

BIOSIMILARS: HOW MUCH ENTRY AND PRICE COMPETITION WILL RESULT?

Based on the proceedings of an OHE Conference
held on 2 June 2009

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Office of Health Economics

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- Commission and undertake research on the economics of health and health care;
- Collect and analyse health and health care data from the UK and other countries;
- Disseminate the results of this work and stimulate discussion of them and their policy implications.

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FOREWORD

Competition among and with biosimilars still is a relatively new phenomenon; uncertainty remains about how much competition will develop and in what ways. This publication focusses on that uncertainty, examining how key factors may affect the market going forwards and suggesting responses for policy makers and manufacturers.

Since the workshop, events have further defined the landscape. In March 2010, as part of the health care reform law, the US enacted the Biologics Price Competition and Innovation Act. This legislation sets data exclusivity at twelve years, broadly describes data requirements for abbreviated approval, defines 'interchangeable', leaves the determination of interchangeability in the case of particular products to the FDA, and sets rules for the exchange of patent information between the originator and biosimilar manufacturer. Many of the specifics, however, require that the FDA develop regulations, a process likely to require two to three years.

In May 2010, the UK's National Institute for Health and Clinical Excellence (NICE) published final guidance on the relative cost and effectiveness of somatropin products to treat growth deficiencies in children¹. Omnitrope is listed as one of seven recommended products. This is the first time that NICE has recommended the use of a biosimilar.

The authors have updated their contributions where necessary to take account of these recent changes. In addition, Prof Grabowski has supplemented his marketing forecasting analyses with more recent work.

The Editors

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¹ <http://guidance.nice.org.uk/TA188>

Chapter 1

Introduction

PROFESSOR BENGT JÖNSSON

Experience with biosimilars is very limited, as is reliable information about their impact on pharmaceutical markets. As a result, behaviour and expectations by all stakeholders currently is based more on assumption than on fact. It is important to develop a more accurate *ex ante* understanding of what is likely to happen in this market.

One questionable assumption is that the 'traditional generics' model can be used to forecast how the biosimilars market will evolve over the next years. This is risky because several important differences between biosimilars and generics, and their markets, mean that barriers to market entry also are different. First, as the word suggests, 'biosimilars' are not identical to the original molecules. This means that the regulatory pathway for these drugs will be different and, at least initially, considerably more demanding than for generics. Second, the cost of collecting data to satisfy regulatory requirements, particularly for safety and effectiveness, is higher for biosimilars than generics. Third, production costs are higher for biosimilars than for small-molecule generics. Overall, then, the barriers to entry will be higher for biosimilars. As a result, the number of entrants will be fewer and this, in turn, will mean fewer price reductions spurred by competition among competing versions.

Some stakeholders, particularly payers, expect the marketing of biosimilars to offer opportunities for cost savings. Estimates of these savings vary significantly. The highest estimates usually are based on the assumption that this market will behave like the generics market in the US, with very aggressive price competition and price reductions of up to 80 percent very soon after generic market entry. The most realistic estimates, however, are for rather modest savings.

The potential for savings in Europe seems somewhat less than in the US. Regulation in Europe means that prices seldom rise – indeed, prices tend to slowly move downwards. Moreover, the market for generics is generally less competitive in Europe, although a more aggressive generics market is developing in some countries – The Netherlands and Sweden are examples.

Even in a highly competitive market, the potential for cost savings as a result of biosimilars is modest. According to some estimates, the total market exposed to biosimilar competition is around 10 percent and 5 percent of the US and European pharmaceutical market respectively, representing 1 percent or less of total healthcare expenditure. In addition, any savings from biosimilar competition will accrue only over the next ten years or so, not in the short-term.

The market evolution of Tamoxifen in Sweden provides an illustration. Price reductions of 20-25 percent, after patent expiry, were achieved only over a long period of time (1988-2008). Nominal prices remained stable for a considerable period, with inflation cutting into real prices in a price controlled environment. It is only recently, however, that more aggressive price competition has occurred, although this is due in part to the introduction of generic substitution in Sweden.

What has changed in recent years that can influence how the market for biosimilars will evolve? First, potential entrants into the biosimilar market have the substantial resources and the extensive competence necessary to withstand the higher costs and uncertainties. Nevertheless, since the cost and risk are greater than for most generics, incentives for entry must be also.

Regulators and payers will play key roles in the evolution of the biosimilars market. Payers likely will be both more influential and more engaged in shaping the biosimilars market than has been true for traditional generics. They are likely to work more closely with regulators and seek advice from them. Payers also are beginning to organise and finance follow-up studies to assess the safety and effectiveness of new medicines, which may become crucial to uptake and effective competition in the biosimilars market.

This seminar provided a solid overview of the issues outlined above. Economic theory and the existing models for market entry and pricing of biosimilars were examined for insights into what can happen and when. Included were both forecasts for the US and examples of European pricing strategies for biosimilars. The impact of regulatory issues on market entry was considered as well as options for payers looking for savings in newly-competitive biologics markets.

Chapter 2

Biologics and Data Exclusivity: Balancing Incentives for Innovation and Cost Savings

PROFESSOR HENRY GRABOWSKI

Data exclusivity is the period of time after a drug is approved before a biosimilar product can enter the market based on an abbreviated filing that relies at least in part on the innovator's safety and efficacy data.

Passed in 1984, the Waxman-Hatch Act provides for five years of data exclusivity for new chemical entities (NCEs) in the US, with an additional two and a half years to resolve patent disputes. This law spurred the growth of generics industry, provided some patent restoration and created considerable litigation. The central issue related to biologics was whether the exclusivity period should be longer than for NCEs. The two bills that were most discussed varied considerably – 12 years of data exclusivity under Congressmen Eshoo's and Inslee's bill, but only five under Congressman Waxman's bill. The bill that was passed, as a subtitle of the US health care reform law (H.R. 3590--111th Congress, 2009), provides for 12 years of data exclusivity for the original biologic and 12 months of data exclusivity for the first biosimilar approved that is interchangeable with the reference product. The EU, in comparison, has ten years of data exclusivity for both biologics and chemical entities, with an additional year possible for a new indication.

BIOSIMILARS DIFFER FROM GENERICS IN IMPORTANT WAYS

Complexity and patents

Generics are small-molecule compounds that are chemical-based; biologics are large and complex molecules derived from cell cultures. Epoetin can provide an example; it has approximately 100 atoms for every atom in ranitidine (a small-molecule anti-ulcer drug). As argued by Dr. Janet Woodcock, director of the Center for Drug Evaluation and Research (CDER) at FDA, biosimilars will not be identical to the innovator product for the foreseeable future (Woodcock, 2007). This has important implications for intellectual property (IP) rights and how the marketplace will evolve.

Data exclusivity and patents have separate but complementary roles. Patents are awarded for invention based on well-known criteria: novelty, utility and not-obviousness. Data exclusivity, or data protection, recognises that after invention – typically before clinical trials – a long, risky and

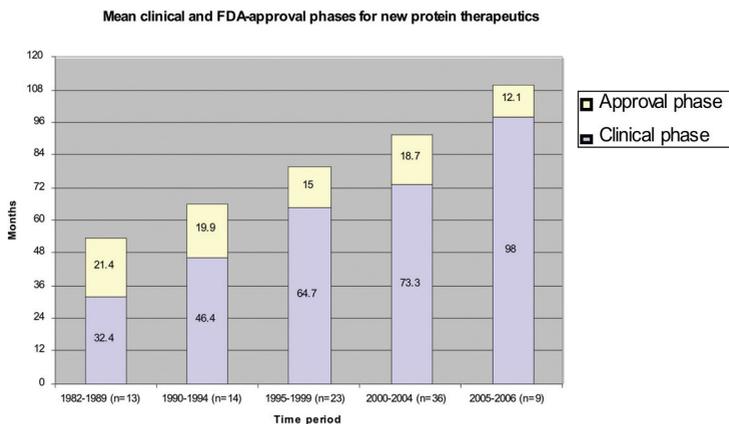
costly R&D process remains. In the US, effective patent life is often uncertain because it cannot be assessed until after FDA approval and resolution of any patent challenges; data exclusivity provides a more predictable period of protection.

The great protection afforded by data exclusivity is particularly important for biosimilars and biologics because their patents often are narrower in scope than those for small-molecule drugs. Biologics usually rely only on formulation or process patents; given that a biosimilar will be slightly different in its composition and/or manufacturing process, it may not technically infringe the innovator's patent. This presents a contradictory scenario: on the one hand, a biosimilar may be different enough not to infringe the innovator's patents but, on the other hand, it may be similar enough to qualify for an abbreviated approval pathway. In such cases, data exclusivity basically is an insurance policy for when patents are narrow, uncertain or near expiry. In practice, moreover, potential litigation has become an important consideration in whether to move forward with R&D for specific products. Data exclusivity can provide enough certainty to encourage the risks that innovation entails.

R&D costs

DiMasi and Grabowski (2007) recently estimated that the development of a typical new biologic costs \$1.2 billion in capitalised R&D costs. This compares with an earlier study of the cost of an NCE, estimated at roughly \$800 million (DiMasi et al., 2003). Our research also found that, compared to NCEs, biologics cost more to discover, take longer to develop and require greater capital investment in manufacturing plants because they rely on cell cultures. Figure 2.1 shows related data on development times for new protein therapeutics provided by the Tufts Center for the Study of Drug Development.

Figure 2.1 Development Times for New Protein Therapeutics



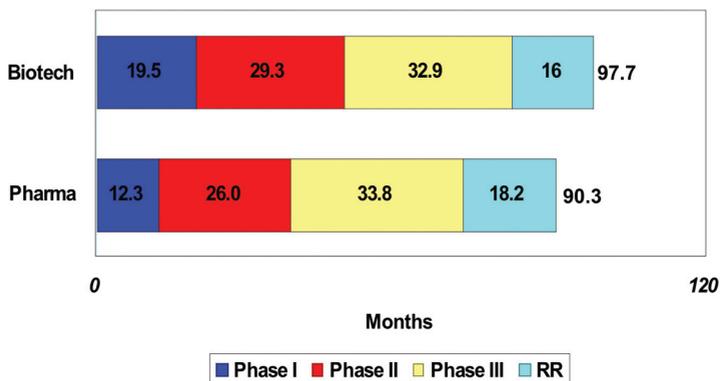
Note: Development times include only clinical phases and regulatory review periods. Preclinical times are not included.

Source: Tufts Center for the Study of Drug Development

Biologics introduced in the early 1980s were synthetic or reconstituted forms of natural products – insulin and human growth hormone. These had development times that were relatively short, slightly more than four years, from the start of clinical development to approval. Later on, with the appearance of monoclonal antibodies and other biologics more difficult to make and to research, development and approval time increased to nearly 10 years. This does not include the time required for discovery, which can be lengthy for some novel products.

The research we published in 2007 also compared the development times of biotechnology and pharmaceutical companies. As Figure 2.2 shows, the total clinical development time (from Phase I to Phase III) is a little longer for the biotech firms, particularly in Phase I and Phase II, but less for biotech firms in Phase III and regulatory review times.

Figure 2.2 Clinical Development and Approval Times



Source: DiMasi and Grabowski (2007)

Another difference between biologic and NCE development is that biologics usually are discovered at universities, then move on to smaller start-up firms that often are backed by venture capital (VC), and then on to larger firms through partnerships. VC-backed firms constitute 40 percent of total employment in the biotech sector (Lawton et al., 2009). Financing with VC is quite expensive because such VC firms take equity positions that are fairly high in cost and capital. VC firms also are not necessarily dedicated to biologic research as a focus; they will rather quickly shift investment away, for example, from risks that appear significant because of very short data protection periods.

CHARACTERISTICS OF BIOLOGICAL INNOVATION

Compared to small-molecule chemicals, biologics have accounted for a large share of novel and first-in-class therapies over the past two decades (Grabowski and Wang, 2006). More than 600 biologics currently are in clinical testing. Nearly half (250) are for oncology indications; others are aimed at autoimmune diseases, rheumatoid arthritis, psoriasis, multiple sclerosis and neurological diseases. Moreover, many biologics have multiple indications across diverse therapeutic areas. For instance, interferon-alfa, used in oncology, treats hepatitis C; various rheumatoid arthritis drugs also are used in oncology and for the treatment of Crohn's

disease. Many of the oncology drugs are being investigated across a wide variety of indications, which also supports arguments for a longer exclusivity period.

WHAT CONSTITUTES A REASONABLE EXCLUSIVITY PERIOD?

