimilar product rather than a competitive fringe. Thus, we have a duopolistic market. Second, we assume both products are differentiated in the price sensitive segment, where the originator and the biosimilar compete. Formally, we have the following (general) demand functions for the originator (labelled subscript 1) and the biosimilar (labelled subscript 2):

$$Q_1 = q_{11} (p_1) + q_{12} (p_1 , p_2);$$

$$Q_2 = q_{22} (p_2 , p_1),$$

where q_{11} is the demand for the originator product in the "loyal" segment, depending only on its own price p_1; q_{12} is the demand for the originator product in the price-sensitive segment (and thus depends negatively on its price and positively on the price of the biosimilar p_2); and q_{22} is the demand for the biosimilar product, which depends on the prices of both products. We justify the two market segments for the originator product as arising from two types of patients: the "loyal" segment places a very large weight on safety (in the sense both that the biosimilar may have side effects that have not been identified and that it may not deliver the same effectiveness as the originator product) and therefore never uses the biosimilar, while the other segment (price sensitive) is less risk averse.

Our model uses three linear demand functions: demand for the originator in the loyal segment; demand for the originator in the price sensitive segment; and demand for the biosimilar in the price sensitive segment. The intercept on the quantity axis (i.e. when prices are zero) measures the potential total demand for that product. This parameter can also be interpreted as the total market size for each product in its respective segment. The sum of these three parameters from the three demand functions will give the potential total market size (the originator and the biosimilar).

In the cost function, for simplicity we assume that the marginal cost and the fixed costs for both products are identical (and set equal to zero).

Thus, for the originator firm we use:

$$q_{11} = a_{11} - b_{11}p_1$$

$$q_{12} = a_{12} - b_{12}p_1 + \theta p_2.$$

[2] This model was later adapted by Mestre-Ferrandiz (1999) to assess the incentives of originator firms to produce their own generic version.

The linear demand curve faced by the biosimilar is:

$$q_{22} = a_{22} - b_{22}p_2 + \theta p1$$

where $0 \leq \theta < 1$ is the degree of product differentiation. When $\theta = 0$, products are completely differentiated (and thus we have in essence two monopolies); in the limit when θ tends to 1, products are homogeneous. Note that the linear demand functions cannot be defined when $\theta = 1$, as completely homogeneous products cannot sell for different prices. The parameters a_{11}, a_{12} and a_{22} define the potential total demand for each product in each segment (i.e. when prices are zero); a_{11} measures the potential total demand for the originator firm in the loyal segment, while a_{12} and a_{22} measure the potential total demand for the originator product and the biosimilar respectively in the price-sensitive segment. The different 'b' parameters measure (partially) how quantities change as prices change . The bigger the value of any one 'b' parameter, the bigger will be the response in demand to a change in price, ceteris paribus. As illustrated later, all of these parameters determine equilibrium values.

In terms of the cost function, for simplicity we assume that the marginal cost and the fixed costs for both products are identical (and set equal to zero). Thus, we obtain the following profit function for the originator and the biosimilar respectively:

$$\pi_1 = p_1 q_{11} + p_1 q_{12}$$

$$\pi_2 = p_2 q_{22}$$

Firms choose prices simultaneously in order to maximise profits. The equilibrium prices (defined as p_1^* and p_2^* for the originator and biosimilar respectively) are as follows:

$$p_1^* = \frac{2b_{22}(a_{11} + a_{12}) + \theta a_{22}}{4b_{22}(b_{11} + b_{12}) - \theta^2} \qquad (1)$$

$$p_2^* = \frac{2(b_{11} + b_{12})a_{22} + \theta(a_{11} + a_{12})}{4b_{22}(b_{11} + b_{12}) - \theta^2} \qquad (2)$$

In terms of comparative statics, when individual parameters change (rather than several of them changing simultaneously – see later), we have the following inequalities for the originator's price in equilibrium:

$$[(\partial p_1^*/\partial a_{11}) = (\partial p_1^*/\partial a_{12})] > (\partial p_1^*/\partial a_{22}) \Leftrightarrow b_{22} > \theta/2 \ (3)$$

Thus, in equilibrium we find that the magnitude of the response of the price of the originator is the same when the potential market size of either the loyal or the price-sensitive segment changes (a_{11} and a_{12} respectively).

