

OPPORTUNITIES AND BARRIERS IN THE BIOSIMILAR MARKET: EVOLUTION OR REVOLUTION FOR GENERICS COMPANIES?

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Summary

Biopharmaceutical drugs (or biologics) have outperformed the pharmaceutical market as a whole largely due to two factors: they address areas of clinical need that are unmanageable with conventional therapeutics (including many cancers and genetic diseases) and they are able to command a premium price. At some point the patents protecting the successful biologic will expire and the potential of a sizeable market will attract generic companies. However the process to develop a biosimilar – essentially generic version of biopharmaceuticals – is more complex than that of developing a generic copy of a chemical-based compound. The regulatory pathway is not completely finalised, whilst the EMEA approved the first biosimilar (Sandoz's Omnitrope (somatropin; somatrophin) in April 2006), the FDA has not yet approved any. Nevertheless, the biosimilars markets in Europe and the USA have the potential to generate sales of \$16.4 billion by 2011 (Frost & Sullivan).

This chapter considers the commercial implications and the market entry requirements for biosimilars by reviewing:

- the commercial factors driving the biosimilar market.
- the most likely therapeutic and geographical targets for generic manufacturers.
- ways in which conventional generics companies will have to reconfigure their business models if they are to become competitive in the biosimilars market.

While on the surface the market for biosimilars may seem very attractive, several significant obstacles will prevent its smooth growth:

- Sales of most biopharmaceuticals are markedly higher in the USA than the rest of the world. However, there is unlikely to be a regulatory pathway for most biosimilars in the USA until after 2010. The commercial decision about which products to develop will depend, in the first instance, on what level of sales a biosimilar can generate in Europe.
- The biosimilar market will be characterised by price competition, even when there is only one or a very limited number of players for a given product. This will constrain the size of the commercial opportunity. A small price differential reduces the incentive to switch. The consensus seems to be that a 20-25% discount is optimum to increase the switch back to first generation products.

- Manufacturers of branded products are likely to use sophisticated defensive tactics, including the development of complex biopharmaceuticals, to maintain share
- Several potential biosimilars face competition from second-generation products with more convenient administration schedules. In many cases, the same companies market the original and second-generation products and there may not be a marked difference in price.
- The cost of development will be significantly higher than for chemical-based generics and there is a lower probability of successful launch that puts R&D investment at risk. This is new territory for many generics companies and we may find other players who already manage these risks, such as branded pharma, entering the biosimilars market.
- The required capital investment and operating costs of manufacturing will be much higher for biosimilars than for generic drugs.
- The supply chain for biosimilars will be very different to the current range of generic drugs. Biopharmaceuticals are less stable than chemical based pharmaceuticals and thus require cold chain distribution and have a shorter shelf life. This increases the cost and complexity of distribution.
- Post-approval safety monitoring is expected to be compulsory, at least for the first few biosimilar products approved.
- European guidelines state that prescribers should specify the International Nonproprietary Names (INN) or brand. This hinders generic prescribing and substitution.
- Brand development will be very important and direct marketing to small numbers of specialists is likely to be highly competitive.
- Physicians will be cautious about the relative safety and efficacy of biosimilars in the short term at least and so high promotional investment will be required. Generics players without experience marketing their products will need to set up a sales team, either fully in-house, using a contract sales force or both, or partner with a bigger pharmaceutical or generic company.
- Improved delivery devices can add significant value and enhance product differentiation. There are, however, a limited number of drug delivery companies, many of which are already working exclusively with the branded incumbents.

To make the most of the opportunity, generic companies will have to change their business model. The current model consists of launching new generic products regularly to maintain growth. Entry barriers are relatively low and there tends to be severe price competition from several generic competitors reducing sales significantly after the first year on the market. It is not clear if there will be enough biologic candidates for a company that is focused on launching biosimilars to sustain growth. There are not enough possible biosimilars for a company to rely on these alone to launch a new product every year.