Economists have been thinking about exclusivity issues for a long time, usually in terms of patent life. More than three decades ago, William Nordhaus sketched out a trade-off model. He argued that longer exclusivity periods produce more R&D, but they also delay imitative competition (see for instance, Nordhaus 1969a, 1969b, 1972). In deciding how to balance these trade-offs for a particular industry, two characteristics support a significant exclusivity period: (1) costly, risky and lengthy R&D and (2) innovation that has important spillover benefits to society that are not captured by the innovator. Biologics generally satisfy these criteria.

Economic analyses aimed at suggesting an appropriate data exclusivity period should begin with a portfolio of products. Looking at just a few products is too narrow: while some drugs, such as Herceptin, do recover their R&D costs relatively quickly, not every drug will be as successful. Thus, the question should be: “What is the exclusivity period that might justify a portfolio where some products produce billions of dollars of revenue at their peak but others produce \$100 million or less?” In Grabowski (2008), I created a stylised portfolio by combining R&D data from DiMasi and Grabowski (2007) and sales data on drugs that had been on the market for a significant period by the mid-2000s.

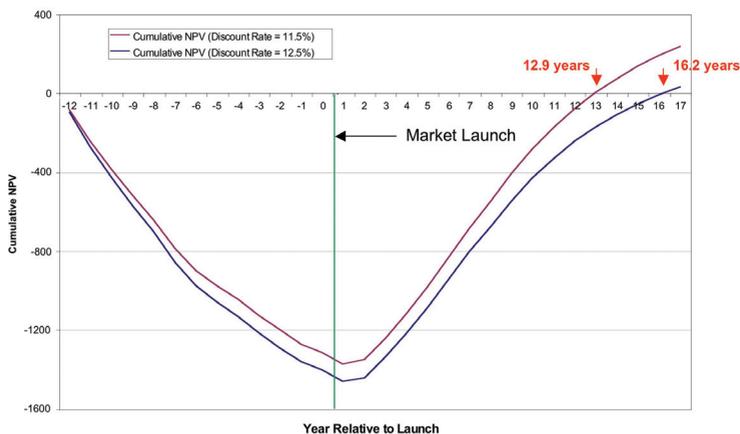
The products included were divided into four quintiles based on peak sales: \$2 billion, \$500 million, \$250 million and \$100 million. The products in this stylised portfolio were matched to R&D costs to determine what period of time on the market typically would be required to break even. Applying templates on market growth and maturity, the representative product in this portfolio would have reached mean peak sales of \$700 million. However, this mean is strongly influenced by the few drugs that are in the most successful, upper quintile. Biologics exhibit the same skewness in outcomes; the greatest successes drive the whole enterprise to some degree, although this may change over time.

My break-even calculations rest on some key assumptions:

1. A 50 percent margin on sales after the first two years post-launch, calculated as sales over variable costs; R&D costs are omitted; production and marketing costs are included.
2. Firms are able to use existing plants.
3. Rates of product obsolescence from factors other than biosimilar entry are low, at 3.5 percent starting in year 10.
4. The cost of capital is between 11.5 and 12.5 percent.

Overall, these are conservative assumptions.

Figure 2.3 **Estimated Cumulative Net Present Value for Average Biological Drug**



Source: Grabowski (2008)

Figure 2.3, which presents the results of the analysis using break-even curves, shows a 12-year period of outlays for R&D costs over time, accumulating negative present values (NPV) at 11.5 or 12.5 percent. One year or so of launch costs occurs before positive cash flow begins. Using a cost of capital of 11.5 percent in this model, nearly 13 years (12.9) are required to generate a positive NPV; using a cost of capital equal to 12.5 percent, over 16 years (16.2) are necessary reach a positive NPV. Thus, in this portfolio model, break-even lifetimes range from 12.9 to 16.2 years.

This analysis is a first cut. It does not provide a definitive answer, but it does suggest that a fairly long time frame is necessary to reach the break-even point.

The next step would be to explore how these results change as assumptions change. Alex Brill (2008), for example, used my model and applied the following modifications:

1. Innovators retain a significant share of the market after biosimilar entry.
2. A contribution margin of 60 percent, higher than I used in the baseline.
3. A baseline cost of capital of 10 percent.

Using these assumptions, he argues that seven-year data exclusivity periods can be justified, as it is compatible with positive returns in a reasonable timeframe.

A 2009 Federal Trade Commission report (FTC, 2009) also argued that a data exclusivity period was unnecessary for most biologics, given the availability of patents and early-mover advantages for the originator's product. In contrast to the market for generics, they foresee relatively few biosimilar entrants and the likelihood of non-interchangeability with the reference brand as factors substantially reducing biosimilar market penetration.

The expected rate of erosion of market share is a key issue. In Grabowski et al. (2007) we show that market penetration will be slower and price erosion less for biosimilars than for generic drugs. Table 2.1 shows the range of assumptions around this issue in some recent studies.

Table 2.1 Biosimilar Market Share Assumptions, Recent Studies

| Source | Peak Biosimilar Penetration Rate | Basis | Biosimilar Price Discount (Relative to Pre-Entry Brand Price) |
|-------------------------|----------------------------------|--|---|
| CBO (2008) | 10% (year 1) 35% (year 4) | Similar market situations | 20% (year 1) to to 40% (year 4) |
| Grabowski et al. (2007) | 10 – 45% | Higher estimates correspond to complex small molecules | 10% – 30% (year 1) |
| Express Scripts (2007) | 49% | Therapeutic alternatives | 25% (year 1) |
| Avalere Health (2007) | 60% (largest markets) | Average small molecule generic drug penetration rates | 20% (year 1) to 51% (year 3) |

As Table 2.1 makes clear, both the rate of market penetration and the price discounts for biosimilars vary widely in the studies. In assessing price competition, two factors need to be taken into account. From the supply side, development costs for biosimilars are higher than for traditional generics; for instance, it may take tens of millions of dollars to enter these markets, depending on the structure of the molecule, compared to small-molecule chemicals that require a million dollars or less. From the demand side, biosimilars are not likely to be interchangeable. The speed with which the market evolves will be affected by how the payers behave in terms of encouraging use and by how comfortable providers are with substituting products. Overall, however, market penetration and price erosion for biosimilars will be slower than for generics.

The Congressional Budget Office (CBO) report (CBO, 2008) estimated peak biosimilar penetration rates that varied from 10 to 35 percent over four years. It expected biosimilars price discounts to vary from 20 to 40 percent, lower than for generics because of the smaller number of competitors. The CBO report argues that even without a price response from the innovator, prices will be lower than would be expected without biosimilars. CBO did not specify how much lower, an issue still under review.

The Express Scripts study is at the higher end of the estimates, with a peak biosimilar penetration rate of 50 percent and price discounts at 25 percent. The remaining study in Table 2.1 (Avalere Health, 2007), broke estimates down by markets; the largest markets were projected to have more entrants and a higher penetration rate.

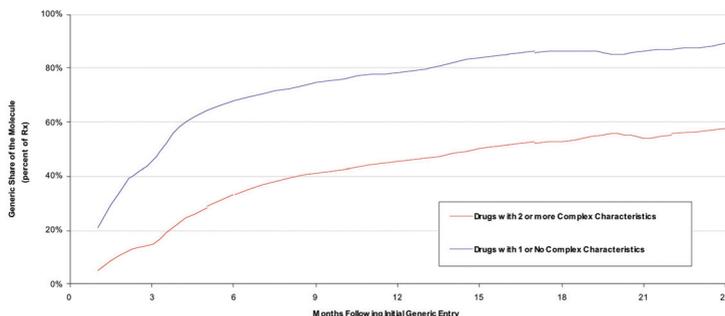
Recent work by the Analysis Group (Grabowski et al., 2007) did look at biologic market variations and found differences across them. The discounts in the human growth hormone market might be very small, for example, while discounts in other markets might be close to 50 percent, with discounts of 10 to 30 percent.

The basis of this analysis was 35 small ‘complex molecules’ that experienced generic competition in the late 1990s to mid-2000s. We grouped the molecules by ‘complexity’, for example (a) the difficulty of producing the molecule, as with some hormonal products, (b) whether the therapeutic index¹ is narrow, as with Coumadin, for example and (c) whether the product is used primarily by specialists or oncologists, and so

¹ Drugs with a narrow therapeutic index are those drugs that exhibit the desired therapeutic effect at a dose level close to the toxic dose level for that drug. As a result, small deviations from the appropriate dosing level could have significant harmful effects.

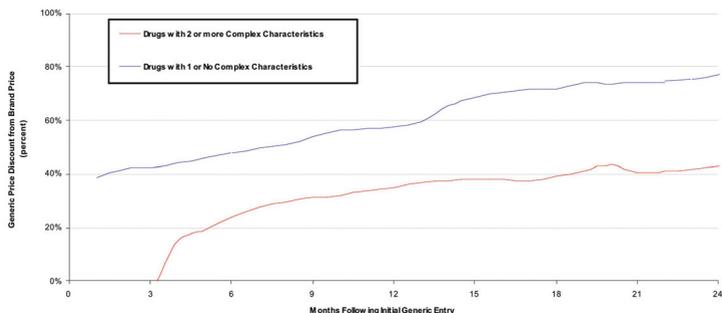
on. In total, we developed five or six of these complexity characteristics, then we asked how the presence or absence of these characteristics would affect penetration rate. We found a very noticeable difference over the first two years. For drugs without the complex characteristics, the innovator lost 80 percent of the market over two years; drugs with the more complex characteristics only lost about 40 percent over two years. Indeed, this curve is not too different from what the CBO and some others have been assuming. Figure 2.4 shows average generic shares while Figure 2.5 shows average generic price discounts from the brand, according to complexity.

Figure 2.4 Average Generic Share of Molecule by Complex Drug Characteristic



Source: Grabowski et al. (2007)

Figure 2.5 Average Generic Price Discount from the Brand for the Molecule by Complex Drug Characteristic



Source: Grabowski et al. (2007)

Figure 2.5 shows the generic list price for the sample: the more complex molecules were at a discount of approximately 25 percent after one year, moving up to 40 percent over two years. This is roughly half of the discount for the drugs without complex characteristics. This adds to our model by providing some new assumptions about market penetration/erosion after biosimilar market entry, at least for the foreseeable future.

The group also considered what might be a reasonable range of cost of capital for biotech entry. Golec and Vernon (2007) looked at a wider sample and calculated a 16.25 percent nominal real cost to capital; after subtracting inflation of about 3.5 percent, the real cost of capital becomes 12.75 percent. Ibbotson (2008) estimates a real cost of capital of around 14 percent. He uses a Fama-French model, broader than the capital asset pricing model (CAPM), and takes into account firm size. Table 2.2 summarises the empirical literature.

Table 2.2 Cost of Capital Estimates for the Biotechnology Industry

| Source | Sector/Group | Model | Cost of Capital | |
|-------------------------------|---|-------------|-----------------|-------------|
| | | | Nominal | Real |
| Golec and Vernon (2007) | Biotech industry-wide | Fama-French | 16.25% | 12.75% |
| Ibbotson (2008) | Median | Fama-French | 17.49% | 14.07% |
| Grossman (2003) | Biotech with ≥ 1 drug approved Biotech drugs in phase II or III | CAPM | 18.70% | 15.24% |
| | | CAPM | 27.40% | 23.69% |
| Myers and Shyam-Sunder (1996) | Medium-sized public firms "Small" biotech firms | CAPM | 19% | 14% |
| | | CAPM | | 16% |
| Grabowski (2008) | Large biotech firms | CAPM | | 11.5%-12.5% |

Compared to these estimates, my model is conservative. Generally, a broader sample produces a higher cost of capital than my upper estimate of 12.5 percent.

The next step is to explore a reasonable contribution margin for a biotech product. In his analysis, Brill looked at the first six firms included in Table 2.3 (Gilead, Genentech, Amgen, Celgene, Genzyme and Biogen), which he market-weighted.

Table 2.3 Contribution Margins for Public Biotech Firms

| Company | Average Margin | Comments |
|----------------------|----------------|---------------------------------------|
| Gilead Sciences, Inc | 63.7% | Substantial small-molecule drug sales |
| Genentech, Inc | 63.3% | |
| Amgen, Inc | 60.4% | |
| Celgene Corp | 50.0% | Substantial small-molecule drug sales |
| Genzyme Corp | 44.4% | |
| Biogen Idec Corp | 43.4% | |
| Chiron Corp | 35.8% | Not included in Brill's sample |
| MedImmune, Inc. | 33.6% | Not included in Brill's sample |

Predictably, market-weighting Gilead and Genentech give these companies the highest scores, producing an average 60 percent margin. Taking a whole spectrum of firms (for instance, including Chiron and MedImmune) and not weighting firms with mainly small molecule sales, like Gilead and Celgene, produces contribution margins from less than 40 percent to 60 percent, using public data. This likely is more accurate.