For the biosimilar, we have:

$$(\partial p_2^*/\partial a_{22}) > [(\partial p_2^*/\partial a_{11}) = (\partial p_2^*/\partial a_{12})] \Leftrightarrow b_{11} + b_{12} > \theta/2 \ (4)$$

Comparing between the changes in the price of the originator and the biosimilar, the following inequality is obtained:

$$(\partial p_2^*/\partial a_{22}) > [(\partial p_1^*/\partial a_{11}) = (\partial p_1^*/\partial a_{12})] \Leftrightarrow b_{11} + b_{12} > b_{22} \ (5)$$

The price of the originator (p_1^*) will be higher in equilibrium than the biosimilar's (p_2^*) when the following inequality holds:

$$p_1^* > p_2^* \Leftrightarrow (a_{11} + a_{12})(2b_{22} - \theta) > a_{22}(2(b_{11} + b_{12}) - \theta)$$

The intuition behind this inequality is as follows: if the combined (potential) market size of the originator in both the loyal and competitive segment (which is given by the sum of a_{11} and a_{12}) is relatively higher than the potential market for the biosimilar (determined by the magnitude of a_{22}), then the originator can charge a higher price than the biosimilar in equilibrium.

Let us examine how the accumulation of PSYs over time might affect prices. We look at the scenarios in turn.

The first scenarios assumes the following: over time, as PSYs increase, a_{11} falls and a_{22} increases. The loyal market shrinks while the market size for the biosimilar grows. The rationale for this is simple. The PSY data are assumed to show increasing evidence that the products are in clinical practice equivalent for patients in effect and safety profile. In other words the case for loyalty is diminished.

Assume for the moment that the effect on a_{12} is small and can be ignored. A decrease in a_{11} and an increase in a_{22} have respectively negative and positive effects on both p_1^* and p_2^*, but the magnitudes in the changes are different. Thus, depending on the size of the parameters, we can obtain a decrease in p_1^* and an increase in p_2^*. In particular, for p_1^* we have:

$$[(\partial p_1^*/\partial a_{11}) = 2b_{22}/A] \text{ and } [(\partial p_1^*/\partial a_{22}) = \theta/A];$$

where $A = 4b_{22}(b_{11} + b_{12}) - \theta^2 \ (>0)$

Thus, under the 'dynamic' scenario of a_{11} falling and a_{22} increasing (by the same magnitude) as PSYs accumulate, the price of the originator will decrease when $b_{22} > \theta/2$.

For the biosimilar, we have that $[(\partial p_2^*/\partial a_{11}) = \theta/A]$ and $[(\partial p_2^*/\partial a_{22}) = 2(b_{11} + b_{12})/A]$, where A is defined as above. Thus, under this 'dynamic' scenario, the price of the biosimilar will increase when a_{11} falls and a_{22}

increases when $(b_{11} + b_{12}) > \theta/2$. This relates back to the inequalities expressed in (3) and (4). From (5) we can conclude that when $b_{11} + b_{12} > b_{22}$, the change in the price of the biosimilar will be higher in magnitude than the change in the price of the originator.

To obtain a decrease in the price of the biosimilar, we need that $(b_{11} + b_{12}) < \theta/2$, i.e. the negative effect of the decrease in a_{11} is higher than the positive effect of the increase in a_{22}. Table 1 summarises the conditions under which both prices decrease as a_{11} falls and a_{22} increases.

It shows that the effect of PSYs on the degree of differentiation between the products (defined in our model as θ) is key. On the assumption that the increase in PSYs sufficiently diminishes θ such that the first scenario of Table 1 holds, then the prices of both products will fall.

Let us consider a second dynamic scenario. This time as PSYs increase, a_{12} falls (rather than a_{11}) and a_{22} increases, i.e. the effect on the originator is only on the price sensitive segment rather than the loyal one. If the changes of these two parameters are the same in magnitude, this will have the same effect as the first dynamic scenario. In other words we can model the impact of PSYs on θ as an exogenous fall in either a_{12} or a_{11} or both.

If we now turn our attention to the direct relationship between θ and prices, we see there is a positive relationship between them (from (1) and (2)). Thus, if the increased stock of PSYs over time leads to a lower value of θ, then (in addition to any exogenous effect) both prices will fall.

In other words the potential impact of PSYs in our model depends on its impact on θ. On the assumption that PSY data provide increasing evidence that the products are in clinical practice equivalent for patients in effect and safety profile then θ falls. If it does not then the originator can be expected to maintain a price premium. Should the biosimilar demonstrate positive effect or safety characteristics that the originator does not have, then θ will be high but to the advantage of the biosimilar.

There are a number of restrictive assumptions in the model. Two of the more important ones that may affect outcomes are:

- The originator charges the same price in both the loyal and competitive markets. If it were able to price discriminate then the competitive dyamics would be more complex.