We performed a further break-even analysis, summarised in Table 2.4, that combined the following parameters:

1. Cost of capital: 11.5, 12.75 and 14.1 percent;
2. Contribution margin: 60, 50 and 40 percent;
3. Data exclusivity period: 7, 10, 12 and 14 years.

The key assumptions were:

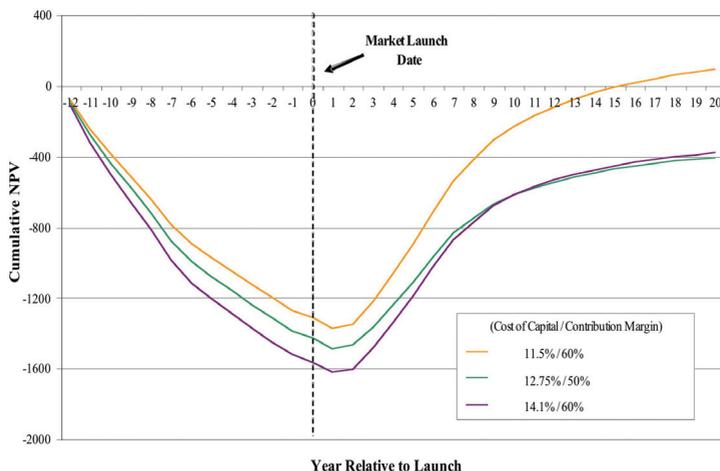
1. Biosimilar entry occurs at the end of the data exclusivity period;
2. Biosimilars capture 10 percent of the market in the first year, increasing to 35 percent by the fourth year, as per CBO;
3. The innovator product experiences a price discount of 10 percent in the first year of biosimilar entry and 20 percent after four years;
4. All other assumptions are consistent with Grabowski (2008).

Table 2.4 Break-Even Results Under Alternative Data Exclusivity Periods

| 7-Year Data Exclusivity Period | | | | | 12-Year Data Exclusivity Period | | | | |
|---------------------------------|--------|------|------|-----|---------------------------------|--------|------|------|-----|
| Contribution Margin | | | | | Contribution Margin | | | | |
| CoC | | 60% | 50% | 40% | CoC | | 60% | 50% | 40% |
| | 11.5% | 15.4 | >50 | >50 | | 11.5% | 10.4 | 13.4 | >50 |
| | 12.75% | >50 | >50 | >50 | | 12.75% | 12.5 | >50 | >50 |
| | 14.1% | >50 | >50 | >50 | | 14.1% | >50 | >50 | >50 |
| 10-Year Data Exclusivity Period | | | | | 14-Year Data Exclusivity Period | | | | |
| Contribution Margin | | | | | Contribution Margin | | | | |
| CoC | | 60% | 50% | 40% | CoC | | 60% | 50% | 40% |
| | 11.5% | 10.5 | 18.0 | >50 | | 11.5% | 10.4 | 12.9 | >50 |
| | 12.75% | 14.8 | >50 | >50 | | 12.75% | 12.4 | 27.1 | >50 |
| | 14.1% | >50 | >50 | >50 | | 14.1% | 22.9 | >50 | >50 |

The analysis suggests that an exclusivity period in the 10- to 14-year range is required. For example, in the first table in the upper quadrant, under a 7-year data exclusivity period, only one combination produces a break-even point at around 15 years (cell shown in yellow) – this is a 60 percent contribution margin and an 11.5 percent cost of capital. All other combinations yield break-even periods higher than 50 years. As the data exclusivity period increases to 10 years, 12 years and 14 years respectively, more yellow cells with positive break-even points appear. Estimated cumulative NPV with 7-year data exclusivity is shown in Figure 2.6, using a combination of assumptions for the cost of capital and contribution margin.

Figure 2.6 **Estimated Cumulative Net Present Value with Seven Year Data Exclusivity**



Seven years after market launch the curve starts flattening with biosimilar entry. The median case and the upper-band case show that under these assumptions a stylised company may never break even. Assuming a low cost to capital (11.5 percent) and a high margin (60 percent), the stylised company will break even in less than 20 years.

Figure 2.7 **Estimated Cumulative Net Present Value with 14 Year Data Exclusivity**

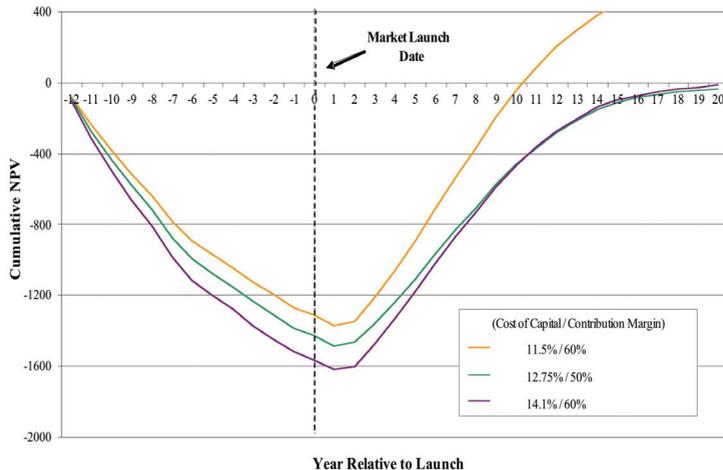


Figure 2.7 replicates Figure 2.6, but assumes a 14-year data exclusivity period. Under this scenario, break-even is obtained for nearly all ranges of the values analysed – or close to break-even for the median case. This analysis suggests circumstances exist where the data exclusivity period, rather than patent life, will govern the market entry of new biologics and be important for R&D incentives. After market launch, data exclusivity and patent protection run concurrently. Data exclusivity provides additional market exclusivity when patents can be circumvented by a biosimilar in the early stages of the product’s life cycle, or the core patent time is short because of long development and approval times for a new biologic.

A Monte Carlo analysis that was performed subsequent to the OHE Conference allows one to gain further insights on when data exclusivity and patent protection are the key incentives in terms of overall market exclusivity (Grabowski, Long and Mortimer, 2010). In this analysis, market exclusivity is the longer of the patent protection and data exclusivity periods. The effect of different exclusivity periods on break-even lifetimes are considered under scenarios of weak patent protection (7 years on average) and strong patent protection (14 years on average). The analysis is based on 1,000 Monte Carlo simulations for each scenario and breakeven period. The simulation draws are based on normal distributions

on all the model parameters (contribution margin, cost of capital, biosimilar penetration and discounts) as well as for the two scenarios for expected patent life. The sample means and standard deviations are based on various empirical studies discussed above (Tables 2.1, 2.2 and 2.3).

The results of this analysis indicate that when patent protection is strong (an expected value of 14 years with 95 percent of the draws between eight and 20 years), patents are the binding constant in most instances and are sufficient to maintain investment incentives. In these instances, data exclusivity periods up to 14 years have only a minimal effect on market exclusivity and biosimilar entry and, hence, on health care costs. On the other hand, to the extent that biologic patents are less certain and more vulnerable to challenges (the limited patent scenario with an expected term of seven years and 95 percent of the draws between 2 and 12 years), a data exclusivity period of 12 years or more is generally necessary for a majority of simulations to achieve break-even status. Hence, the 12 year data exclusivity period adopted by the US Congress (and the 10-11 year period in the EU) should be viewed as ‘an insurance policy’ to encourage innovation when patent protection is relatively limited and useful products might otherwise be undeveloped.

Data exclusivity could have some unintended effects. First, for example, some observers are concerned that data exclusivity may lead to ‘evergreening’ i.e. the data exclusivity period would re-start for relatively modest changes. The new US law has some provisions designed to address this issue. In order for a second generation product to get its own 12-year data exclusivity period, it must demonstrate a structural modification that is significantly different in terms of safety, efficacy or potency. Moreover, new indications, dosage forms, delivery systems or strengths are not eligible for a new 12-year period. A second issue is whether data exclusivity diminishes incentives for firms to make product advances. Incentives will not be reduced if there is robust competition among branded alternatives, which usually is the norm. Finally, some charge that data exclusivity will prevent competitors from building on the existing stock of knowledge. This seems unlikely for a number of reasons, including that process and formulation patents still will be filed and patent information is publicly available.

CONCLUSIONS AND POLICY RECOMMENDATIONS

An abbreviated process of approval of biosimilars is important, given the cost of biologics and their importance in health care. However, it also will be important to balance short-term cost savings against long-term incentives for medical breakthroughs. This clearly requires a significant data exclusivity period.

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Chapter 3

The Market for Biosimilars: Evolution and Policy Options

PROFESSOR ADRIAN TOWSE AND DR. JORGE MESTRE-FERRANDIZ

OHE's research on the impact of biosimilars on markets was first published in an OHE Briefing (Chauhan et al., 2008). This presentation is based largely on that work and will cover six topics: (1) how the biosimilar markets are different from traditional small-molecule generics markets, (2) substitutability and interchangeability and how these relate to patient safety data, particularly post launch, (3) the market environment for different biologics markets, identifying dissimilarities among them, (4) our economic framework and some of the models we have used to speculate on the potential savings from biosimilars, (5) what we think those models are saying about price trajectories, and (6) options for payers.

BIOSIMILARS ARE DIFFERENT

Assessments of the impact of biosimilars include some very optimistic estimates of both the size of savings for payers and the speed with which those savings will occur. Models that promise the least realistic cost savings start with a list price and assume that the price will almost immediately fall after patent expiry to the level of a chemical generic. However, the biosimilars market is not a low-cost commodity business based on price deals with pharmacists. Also, payers are not going to be able to shift substantial volumes of market share from the originators to the biosimilars without persuading clinicians that these products can be used interchangeably and safely with their patients. Therefore, seeking to treat biosimilars as 'biogenerics' from the beginning will delay the achievement of an efficient biosimilars market for three reasons.

First, if legislation were to insist that the licensing body categorise biosimilars as effectively substitutable, as biogenerics, the regulators would find it extremely difficult to have the information they need to issue a license at all. Second, clinicians would be very uncomfortable prescribing on this basis when the evidence is not there to suggest that these products can safely be used interchangeably. And, third, payers will try to find some way of driving down the price to produce an immediate saving on the innovator's product once the biosimilar has entered the market. However, this may be counterproductive and delay the entry of competitive products as likely profits will be much lower with a large price cut, thus reducing, not increasing, the overall savings that payers can realise in the long run.

A realistic progression in a therapy area from ‘biosimilars’ to ‘biogenerics’?

It is inappropriate for licensing bodies to be told or encouraged to think about the licensing of biosimilars as being the licensing of biogenerics substitutable at the pharmacy level. It is appropriate, at least in principle, to expect that the market will change in this direction over time.

Initially, biosimilars will enter with information on similarity. This would be followed by a period of collection of post-launch data, which we call ‘Patient Safety Year’ (PSY) data. The purpose of collecting these data is twofold: to satisfy pharmacovigilance requirements and help clinicians understand the extent to which these products can be used interchangeably in their own patients. In addition, patient-reported outcome data will inform more general value-for-money considerations in the appropriate area.

Gradually, clinicians will build up confidence in biosimilars, although the speed of that will vary across markets. This assumes, of course, that the post-launch data studies warrant it. Potentially, therapy area by therapy area, over a period of time, subsequent interchangeability studies will suggest products that can be used interchangeably; the licensing body’s requirement for clinical evidence (i.e. pre-launch clinical data) will diminish in subsequent entry submissions. From the licensing body’s perspective, products in a particular therapy area will become akin to chemical generics.

Likewise, as post-launch experience with these products accumulates, the licensing body and the government will be more comfortable about treating subsequent entrants in a particular therapy area more like biogenerics than biosimilars. The crucial point to stress is that how we treat biosimilars in the beginning will determine the extent to which entry requirements are lowered subsequently.

SUBSTITUTABILITY AND INTERCHANGEABILITY

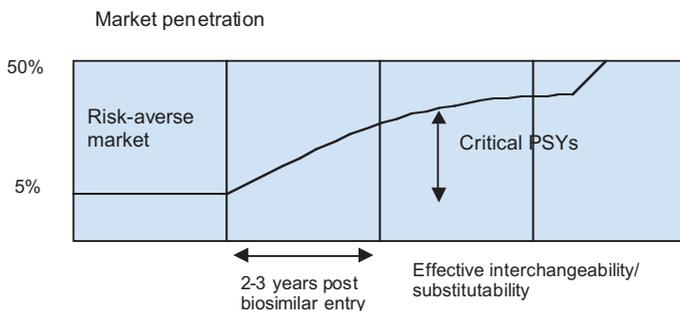
Substitutability, which refers to substituting one product for another at the pharmacy level, must be distinguished from interchangeability at the clinician level. Our research focused on how to achieve a degree of comfort on the part of clinicians so that they are willing to use products interchangeably.

European Medicines Agency (EMA) legislation allows for licensing of biosimilars on a case-by-case basis. Biosimilars require a full dossier with clinical quality and safety studies, which varies depending on the product area of the characteristics of the products. Most EU country-level policies defer to EMA. Thus, if EMA says that products effectively are substitutable, then substitution laws in the individual countries will allow substitution. In the case of biosimilars, the EMA is not saying they are substitutable and therefore pharmacy substitution law would not apply to biosimilars or even to biogenerics. Moreover, there are a number of countries that have explicitly ruled out substitution in the case of biosimilars, such as France and Spain. We expect no substitution in the short run, then, and the extent to which clinicians will use the products interchangeably is an issue.

PSY data are crucial to building market share

Figure 3.1 illustrates our expectation about when we potentially can observe effective interchangeability and substitutability.

Figure 3.1 **Strategic Overview of Patient Safety Data (PSY)**



Source: Chauhan et al. (2008)

Our expectation is that initially the penetration achieved by biosimilars will be low (less than 5 percent market share) because of clinical conservatism, reflecting a lack both of cumulative safety data on the products and data on their interchangeability. In other words, the fact that the products launched are similar does not mean they are interchangeable and clinicians will be reluctant to prescribe them until there is evidence of that. As PSY data are accumulated, more new patients will be started on biosimilars; assuming the evidence outcomes are similar to the innovator,

an increasing number of clinicians will have the confidence to both switch patients to and start new patients on biosimilars. The critical point may be two or three years after entry, when there is enough data accumulated to encourage clinicians to opt for 'automatic' interchangeability in some markets. This will lead to much greater biosimilar penetration and, possibly, further on, to pharmacy substitution.

Thus, what we are effectively saying is that penetration is initially very difficult for biosimilars because evidence of interchangeability is absent. Gradually, as patient data in interchangeability studies demonstrate interchangeability, it will be increasingly possible for biosimilars to capture market share. At some point, these products will be widely accepted as interchangeable and competition will be based substantially on the price.

What are the incentives to generate PSY data? Initially, biosimilar entrants may argue that the licencing procedure is enough to encourage use as it demonstrates safety and efficacy. The licencing body, however, will impose pharmacovigilance requirements. The innovator may try to preempt patient safety data collection by essentially not allowing the biosimilar entrant to take enough market share to gather enough evidence to conduct interchangeability studies. It could do this by offering additional discounts.

We argue that the optimal strategy for a biosimilar entrant is to plan to collect patient experience data. The biosimilar entrant must be able to demonstrate that its product can be used interchangeably with the innovator's product. Although some price discounting is necessary, patient safety data are also crucial in winning market share. Discounting alone will not win a large market share.

We also argue that payers should facilitate the data collection process to extract value for money in this market. It would make sense for payers to ensure that their providers are instructed to enable the sort of interchangeability studies that the market needs.

BIOSIMILAR MARKET SEGMENTS DIFFER

Two crucial dimensions need to be taken into consideration when analysing how the market would respond to biosimilar entry. First, treatment with biosimilars may be led by hospitals/specialists or by primary care providers (i.e. pharmacists). Second, different product or therapeutics areas have different levels of demand.

In most European markets, biopharmaceuticals are specialist- and hospital-led. Although some consolidation of hospital buying groups has occurred, considerable variation in bargaining power exists across Europe, segmenting markets. Purchasing pharmacists are much more price-sensitive and more willing to switch patients between products in any therapeutic area than their clinician colleagues. Thus, the aggressiveness of the purchasers will in part be determined by who those purchasers are.

The second dimension is that different product areas have different levels of demand. In our publication, we looked at three markets with quite different characteristics: the erythropoietin (EPO), Granulocyte-Colony-Stimulating-Factor (G-CSF) and the growth hormone markets. The elasticity of demand in the EPO market is already high. Competition exists between innovator products; for instance, the National Institute for Health and Clinical Excellence (NICE) in England and Wales argued that all products in this market are equally effective, indicating a lack of differentiation. Moreover, evidence exists of competition between the products and of patients having been switched.

In the growth hormone market, most patients are children. As you might expect, and as the evidence suggests, clinicians are much more reluctant to switch patients in this market.

The G-CSF market lies between the EPO and the growth hormone markets. Three products currently are on the market and a second wave of new products is appearing, differentiated primarily by method of administration. Clinicians, however, appear to be unconvinced as yet about the importance of these differences.

AN ECONOMIC FRAMEWORK FOR BIOSIMILARS

Grabowski et al. (2007) model the biosimilars market as monopolistic competition. This entails a large number of sellers; entry and exit costs are zero. Their research objective was to examine how cost structure affects the actual number of potential entrants into the biosimilars market; the finding was that, given market share, the number of entrants will decrease as the fixed costs and the marginal costs of production increase.

The assumption of increased fixed costs is a proxy for the higher clinical development costs for biosimilars compared to chemical generics. How incumbents react to the entry of biosimilars is not explicitly modelled.

This is one of the reasons that our research intended to expand this theoretical model. The Grabowski et al. research also is a very good starting point for economic analysis of the biosimilars market because it assumes that products are differentiated and the market is segmented.

Our second starting point was the market segmentation model in Frank and Salkever (1997). This model was first developed to explore the price dynamics for the generics market. Its key contribution was the segmentation of the market after generic entry into two parts: price-sensitive and price-insensitive consumers. The price-insensitive segment is composed of the 'loyal' segment where demand for the originator does not depend on the price of the competitor – in our case, the biosimilar. In the price-sensitive segment, the demand for the originator and the new entrant depends on the price difference between the two.

We simplified our market-segmentation model into duopoly: the originator and one biosimilar. We further assumed that the price of the originator was the same between the two segments i.e. for both loyal and price-sensitive consumers. Thus, the two segments are linked because the price charged by the originator will affect demand in both the loyal and the price-sensitive segments.

Our results show that the biosimilar entrant's strategy might be to offer price discounts to win market share. Given that the originator cannot charge different prices to the two segments, then if the originator matches this price discount that discount applies also to the loyal segment. Because the loyal segment is willing to pay a higher price, the originator might be reluctant to match the biosimilar's reduced price. For the biosimilar, however, a high discount strategy may not work anyhow since a lack of clinical confidence in similarity may mean discounts are not sufficient to create demand. Moreover, and especially in the different European markets, once a price has been decreased, it is very difficult to raise it later. Thus, offering a discount for the biosimilar in the first instance could be self-defeating.

The accumulation of PSY data is potentially the driving force in converting the biosimilars market into a so-called biogenerics market. In terms of the impact of PSY on the economic model, we argue that the biosimilar and the originator are different products. The accumulation of patient safety data, however, reduces this degree of differentiation, potentially making

the biosimilar comparable to the innovator. At given prices, 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, which in turn can generate more patient safety data. The originator is left with little choice but to cut price or see an erosion of its market to the point that, eventually, it has only the (now small) loyal market left – at which point the originator may seek to increase its price as happens in conventional chemical generic markets.

We completed further analyses relaxing some assumptions. The original model assumes that the linkage between the two segments, the price-sensitive segment and the loyal segment, is through a uniform originator price. This linkage wanes according to the degree of product differentiation. The degree of product differentiation can be made endogenous by linking it to the generation of PSY data through market share gain. Under this scenario, the originator company may be willing to accept a lower price in one market segment in order to reduce the ability of the biosimilar entrant to gain the market share needed 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 discounting. Thus, it may make more sense for biosimilar entrants to find ways to gain the market share necessary to generate PSY data that involve no or limited price discounting.

Taxonomy of a biosimilar business model

Taking the previous analysis into consideration, two business models may apply in biosimilar markets. The first is a follow-on (me-too) biologic business model whereby the biosimilars have attributes that encourage starting new patients on that product and possibly switching patients to the product. Companies will invest in new devices/formulations (if feasible) and in sales and marketing and account management skills. Possibilities for price discrimination will exist. Attention will be paid to the impact of their own pricing behaviour on the response of the incumbents. Generating PSY data will be an important investment.

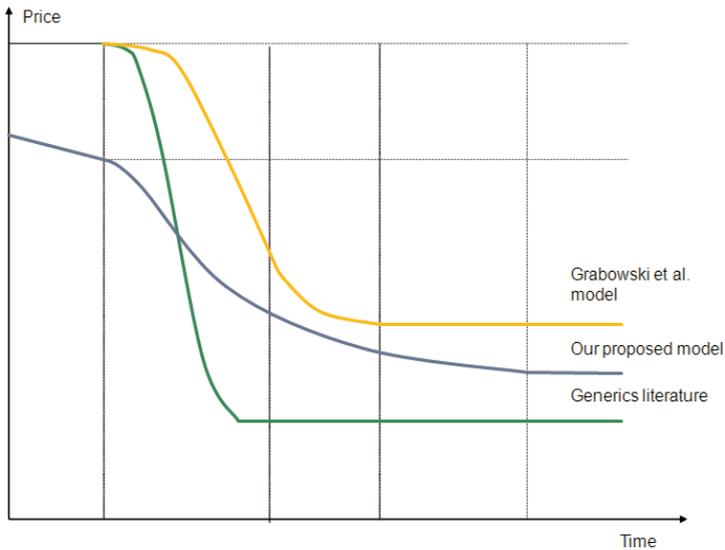
The second potential business model is what we have termed 'biogeneric'. The biosimilar will be positioned as a biogeneric, offering the same benefits at a lower cost than the innovator product. Minimal sales and marketing would take place.

Most established generic companies are not equipped for the ‘follow-on’ approach and none of the first wave of biosimilar companies can follow a biogenerics business model. What we had not anticipated when we started this research was that a number of established pharmaceutical companies are planning to enter the biosimilars market.

PRICE TRAJECTORIES

We examined price trajectories that might develop over time, which is important in suggesting how payers might organise markets most effectively to reap the greatest possible savings over time from biosimilars. Figure 3.2 summarises our findings on price trajectories and price discounting strategies.

Figure 3.2 **Summary of Findings on Price Discounting**



Source: adapted from Chauhan et al. (2008)

The first difference between our model and the published literature (Grabowski et al. and the literature on generics) is that our starting price is lower. The literature uses list prices as the starting point; we believe this does not accurately reflect transaction prices in many markets because of

the hospital discounts that occur in practice. Second, we believe the market price at the time of biosimilar entry will be lower, based both on a lower starting price and expectations for further discounting before biosimilars enter. We will see slower erosion towards the ‘equilibrium’ price in the short term because of the need for post-launch PSY data to encourage clinicians to use products interchangeably.¹

We also are anticipating a long-term equilibrium price that falls between that of the Grabowski et al. model and the ‘pure’ chemical generic level. Equilibrium cannot reach the low chemical generic level because biosimilars entail higher variable costs in manufacture and higher fixed costs for development. Under the standard chemical generic model, a substantial discount of around 80 percent with multiple entrants is observable, with the price in the longer term being close to manufacturing cost. Grabowski’s initial biosimilars model assumed relatively few entrants and prices falling to around 45 percent. This lesser discount reflects higher manufacturing costs as well as the need to do some clinical development work.

We foresee a slower rate of decline in our model for two reasons. First, the starting point is lower using true transaction price rather than list price. Second, the extent of competition in the market is not as strong (at least initially): it takes time for biosimilar entrants to gain market share and price competition initially will not be intense. Over time, however, we expect to see price competition driving prices down to something between Grabowski’s speculated level and the generics level. This also reflects our hypothesis that, over time, the clinical development requirements at the later stage in a particular therapeutic area will diminish as licensing bodies become more confident in the equivalence of these products and reduce the extent and nature of the clinical development data required.

OPTIONS FOR PAYERS

This leaves payers with three options in this market, as in others.

1. Payers may introduce substitutability rules, whereby governments permit pharmacists to substitute one biologic/biosimilar for another.

¹ As shown by Liefner in this publication (chapter 6), the discount offered for the first biosimilar entrant in the EPO market in Germany was 19 percent, increasing to 27 percent with two additional entrants. This is slightly higher than our predicted range. The German Reference Price System (RFP), however, has special characteristics that could affect discounting. In particular, patient co-pay is zero if manufacturers offer discounts sufficiently below (about 30 percent) the reference price. Discounts in other European countries have been more modest and more in line with our estimates. Note that the German market has been consistent with our projections in its slow uptake of biosimilars.

2. Direct price intervention may be used to push down originator prices, either by including the originator and biosimilars in the same reference price group or by imposing price cuts, either on the biosimilar or, post patent-expiry, on the innovator.
3. Payers might adopt a ‘market support’ policy that could include infrastructure investment to monitor outcomes and to collect PSY and other pharmacovigilance data.