- There is only one biosimilar entrant. If there were more entrants then price competition would increase if θ fell, i.e. the products were less differentiated.

Table A1: Conditions under which both prices decrease as a_{11} falls and a_{22} increases

'Dynamic' scenario: $a_{11}\Downarrow$ and $a_{22}\Uparrow$	Effect on p^*_1	Effect on p^*_2	Effect bigger for p^*_1 or p^*_2?
$b_{22} > \theta/2 > (b_{11} + b_{12})$	$\Downarrow$	$\Downarrow$	p^*_1
$(b_{11} + b_{12}) > b_{22} > \theta/2$	$\Downarrow$	$\Uparrow$	p^*_2
$\theta/2 > (b_{11} + b_{12}) > b_{22}$	$\Uparrow$	$\Downarrow$	p^*_2
$(b_{11} + b_{12}) > \theta/2 > b_{22}$	$\Uparrow$	$\Uparrow$	p^*_2

GLOSSARY

Biogenerics A term sometimes used interchangeably with biosimilars. In this paper it is used to refer to a possible point in the development of biologics where the demonstration of equivalence can be undertaken with limited clinical work.

Biologics/biopharmaceutical agents Medicines that originate from biotechnology processes.

Biosimilars Term used by the EMEA to refer to off-patent versions of innovative biopharmaceutical products to emphasise the difficulty in creating a copy of an innovator biologic product.

Biotechnology processes The use of micro organisms, such as bacteria or yeasts, or biological substances, such as enzymes, to perform specific industrial or manufacturing processes. Applications include the production of certain drugs and synthetic hormones.

Chemical generics Generic versions of small molecule standard pharmaceutical products.

Equivalence The process whereby a series of tests seeks to establish whether a generic version of a product can be expected to have the same profile (of efficacy and safety) as the originator product.

Erythropoietin (EPO) A hormone that stimulates the production of red blood cells, which is produced mainly by the kidneys. Synthetic EPO products are used to combat anaemia in kidney failure or anaemia caused by chemotherapy.

Granulocyte-colony-stimulating-factor (GCSF) A growth factor that stimulates the bone marrow to make white blood cells. Synthetic GCSF manufactured by biotechnology processes is used to increase white blood cell count after a bone marrow transplant or after chemotherapy.

International Non-proprietary Name (INN) The official non-proprietary or generic name given to a pharmaceutical substance, as designated by the World Health Organization (WHO).

Interchangeability Refers to the clinical decision at the formulary committee or at the prescribing clinician level around product substitution.

Monoclonal antibodies An antibody is a complex protein of high molecular weight normally produced by special white blood cells in the body as part of an immune response. Monoclonal antibodies are a type of antibody produced in large quantities in a laboratory. In therapeutics, monoclonal antibodies are constructed to target specific cells and stimulate a specific cellular response.

Monopolistic competition Monopolistically competitive markets have the following characteristics:
- There are many producers and many consumers in a given market.
- Consumers perceive that there are non-price differences among the competitors' products.
- There are few barriers to entry and exit.
- Producers have a degree of control over price.

The characteristics of a monopolistically competitive market are almost the same as in perfect competition, with the exception of heterogeneous products, and that monopolistic competition involves a great deal of non-price competition (based on subtle product differentiation).

Non-glycosylated biologics Absence of saccharide (i.e. sugar) groups within the structure of the therapeutic protein, making it less complex.

Omnitrope A growth hormone biosimilar product.

Patient Safety Years (PSYs) A measurement of the accumulation of patient safety data post-launch. In the biosimilars market this will be key to providing clinicians with comfort on the safety of interchanging products.

Reference pricing There are three possible types of reference pricing (RP): generic RP, therapeutic RP and international RP. For the purpose of this paper, we are only interested in the first two. Therapeutic RP involves grouping patented branded medicines, unless deemed "innovative", together with (usually much cheaper) generic versions of off-patented branded therapeutic competitors to determine the price third party payers will pay for new branded medicines. Generic RP only groups medicines with the same active ingredient once the originator brand goes off-patent. The basic principle behind generic RP is the same as with therapeutic RP: there is a limit to the amount reimbursed for all products containing the same active ingredient and the patient needs to pay some additional charge when the price of any medicine within the group is higher than this limit.

Substitutability Refers to the substitution decision made at pharmacy level, where a prescription has already been written and the pharmacist makes a decision to substitute if permitted by relevant national initiatives.

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