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 of limited value in any case for products prescribed in a hospital setting.

Direct price intervention, option (2), is likely to be counter-productive. Reference pricing will assume a degree of interchangeability that is not likely to be reflected in clinician behaviour. This option also will discourage biosimilar entry by reducing potential profits. Without a follow-on biologic stage in biosimilar market development, the PSY data required to enable the market to evolve towards a biogeneric market may never be collected. Thus, a biogenerics market cannot be jump-started by forcing down prices or by imposing substitutability. Governments and other payers need to be careful in thinking through their choices.

What advocate the third option, which we call ‘market support’. Governments and payers should take a more strategic approach and create incentives for the generation of high quality data on outcomes. This would include data not just on safety, but also on value for money. The marketplace then can drive competition, and clinicians and players will be better able to gauge value for money. We believe this approach better identifies benefits for patients and also secures a path towards maximising price competition over time. Payers then should be able pass on substantial savings to patients and taxpayers.

CONCLUSIONS

In summary, because biosimilars are not biogenerics, the biosimilars market will evolve very differently than the traditional small-molecule chemical generics market. For biosimilars, regulators will need clinical trial evidence of efficacy and safety pre-launch, while clinicians will require post-launch PSY evidence. Governments and other payers need to avoid post patent-expiry price cuts, which reduce incentives for biosimilar

entry and threaten long-term savings. Instead, governments and other payers should encourage pharmacovigilance and other outcomes studies that produce the PSY data that can encourage the interchangeability that will allow greater price competition. Better outcomes data also will help gauge value for money. Over time however, we expect PSY data, if positive, to enable particular biosimilars markets to become biogeneric markets.

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Chapter 4

How much price competition can we expect from biosimilars?

PROFESSOR RICHARD G. FRANK

Three sets of factors have an important impact on the realization of expectations about the biosimilars market now and in the future: (1) drivers of existing models of market entry and pricing for biosimilars and the assumptions that lie behind them, (2) forces that may affect these market outcomes that are not sufficiently addressed in the existing models, and (3) long-range strategic responses that may affect both price competition and the balance between data exclusivity and patents.

EXISTING MODELS OF MARKET ENTRY AND PRICING

Virtually all the models that have been developed in this area start with the idea of monopolistic competition. Prices and quantities are determined by the state of productive technology, the cost structure, demand responses to these new products and their prices, and patents – how complete they are, how well-defined they are, and so on. The model presented by Chauhan et al. (2008) is a first step beyond those models and introduces some dynamics into this standard monopolistic competition model.

Policy choices really matter. We have focused heavily on the drug regulatory agencies, but we have focused far less on some of the policy and regulatory activities such as reimbursement regulation, the management of pharmacy benefits, and patent regulation.

Finally, all the models discussed so far rely on analogies; the absence of data requires us to think about which analogy is most reasonable, or ‘best’, or most informative. It turns out to that it makes a substantial difference which analogy is applied. This is illustrated clearly by Professor Grabowski’s refining of the analogies he used in his initial research.

Assessment of the existing models

Several assumptions about data and behaviour underlie the models. First, entry costs for biosimilars are higher and regulatory hurdles greater than for traditional generics. Professor Grabowski cites \$250 million to \$400 million in capital outlays (Grabowski et al., 2007). Marginal costs for biologics are higher than for small molecules, and moreover, rather than being essentially horizontal (i.e. they do not change with output), marginal cost curves are upward sloping, i.e. they increase with output.

On the demand side, the demand response for biosimilars is thought at least initially to be more sluggish than for generics because of a combination of physician reticence, consumer nervousness and perhaps regulatory uncertainty. The implications of those widely held assumptions leads to a logic that says that the level of entry will be lower and more sluggish over time than it has been in the small molecule area. In general, demand for biosimilars will be less responsive i.e. the cross-elasticity of demand will be lower; and for any price differential less switching will occur because of a general reticence about biosimilars by both doctors and patients. When these factors are combined with the fact that the cost structures are somewhat different, the equilibrium result is that price competition is less intense. While the long-run equilibrium weighted average price of a therapy will decline, it will do so modestly relative to what we have seen for small molecule generics.

Table 4.1 summarises some published estimates on the evolution of the market. It seems that all observers take the two first studies (Grabowski et al., 2007 and the CBO, 2008) seriously, but after that opinions diverge. According to these studies, initial penetration rates range somewhere between 10 and 25 percent; long-run, or longer-run, price responses range from 20 to 35 percent. These estimates generally cluster; the range is actually somewhat smaller than might be expected from economists. The models do not generate similar savings estimates, however. The reasons are twofold: (1) large differences in the forecast of spending growth over time, and (2) major differences in the number of molecules expected to be subject to various levels of competition.

Table 4.1 Examples of Impact Estimates

| | Penetration | Price |
|----------------------------|--------------------|-------------------|
| CBO (2008) | 10% (1st yr) | -20%-25% (1st yr) |
| | 35% (4th yr) | -40% (4th yr) |
| Grabowski et al. (2007) | 3 entrants | -25% |
| Merrill Lynch Mid Range | 3% (1st yr) | -20% (1st yr) |
| | 25% (4th yr) | -35% (4th yr) |
| Shapiro et al. (2008) | | -35% (4th yr) |

OTHER FORCES THAT WILL AFFECT MARKET OUTCOME

Three sets of issues are key in determining the accuracy of forecasts about the impact of biosimilars.

1. Market entry: How much entry will occur, and why? What are the forces both restraining and potentially promoting entry? How much is really needed?
2. Cost structure: How much potential for entry exists? How strong is the friction restraining entry? What should expectations be about the long-run cost structure, given that China and India potentially are so important in this market?
3. Demand response: What happens as well-recognised firms with very good reputations become important players in the biosimilars market? Will that diminish the reticence of doctors and patients to use biosimilars?

Entry and cost structure

Table 4.2 shows worldwide counts by major therapeutic category of (1) the actual number of firms that have entered and (2) the number of firms that have obtained marketing approval, but have not entered the market for one reason or another. Each category includes a substantial number of firms that are either in, or ready to be in, these markets. Clearly, regulatory scrutiny can affect actual entry, but this gives us some important empirical clues.

Table 4.2 Potential Worldwide Entry

| Drug | Actual Entrants | Approved, Not Entered |
|-------------|-----------------|-----------------------|
| EPO | 7 | 9 |
| HGH | 7 | 5 |
| Insulin | 6 | 2 |
| G-CSF | 8 | 14 |
| Interferons | 7 | 7 |

Source: Shapiro et al. (2008) and Espicom Business Intelligence Report (2008)

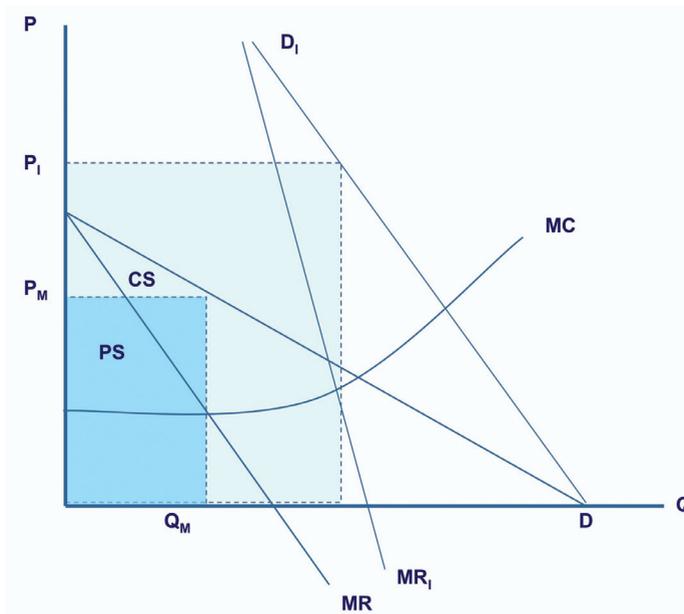
It is important to emphasise that some abbreviation actually takes place already in the regulatory assessment of biosimilars. Some observers have argued that so much uncertainty exists that abbreviation in practice will mean 'not very much abbreviation'. Still, in Europe, and even in some early FDA experience, abbreviation has occurred. Fewer trials are requested for biosimilars and/or trials may be smaller, both of which reduce the friction somewhat. It is clear, however, that none of this can be taken to imply that the regulatory pathway for biosimilars will be as abbreviated as for small molecule generics.

Based on industry sources, trade literature and surveys by consulting firms, about 15 to 30 biosimilar firms or partnerships currently are developing products or have products on the market. These firms come from all over the world: Canada, the US and the UK as well as India and China. India and China are investing a great deal of money in biological manufacturing infrastructure. Indeed, India and China are ranked number two and number three in terms of FDA-approved facilities around the world, just slightly trailing the US. Variable costs in these countries may be considerably lower, even when facilities are owned by US manufacturing entities. This means a considerable potential for entry exists and some of that potential entry may be possible at lower costs than what we now see in the US and in the EU.

The basic problem, which makes regulators nervous, is that much uncertainty exists about how to interpret test results when they are not done in vivo. As Chauhan et al. (2008) argue, a regulatory authority's experience with a product type reduces uncertainty. This suggests that the frictions surrounding entry will be reduced over time; price and entry responses would be expected to respond accordingly. This is a very important insight that has not been factored enough into many of the existing projection models.

Another determinant of market entry is explained in a set of models by Dorfman and Steiner (1954) and more recent empirical research by Scherer (2007). They suggest that entry into a given market is driven by mark-ups; higher mark-ups produce more market entry. This important point is illustrated in Figure 4.1; the model is similar to that used by Chauhan et al. (2008).

Figure 4.1 **Insurance and Mark-ups**



At least at this point in history, biologics are more likely to be unique than are small molecules and are more likely to be first in class. The corollary is that these markets will resemble a monopoly model more than a monopolistic competition model. Figure 4.1 illustrates two scenarios. The first model, which results in equilibrium $P_M Q_M$, is the equilibrium for a monopolist with a unique product but without insurance; the situation generates a reasonable mark-up.

Combining patents with a unique product and insurance creates the second scenario. The demand curve is now represented by D_I so that the resulting price equilibrium is P_I . Substantial mark-ups are generated whether the cost function is horizontal or upward sloping and it is a function of the degree of cost sharing. For example, if cost sharing for a drug is 5 percent, the shift over the uninsured price will be a 20-fold difference.

This shows that while some frictions and barriers to entry restrict potential entry, another force is pushing in the other direction – namely, higher mark-ups.

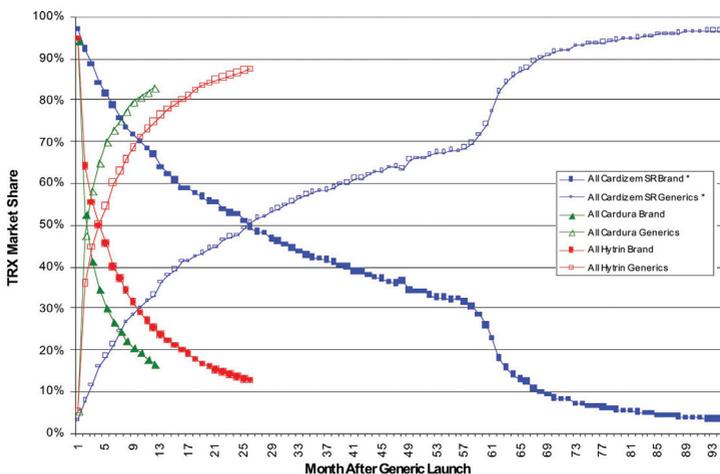
Demand response

Just how much entry is needed to generate price competition? Economic orthodoxy says that with three entrants, intense price competition begins. This was first argued by Bresnahan and Reiss (1991) and has been replicated in a variety of other studies and simulations.

Most projections of competition among biosimilars rely on analogies. For instance, Grabowski et al. (2007) uses small molecules prior to 1999, although the more recent work [included here] takes greater account of the specific characteristics of a drug. The CBO analysis (CBO, 2008) used early generic competition experience in the US. Few models have incorporated early biologics/biosimilar experiences; Chauhan et al. (2008) did some of that.

Figure 4.2 Possible Analogies

Generic Penetration Curve Comparisons



* Note: IMS data was used for Cardizem SR and its respective generics from December 1993 through December 1996. Scott-Levin data was used thereafter for Cardizem SR, and for all months for Cardura and Hytrin.

Figure 4.2 shows data on market penetration by generics for three cardiovascular drugs in the US. Although these examples are not a particularly good analogy, they emphasise how sensitive results are to the analogies chosen. Cardizem took over two years to lose 50 percent of its market share to generics. For Hytrin, launched five years after Cardizem, the branded product lost 50 percent of its market share after about five months. For Cardura, it took about 12 weeks for that to happen. Even more extreme examples exist – Prozac, for example, lost 50 percent of its market share in about six weeks and 80 percent in about eight weeks.

What are the elements that shape demand response for biosimilars? A greater positive response may be produced by planned entry of major pharma players – Merck, for example; reputation effects will tend to produce greater confidence in biosimilars. In addition, both payment and pharmaceutical benefit management (PBM) policy can be formulated to drive demand response in important ways.

Factors that might restrain demand include, for example, brand loyalty and the absence of accompanying services that are part of innovative products. Clinical uncertainty also will be important and is directly related to whether regulators designate products as comparable or interchangeable. What regulators ultimately do will send a signal to both doctors and patients about how much uncertainty and how much confidence they should have in substitutability.

Policy and demand response

Payment policies will help drive the evolution of this market. The commission in the US that advises Medicare on payment (Medpac) has been considering its response to an abbreviated pathway for biosimilars. How important seemingly modest differences can be is illustrated using two examples of Medpac options. Medicare Part B is the part of Medicare that pays for physician-administered drugs, which is where most of these products will fit. Under discussion is paying a set amount to the physician that covers both his time and the purchase of the drug. If the FDA designates a biosimilar as interchangeable, Medicare will bundle the physician's time and the price of the drug into one payment, thereby providing an incentive for the physician to buy low for those products that are deemed interchangeable. The alternative is to place all biosimilars in the same class as their originator product unless clinical evidence shows that is inappropriate. This option would have a much more sweeping effect

and presumably make the demand response much larger. This illustrates that seemingly small differences in regulatory action could have a dramatic effect on demand response. Models, then, may be misleading unless they anticipate the potential effect of such choices.

Evidence to date with respect to price competition is certainly not conclusive. Price response generally has been greater than or equal to the forecasted levels, but experience is very limited. For omnitrope, for example, prices of biosimilars have been 25 to 35 percent lower than for the originator; for the EPO market, discounts are around 30 percent. In India, biosimilars are 40 percent below originator price for insulins.

STRATEGIC RESPONSES

Currently, two of the main approaches to protecting profits (or rents) are patents and trade secrets. To simplify, patents are clearly defined, are based on specific standards, have a defined term and require publication of the details of the invention. A vast literature examines the pluses and minuses of the patent system. Trade secrets, on the other hand, protect information and know-how. They do not require publication and are not subject to a time limit, but do entail large risks, e.g., reverse engineering, corporate espionage and other discovery tactics. An abbreviated pathway might change the incentives enough to cause firms to choose a different mix of patents and trade secrets.

Small molecule markets rely primarily on patents because of the ease of reverse engineering. Patent duration is relatively long and, at least in the US in recent years, on-market patent duration has been increasing. In contrast, the biologic market is much more dependent on protecting the manufacturing process; know-how matters more for biologics. Some observers argue that this is a distinguishing factor for biologics. The question arises, then, whether the profit maximising mix of patents and trade secrets differs in the base case for biologics relative to small molecules and whether an abbreviated pathway will change the incentives around that.

The abbreviated pathway effectively reduces the exclusivity period. This could increase the relative payoff for keeping secrets to protect a firm's profits. This, in turn, could result in less reliance on patents and greater emphasis on trade secrets, creating a welfare economics issue – not publishing a patent, of course, reduces the public information available.

The result may be a dampening of inventions and/or an increase in the cost of invention, each of which potentially affects dynamic efficiency negatively. Sufficient data exclusivity periods might bolster incentives to publish patents or at least shift the mix of trade secrets and patents in a desirable direction. Policy makers need to keep in mind how policies may affect the strategic responses of firms and shape policy accordingly.

CONCLUSIONS

Biosimilars markets may well see less intense price competition than generic markets. However, actions taken by regulators, governments and payers, combined with the fact that well-known firms are entering the market, can partially address factors that may attenuate price competition. Many models have been developed under the assumption that price competition and outcomes in these markets are forces of nature. Key factors affecting biosimilars markets, on the contrary, are driven by regulatory choices – acts of man, rather than acts of nature. We need to think about how these acts of man affect long-run strategic incentives.

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Chapter 5

Regulatory Hurdles for Biosimilars

DR. GOPALAN NARAYANAN

Biosimilars are not defined as such in EU regulation. Although biosimilars are not expected to be identical structurally to the original product, they are similar enough that no significant clinical difference exists between the biosimilar and the original product.

Biosimilar products in the EU must pass through the European centralised procedure for a licence, valid in all Member States. The reference product, moreover, must already be licensed in the EU. Six biosimilar products have been approved to date: two somatropins, two epoetins and two G-CSFs. Only two have not been approved, an interferon-alpha and an insulin. More biosimilars have been approved than failed, suggesting that regulatory hurdles are not excessive.

An abbreviated or abridged application is permitted in the EU where relevant guidelines are available. These include overarching guidelines that define the framework and general guidelines that address scientific aspects, quality, non-clinical and clinical issues. The objective is to demonstrate sufficient similarity. All guidelines, both final and in development, are published on the EMA website.

Regulators expect a state-of-the-art characterisation of the product. This is vitally important for a biological product. Clinical pharmacokinetic bioequivalence, which is usually sufficient for most generics, will not be sufficient for biosimilars. Evidence of efficacy and safety from clinical trial(s) is required. If biomarker/surrogate end points are used, these should have already been validated, or justification is required. Assessment of immunogenicity needs to be part of the package because that is an important safety component. In general, studies should aim to exclude differences rather than being mere comparisons. This is because the biosimilar and the reference product would be expected to share several similarities.

THE PRE-APPROVAL PROCESS

From a regulatory approval viewpoint, companies should follow a stepwise approach. The first step is to determine quality. Proving that small molecule chemicals are identical is not difficult. For biological products,

in comparison, where the process defines the product, differences in the manufacturing process mean that products are unlikely to be identical.

Once similarity of the quality is established, the next step is non-clinical animal studies, both in vitro and in animals. The aim is to ensure that no significant difference is seen with the biosimilar as compared to the originator.

Bioavailability studies

The concept for small molecule generics is ‘essential similarities’, which assumes that no physical difference exists between the generic and the originator product. In the case of biosimilars, even if reasonable similarity and quality can be shown, equivalent pharmacokinetics alone is not sufficient for approval at the present time.

Clinical pharmacokinetics

Although pharmacokinetic data alone are not likely to be sufficient, as stated above, for approval of a biosimilar, they do need to be part of the package. Serious difference in pharmacokinetics would cause concern.

Clinical efficacy

For new products, the end points are clinical benefit i.e. proven efficacy and acceptable safety. In the case of biosimilars, it can be argued that the same rationale does not apply. End points could be chosen that are not necessarily clinical end-points as for a new drug, but are sensitive enough to reveal any differences that exist between the biosimilar and the originator products.

That said, the end point is important, especially at the margin, as it is open to debate whether a biosimilar should be different from the originator by 10, 15 or 20 percent. No agreement has been reached on acceptable differences, so these need to be justified case by case. Once experience with a particular class of products develops, however, it may be possible to know what is acceptable.

A question asked frequently is how many patients are required in clinical trials for biosimilars. The number of patients needs to be large to show true differences if they exist. It is important to note that sometimes small sample sizes can hide differences.

Clinical Safety

The duration of the studies for biosimilars tends to vary from six to 12 months. In some cases, it is safety that takes longer because efficacy can be established relatively quickly. In the case of insulin, for example, an intravenous glycaemic clamp test can demonstrate efficacy in 24 to 48 hours.

For biosimilars, safety assessments focus on immunogenicity, pharmacology and any off-target effects that may be observed. Many products have immunogenicity potential simply because they are proteins. Indeed, in some cases up to 100 percent of patients generate antibodies to a given protein. The response does not necessarily affect or harm the product except, fortunately, in a minority of cases. Occasionally, the product can be neutralised completely, making any future administration completely useless and potentially also neutralising the patient's own production of a substance. One of the best examples is a condition called 'pure red cell aplasia'. Some patients who received epoetin had such a severe antibody response to the product, that it not only neutralised the administered product, but also the individual's own product. These patients became dependent on blood transfusions for the rest of their lives, a devastating outcome. Fortunately, such events are rare, but make it clear why regulators are concerned about immunogenicity.

THE POST-APPROVAL PROCESS

The objective of the post-approval process is to minimise risks for patients. The company, the physician and the regulators all have important roles to play.

Risk Management Plans

All new EMA applications now require a risk management plan (RMP). By their very nature, clinical trials are samples. They suffer from the shortcoming of any sample in that they cannot tell the whole story. In an abbreviated development process, unusual side effects are even less likely to be revealed. The RMP is intended to ensure that safety continues to be monitored after approval. This new system is more regulated than the previous system, which relied heavily on voluntary reporting, e.g., through the 'yellow card' system

Switching and Substitution

'Switching' (interchangeability) is at the option of the treating physician; it

could be from an originator to biosimilar or a biosimilar to originator. Substitution happens at the pharmacy level, most often without the involvement of the physician.

Clinicians and patients need to be educated about biosimilars. Some patients, especially those with chronic conditions, are very familiar with their conditions and treatment options and want to be sure they are receiving the best product.

Substitution at the pharmacy level for chemical generics is usually not considered much of a problem. The general recommendation for biosimilars, however, is that they be prescribed by brand name, although clinicians are not legally required to do so. An MHRA Drug Safety Update published in February 2008 recommends that clinicians prescribe biological products by brand name (MHRA, 2008). The British National Formulary recommends brand prescribing, as do other authoritative organisations. The reason is that when a product is prescribed by brand name, dispensing chemists are barred from substituting another brand unless it is an emergency. Should a patient develop an immunogenic reaction, for example, being able to identify the brand makes it more likely that we can track the product and possibly determine the cause. It would not be easy, but at least it would be feasible.

Black Triangle

A 'black triangle' is a warning symbol on drug packaging that alerts prescribers to watch for safety issues. All biosimilars should have a black triangle.

In summary, then, a good post approval plan is an important complement to a robust pre-approval assessment. It assures regulators that safety issues will be monitored and addressed if they arise. This is far better than being surprised by a rash of adverse reports.

CONCLUSIONS

Biosimilars are here to stay, although it will be some time before we have substantial experience in this area. At the same time, the field will continue to evolve; biosimilar monoclonal antibodies already are in development.

Over time, regulatory decisions then can be based more on experience rather than theoretical grounds, but hurdles will not be lower.

In general we recommend that companies engage with regulatory agencies as early as possible to get advice. If data are available to share, that is particularly important. If differences between the biosimilar and the original product do exist, these must be addressed; regulatory agencies can advise how to do this.

Development and regulation are based on science. Regulators do not get involved in the commercial aspects or assess cost-benefit data; we look at the benefits from a purely scientific, clinical viewpoint.

Regulatory interpretation needs to be pragmatic. The experience with generics, knowledge about the originator products, combined with the research conducted on the biosimilar products, contribute to the overall decision making.

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Chapter 6

Biosimilars: Price Dynamics in Europe

DR. MATTHIAS LIEFNER

Small molecules are easy to understand and easy to copy, which implies low barriers to entry for generics. This is different for biologics: they are expensive to produce and to study and they are much harder to copy. Biosimilars also are comparatively huge molecules that require a difficult production process. All in all, barriers to entry appear to be higher than for small molecules.

THE PRICING AND REIMBURSEMENT ENVIRONMENT FOR BIOSIMILARS IN EUROPE

Two areas with biosimilars, EPO and G-CSF, provide a good illustration of the pricing and reimbursement environment in the top five EU markets. In France, biosimilars automatically receive an 'improvement in medical service' (ASMR) score of 5 (no therapeutic improvement over existing therapies) because they are considered to have the same efficacy and safety as the original brand. France requires compulsory discounts for newly-launched generic drugs, a rule that has been applied to EPO and somatropin biosimilars. Discounts, in the range of 10 to 20 percent, also apply to the originator biologic, which constitutes a compulsory price cut. The result is similar prices for the originator and the biosimilar.

In Germany, the most important factor is that the reference price system applies to both EPO and somatropin. The reference price system groups clinically similar products together in one cluster and sets a maximum reimbursement price for all products in the cluster. The German authorities considered the biosimilars and the original biologics for EPO and somatropin to be clinically equivalent, grouping them into reference pricing clusters. At the regional level, the use and prescribing of biosimilars are subject to quotas and guidelines to encourage, or require, use.

Tenders are also an important mechanism that might affect biosimilars. Tenders have not been emphasised as yet in Germany, but have gained popularity over the years and will become much more important in the near future. They usually are a very good instrument for putting pressure on prices. It is likely that biosimilars will be included in tenders.

In Italy, no clear process yet exists for integrating biosimilars into the pricing and reimbursement regime. Italy does tend to follow the French lead; price discounts of 20 to 30 percent are required for generics and this may apply to biosimilars also. It is possible that *The Agenzia Italiana del Farmaco* (AIFA), the national body that regulates the Italian pharmaceutical market, may request similar price cuts for the original biologics.

The UK differs from the countries mentioned above. The individual Primary Care Trust (PCT) decides locally whether to include biosimilars in the formulary and the relative position of biosimilar and the originator products. The PCT's latitude is somewhat less if NICE issues guidance on a product, but this has not yet occurred for biosimilars¹. Of course, voluntary price cuts by the original biologic manufacturer would help to improve its product's formulary position in each PCT.

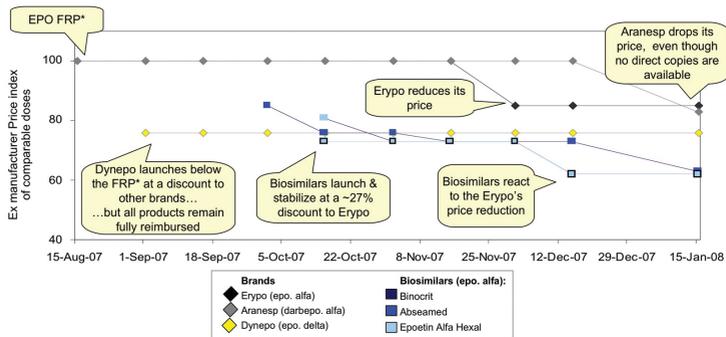
CASE STUDIES: PRICE COMPETITION IN THE EPO AND G-CSF MARKETS

Germany provides the first case study. A fixed reference price (FRP) group was introduced in 2007 for the EPO market and included both Erypo (epoetin alfa) and Aranesp (darbepoetin alfa). This set a maximum reimbursed price for EPO. Dynepo (epoetin delta), a different EPO, was launched in September 2007 about 30 percent below the FRP price. In October 2007, the first biosimilar of epoetin alfa (Binocrit) entered the German market, followed closely by two others (Abseamad and Epoetin Alfa Hexal). The biosimilars were priced similar to Dynepo at roughly 30 percent below the price of the original epoetin alfa.

The original branded product reduced its price before the end of 2007 and the biosimilars reduced prices again, creating a price war. Aranesp also reduced the price in early 2008, even though no direct copies of darbepoetin alfa were available. Figure 6.1 shows this sequence of events graphically.

¹ Editor's note: NICE issued guidance in May 2010 that listed Omnitrope as of one of seven growth hormone products available for use in the NHS. It noted that: 'Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name.'

Figure 6.1 EPO Prices in Germany

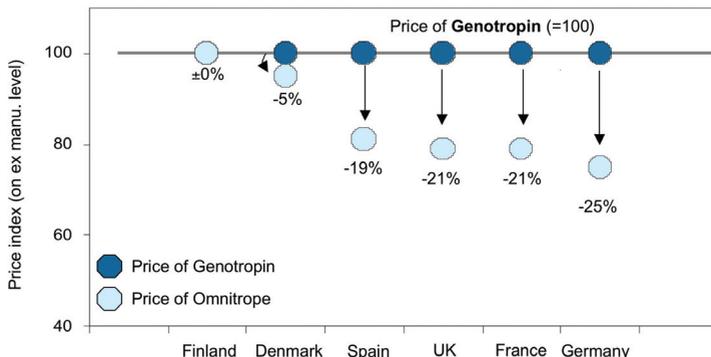


* FRP = Fixed Reference Price

Source: Simon-Kucher and Partners

Figure 6.2 shows price comparisons in the growth hormones from a pan-European perspective. The original branded G-CSF has kept its price stable, at least for the time being, especially in Germany. The biosimilar Omnitrope is priced at a discount in Germany that ranges from zero to 25 percent. In Germany, this is not the end of the story, as an FRP for growth hormones has been implemented. It is very likely that even the original drug will be forced to reduce prices, similar to what occurred in the EPO market. In spite of the discounts, however, the uptake of Omnitrope has been slow because of some concerns about the efficacy and safety of the product, especially in the paediatric population it serves.

Figure 6.2 Omnitrope Price Relative to Genotropin



Source: Simon-Kucher and Partners

PERCEPTIONS AND REACTIONS OF VARIOUS STAKEHOLDERS

The attitudes of players or stakeholders toward biosimilars vary, which affects price dynamics and raises a host of questions for anyone attempting to forecast the market: What do payers expect from biosimilars? What is the pricing and reimbursement environment now for the products and is intervention needed? How do physicians perceive biosimilars? Are they interchangeable? What is their relative value? Is there a delta between these two groups and does the relative perception in terms of value result in a prescription? Are physicians being incentivised by payers to change prescription behaviour? How do the manufacturers of the biosimilars behave? How do they want to position their drugs? What price decrease do they perceive to be necessary on entry to ensure uptake and do they consider aggressive pricing as an option right from the start? Last but not least, how do the manufacturers of the original biologics behave? Are they proactive? How would they prefer to position their drugs? Do they perceive biosimilars as threats to their drug, and do they want to answer that with a price reduction?

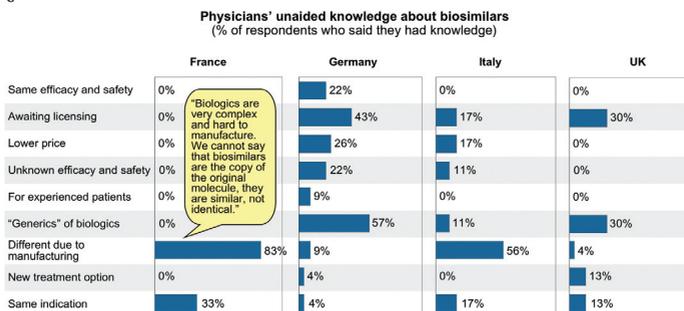
The customer, in our case payers and physicians, always seeks a balanced price/value for the product. In terms of value, clinical data are available for the original drug, but scepticism about the ‘sameness’ of biosimilars is common and questions remain about potential problems with efficacy and safety. Moreover, differences may exist in indications, depending on the type and severity of the disease. Cost pressures clearly are important, especially for payers. Biosimilars usually offer some discount, in the range of 20 percent and perhaps higher, which may be attractive to payers. The point is that a number of factors determine price sustainability for both brands and biosimilars.

How physicians and payers view biosimilars

How much do stakeholders know about biosimilars – particularly payers and physicians? When physicians are asked, ‘What is your general knowledge of biosimilars?’, they say it is somewhat limited. However, and more importantly, asked whether they think biosimilars are the same as generics, physicians say, ‘I am cautious about treating them in exactly the same way’. It is important to remember that physicians still have concerns, especially about safety and the side effect profile.

We asked physicians in France, Germany, Italy and the UK a number of unaided questions regarding their views about biosimilars. Responses are summarised in Figure 6.3.

Figure 6.3 Prescribers' Statements about Biosimilars



Source: Simon-Kucher and Partners

Figure 6.3 shows differences in perceptions across countries. In France, the majority of physicians said: ‘The only thing that comes to my mind when talking about biosimilars is that they are different from the original biologics due to the manufacturing process.’ Italy produced a similar result. But German physicians reacted completely differently; more than half respond that ‘biosimilars are the generics of biologics’. The response in the UK was similar to that in Germany.

We carried out a similar exercise with payers. When asked about their general knowledge of biosimilars, payers in Germany, France and Italy said: ‘We have quite good knowledge about biosimilars already, in terms of what kind of data is present and how to treat biosimilars’. However, when the same payers were asked their attitude toward biosimilars, the response was: ‘It is mixed, we still are somewhat sceptical’. This scepticism primarily is due to uncertainty about safety and side effects.

For payers in Germany, France, Italy and the UK, the key driver for biosimilars is the price difference. In all countries except Germany, moreover, payers consider the clinical data on efficacy and safety side effects, looking closely into the available evidence that is provided by the biosimilar manufacturer. Particularly in France and in the UK, payers are interested in the country of origin of the biosimilar product.

Options for biosimilar manufacturers

What will biosimilar manufacturers do in the future? In France and Italy, we expect these companies to start marketing biosimilars, targeting hospital specialists first; they will offer assurances that their products, available at a lower price, are comparable to the original biologic. Clinical equivalence at a lower price also will be emphasised in Germany. Prices are transparent in Germany, but the recent rebate contracts of some sickness funds have created uncertainty; physicians may be less aware of which product is most economical to prescribe. Biosimilar manufacturers also will target the sickness fund tenders as a way to enter market.

In the UK, overall savings are a key factor driving PCT behaviour. Biosimilar manufacturers are expected to actively approach big PCTs and to present a business case outlining potential savings. How PCTs and biosimilar manufacturers interact also will be affected by what NICE may decide about which indications that can be treated with biosimilars.

VULNERABILITY TO BIOSIMILARS IN THREE DIFFERENT DISEASE AREAS

The growth hormone EPO and long-acting insulin markets provide good examples of what may happen in future with biosimilars, identifying a number of vulnerabilities.

First, the growth hormones are given almost exclusively to children for a defined period of time; the benefits or side effects can be lifelong and are not immediately observable. Typically, few risks are likely to be taken when treating children based on savings alone, particularly since the patient base is small. This is different for the EPOs; these treat adults with a chronic condition and their effects are clear in the short term. The situation for insulins is similar to the EPOs. Patients are adults, diabetes is a chronic disease and the effect of the drug is immediately visible. These factors differentiate the growth hormones market from EPO and the insulin markets and suggest that the originators are most likely to retain market share in the growth hormones market. EPOs and the insulins, however, are clearly a focus of payers since the patient base is large; switching already is common. Table 6.1 summarises the situation.

Table 6.1 Vulnerability to Biosimilars

| | Case 1: Biosimilar of growth hormones | Case 2: Biosimilar of erythropoietins | Case 3: Biosimilar of long-acting insulin |
|-------------------------------------|--|---|--|
| Vulnerability to biosimilars | Rather low | Rather high | In between Cases 1 and 2, but closer to Case 2 |
| Price of biosimilars | Omnitrope's average price in Europe was 30% less than Genotropin | In Germany, biosimilars launched at 19% below Erypo/Eporex price; shortly after launch reduced price to 27% below brand | Potential range: ~20-30% |
| Price of branded | No price adjustments for Genotropin yet; if FRP in Germany, could change | In Germany, Erypo recently reduced price by ~13% | Potential range: ~0-15% |

Source: Simon-Kucher and Partners

Strategic pricing responses from manufacturers

At least in theory, the original manufacturers have two options. The first, maintaining market share by reducing their price, likely will decrease revenue over time. The second strategy, maintaining price position, risks a reduction of market share if some physicians start prescribing biosimilars; revenue and profit could decline. No matter which choice is made, the original biologic manufacturer is unlikely to be able to defend its market position. Instead, originators need to devise strategies to minimise the impact of new entrants.

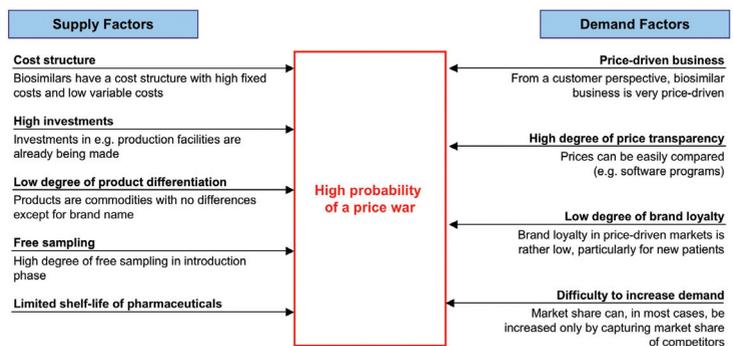
The risk to the originator of reducing price is clear in the price war that has occurred for the EPOs in Germany. The price difference is always the same between the original drug and the biosimilar, leaving relative market shares unchanged, but creating a decline in revenues. Only payers benefit from this situation.

If the originator decides to maintain price (the ‘stay strategy’), revenue still will decrease with market share, but the originator has more room to manoeuvre; for instance, in seeking a niche indication. A new indication matters far less if the originator decreases price immediately after the biosimilar enters the market at a discount because it is virtually impossible to increase the price again.

Certain factors in the biosimilar markets may generate price wars, as shown in Figure 6.4. From the supply side, the cost structure involves high fixed costs/low variable costs and high initial investments. For biosimilars, the degree of product differentiation is low; free-sampling is common and shelf life is limited. At the same time, biosimilars may be positioned more as late-entrant branded products than as ‘generics’.

From the demand side, on the other hand, the market is very price-driven. Payers are pursuing price reductions and cost savings; physicians are sometimes incentivised to seek out lower-priced drugs; biosimilar manufacturers are clearly pushing their price advantage. Prices are highly transparent; finding the prices of all competitors is easy. (Transparency may be less for tenders in Germany, but ultimately prices are available.) Brand loyalty tends to be low, although this may differ across indications. And, finally, increasing the size of the market – total demand – may be difficult, meaning that market share in most cases can be increased only by capturing the market share of competitors.

Figure 6.4 **Factors Influencing a Potential Price War with Biosimilars**



Source: Simon-Kucher and Partners

SUMMARY AND CONCLUSIONS

Payers are expecting substantial savings as a result of biosimilar competition. Whether that will occur, when and how much is not yet clear. Uneasiness about potential safety issues has made physicians somewhat reluctant to use biosimilars, although that varies by country and can easily change in future. Pricing and reimbursement measures are not developed yet, but those that are in place are sufficient to put pressure on price. The manufacturers of the originators know that biosimilar prices can be considerably lower, that market size is constrained for most biologics, and biosimilar manufacturers position their products to look more like a late-entry branded product than generic. The ultimate question for the original manufacturer will be whether to discount and risk a price war, among other things, or maintain price. The optimal strategy depends on vulnerability to competition and takes into account the revenue impact of each option as well as the likely response of the biosimilar manufacturers. Currently, moreover, biologics that are likely to compete with biosimilars in the near future still account for a small percentage of total spending on drugs.

Chapter 7

Estimating Savings from Biosimilars in the US

ALEXIS AHLSTROM

Editor's Note: Since the seminar, the US has passed legislation that provides an abbreviated pathway for approval of biosimilars. Although this resolves long-term debates about what a new law might provide, implementing regulations have yet to be promulgated. Provisions of the new law are outlined at the end of this chapter.

Legislative proposals to create an abbreviated process for approving biosimilars have been debated in the US since 2006. A key argument has been that cost savings would be considerable for both public and private health programs. Bills proposed in Congress have varied in several ways, including how and when a biosimilar would be treated as interchangeable and how long an exclusivity period would be. In part, the differences reflected expectations of savings – or the need for savings.

As efforts to craft health reform legislation proceeded, savings for federal programs from biosimilars were viewed as one of many ways to support the proposed reform package. Legislation in the US is expected to be 'revenue neutral'. This means that any new expense is to be offset either by equivalent savings or by additional sources of revenue, usually over a time frame of five to ten years. Before the final vote on a bill, it must be 'scored' to estimate the change in federal government spending that would be created by its passage and to demonstrate budget neutrality.

The non-partisan Congressional Budget Office (CBO) and the Office of Management and Budget (OMB), which is under the President, both 'score' legislation. In the case of biosimilars¹, the time frame chosen was ten years. Savings for the federal government would derive from lower expenditures in government-sponsored programs, such as Medicare (those 65 and over) and Medicaid (the indigent, costs split with the States).

Key factors considered in both the CBO (2008) and OMB biosimilars models included:

1. Spending levels and projected spending growth rates for biologics;
2. Timing of new legislation and regulations implementing it;
3. Regulatory review times and pathways for biosimilars; and
4. Patent life and exclusivity periods;

¹ Editor's note: Debate in the US before passage of the new law used the term 'follow-on biologic' rather than 'biosimilar'. Since the new legislation uses the term 'biosimilar', however, and this term is common in European usage, we have adopted that terminology here.

5. Brand biologics market share variation and effects on biosimilar entry;
6. Market share attained by biosimilars;
7. Pricing of biosimilars;
8. The proportion of the total change that will affect federal spending.

Passage of the new legislation, in March 2010, removed some uncertainty from this list: the date of the legislation is known, the basics of the regulatory pathway have been sketched out, and provisions for data exclusivity have been specified. Although these are important, they do not resolve questions about the factors that really drive these and other models – in particular, assumptions about pricing and market penetration.

THE AVALERE MODEL

Biologics spending levels and projected growth rates

The first data point necessary to estimating biosimilars savings is baseline spending on biologics. Based on IMS data, spending on biologics in the US in 2008 was about \$45 billion; the biologics market in the US grew about 20 percent a year during 2001-2006. It was this 20 percent rate that was deemed ‘unsustainable’ and drove interest in biosimilars legislation. In 2007 and 2008, however, biologics spending growth actually declined significantly in the US. That creates considerable uncertainty as to the potential savings for the out years, 2015 to 2019; if the spending growth rate is declining, then the ultimate savings from biosimilars also will decline.

The Avalere model reduces the \$45 billion based on two considerations. First, in the 10-year budget window, a number of new products will have appeared on the market. These will not be subject to competition from biosimilars because they will be protected either by patents or data exclusivity. Second, also excluded from that \$45 billion is spending related to insulins, vaccines and the human growth hormones because these have a separate pathway not expected to be affected by this legislation. Eliminating these two categories reduces the baseline by about 15 percent.

Timing of legislation and implementing regulations

The second factor in estimating biosimilars savings is time. Most of the estimates correctly assumed fiscal year 2010 as the year that legislation would be passed. This is just the first step. Before any biosimilar can be approved for marketing, the FDA must develop and finalize regulations to implement the law. CBO assumed this would take two years; we assume

three years, based on the experience with the 1984 Hatch-Waxman Act, which provided for the abbreviated pathway for small-molecule generics. That would mean no savings will be possible during the first three years of the ten-year budget window. Moreover, this might be delayed for more complex biologics classes if the FDA believes more specific guidance is necessary.

FDA regulatory review times and pathways for biosimilars

Our model assumes high interest by manufacturers in submitting biosimilar applications across a variety of classes. However, we believe that the FDA, like the EMA, will be cautious in approving the first biosimilar applications and may ask manufacturers for additional data. We estimate review of these initial applications will require about two years, as they have in Europe.

Adding two years of review time to the three years needed to promulgate regulations means savings can appear only during the last five years of the budget window. This is very important. It means that the estimated \$6 billion to \$9 billion in savings cannot begin before year five.

Patent life and exclusivity periods

Our model did not show much sensitivity based on data exclusivity periods; savings estimates did not change dramatically whether the exclusivity period was eight years, ten years or 12 years. One of reasons was that we assumed the exclusivity period would run in parallel with the patent period. The OMB has recently expressed a very similar opinion on the sensitivity of their model with regard to exclusivity, although the CBO model seems to assume more impact from exclusivity periods.

Brand biologics market-size variation and effect on biosimilar entry

In some biosimilar markets, entry and multiple entrants make economic sense; in others, revenues are so small that biosimilar competition is unlikely. The majority of revenues from biologics in the US are accounted for by ten to 15 biological products; the rest, around 100 to 125 products, make up a very small percentage of total revenue. We made the following assumptions about entry in our model:

- Three biosimilars will enter for every large-revenue, off-patent biologic (>\$1 billion annually).
- Two biosimilars will enter for every medium-revenue, off-patent biologic (\$250 million to \$1 billion annually).

- One biosimilar will enter for every small-revenue, off-patent biologic (<\$250 million annually).

The CBO assumed similar numbers of biosimilar entrants.

Market share attained by biosimilar entrants

In our analysis, we assumed that biosimilar market share will be a function of four factors: FDA findings of comparability versus interchangeability, payer treatment, pricing, and physician prescribing behaviour and consumer demand.

First, unless a biosimilar is deemed interchangeable by the FDA, it will be treated like a therapeutic alternative, not a generic, and market penetration will be much lower. Payer coverage and reimbursement rules, and pharmacy substitution laws, depend on FDA ratings of extent of similarity.

We explored whether, for biologics, payers require physicians to prescribe a cheaper therapeutic alternative. This is an important indicator of whether clinical or cost considerations weight most heavily in payers' decisions. Indeed, for the multiple-branded products now available in the areas we examined, including rheumatoid arthritis and human growth hormone, payers are not expressing a preference for one product over the other.

Market penetration in the US also is affected strongly by state pharmacy substitution laws, which drive the rapid uptake of generics. About a third of biologics are provided through the pharmacy; the remainder two-thirds are provided through the physician's office. As currently written, state pharmacy substitution laws can apply only to biosimilars deemed interchangeable by the FDA.

Price discounts, at least to date, have not been important for biosimilars in the US. Omnitrope, for example, sells at a discount of about 25 percent in the US and has a market share of only about two percent. Clearly, it is not the discount that is driving market penetration; most likely it is concern about clinical interchangeability. Uncertainty surrounds how US physicians and consumers will react to biosimilars. Safety concerns are likely to cause some hesitation in use initially.

We assume, based on current payer dynamics, that biosimilars will capture about a third of the innovator's market share.

Pricing of biosimilar entrants

The fourth factor driving market share of biosimilars is pricing. At this point, data about that are scarce. Our model relies on the work of Professor Henry Grabowski and assumes that barriers to entry include higher development and manufacturing costs, as well as higher distribution and marketing expenses.

In the near term, we expect that the entry of a single biosimilar will have little effect on the market because incentives to provide significantly lower prices would be weak. Omnitrope is on the market in the US at a 25 percent discount, but one cannot assume all biosimilars will be priced at that level.

After three years on the market, we anticipate discounts of 20 to 30 percent, with some decline in the originator's price.

THE IMPACT ON FEDERAL SPENDING

Savings from biosimilars will accrue to multiple payers. Currently, the majority of biologics spending is by payers other than the federal government. In our model, we assume that 30 percent of savings will accrue to the federal government, based on National Health Statistics data on spending.

Our model's findings are similar to those of the CBO, which estimated \$9 billion in federal savings; the national number would be about three times that. The OMB estimate was about \$6 billion in savings over ten years. That \$6-\$9 billion range is less than one percent of total biologics spending and less than half of one percent of spending on total health care in the US. Thus, even though \$6-\$9 billion in savings is significant, it certainly will not bend the curve in terms of total health care spending in the US. It will not contribute substantially to the price of the new health reform legislation and is minor compared to the shortfall in funding for Medicare.

Key Provisions of the Biologics Price Competition and Innovation Act of 2009

(H.R. 3590--111th Congress, 2009)

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| Definition of a 'biosimilar' | A biologic product that is 'highly similar to the reference product notwithstanding minor difference in clinically inactive components' and for which there are 'no clinically meaningful differences [with the reference product] in terms of the safety, purity and potency of the product' |
| Interchangeability | For a biosimilar to be 'interchangeable', the FDA must determine that, for a product administered multiple times, the biosimilar does not increase risks associated with or decrease the efficacy of treatment. 'Interchangeable' means that the biosimilar may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product. |
| Abbreviated approval | <p>Biosimilar manufacturer must provide</p> <ul style="list-style-type: none"> • analytical studies demonstrating that the product is 'highly similar' to the reference product, animal studies (including toxicity), and clinical study of studies (including immunogenicity, pharmacokinetics or pharmacodynamics) that are 'sufficient to demonstrate safety, purity, and potency' of the biosimilar for at least one intended condition of use • certification that the biosimilar uses the same mechanism(s) of action (if known) as the reference product; that conditions of use are the same as for the reference product; and that the route of administration, dosage form, and strength are the same |
| Exclusivity | <ul style="list-style-type: none"> • 12 years' exclusivity for a biologic (the 'reference drug') approved under a BLA (Biologics License Application), extended 6 months for paediatric or orphan indications • For first 4 years after approval, biosimilar applicants may not submit applications to the FDA • A minimum 1-year period of exclusivity for the first-marketed interchangeable biosimilar (absent specific court challenges, specified in the law) |
| Notification and exchange of patent information | <ul style="list-style-type: none"> • Biosimilar applicant must provide information to reference product owner ('sponsor') about manufacturing process(es) within 20 days of FDA acceptance of approval application |

Notification and exchange of patent information
(continued)

- Sponsor has 60 days to notify applicant of possible patent infringement(s)
- Additional interaction between the two parties is required within set time frames
- Applicant must give sponsor 180 days' notice of intention to market the product; sponsor may take legal action under certain circumstances

REFERENCES

Congressional Budget Office (CBO), 2008, Cost estimate: S.1695 Biologics Price Competition and Innovation Act of 2007

H.R. 3590--111th Congress (2009), Patient Protection and Affordable Care Act, in GovTrack.us (database of federal legislation), retrieved August 14, 2010, from <http://www.govtrack.us/congress/bill.xpd?bill=h111-3590>