Companies likely to succeed in the biosimilar market need to have an appropriate marketing structure as well as the financial resources to develop the products and to accept higher upfront risks in development, commercialisation and capital investment.

Biosimilar players will therefore need to adopt different business models and skill sets from those of conventional generics companies. This is new territory for most generic players and there are likely to be fewer players in biosimilars than in traditional generics. In the short-term at least, the commercial benefits from entering most biosimilars markets are likely to be small.

An introduction to the biopharmaceutical market

Robert Swanson and Herbert Boyer founded the first biotechnology company in 1976 when they began investigating how to use genetic technology to make commercially viable therapeutic proteins. ⁱ Over the next 30 years, biotechnology companies produced some notable clinical successes, beginning with human insulin, human growth hormone and erythropoietin (FDA approved in 1982, 1985 and 1989 respectively). Today, biopharmaceuticals account for between 10% and 15% of the world pharmaceutical market, with sales in the USA alone reaching around \$30 billion (Table 1).

Biopharmaceutical drugs have outperformed the pharmaceutical market as a whole largely due to two factors: they address areas of clinical need that are unmanageable with conventional therapeutics (including many cancers and genetic diseases) and they are able to command a premium price. Datamonitor, for example, forecast growth in biopharmaceuticals of 11% a year between 2004 and 2010 compared to 3.4% annually for the total market. Currently, the USA accounts for 55% of the biopharmaceuticals market. By 2010, analysts expect biologic sales in the USA to reach nearly \$60 billion and account for a quarter of overall drug sales.

Many commercially important biopharmaceuticals, including monoclonal antibodies (MAbs) such as Herceptin (trastuzumab), Rituxan (rituximab) and Humira (adalimumab), were launched fairly recently and will not be open to generic competition for many years and many are protected by a complex series of patents that even the biggest, most experienced generics companies find impenetrable. Nevertheless, Table 1 shows that several 'blockbuster' biopharmaceuticals have reached, or are reaching, the end of their patent protection.

Product	Active Substance	Company	Patent Expiry	Worldwide sales (2005 in \$million)
Cerezyme	imiglucerase	Genzyme	2001	933
Humulin	human insulin	Eli Lilly	2001	1005
Novolin	human insulin	Novo Nordisk	2001	1618
Intron-A	interferon alpha2b	Schering-Plough	2002	287
Avonex	interferon-beta	Biogen Idec	2003	1543
Humatrope	somatropin	Eli Lilly	2003	414
Nutropin	somatropin	Genentech	2003	370
Procrit	erythropoietin	J&J	2004	3324
Epogen	erythropoietin	Amgen	2004	2455
Neupogen	figrastim	Amgen	2006	1216
			Total	13,165

Source: Generic Pharmaceutical Association and Company Reports

Table 1: Patent status of leading biopharmaceuticals

Usually, the imminent expiry of a drug's patent leads to companies developing cheaper, bioequivalent versions of the original brand (generics), followed by intense price competition. This approach to the biopharmaceuticals market can yield significant reward: according to Frost & Sullivan, the biosimilars markets in Europe and the USA has the potential to generate sales of \$16.4 billion by 2011 at an average annual growth rate of 69.8%. However, the commercial and scientific hurdles facing biopharmaceuticals hinder the entry of generic biopharmaceuticals (so-called biosimilars and, less accurately, biogenerics) and mean that companies that want to develop biosimilars will need to rethink some fundamental assumptions about the generics market and work according to new business models.

Not really generics...

The widely accepted term for generic biopharmaceuticals reflects the recognition among regulatory authorities, physicians and companies that biosimilars are less likely to be direct copy of the original product than those generics based on small molecules. In part, this difference reflects the nature of biopharmaceuticals and the mode of production.

Biopharmaceuticals are proteins with considerable therapeutic and structural diversity. They tend to be between 100 and 1000 times larger than traditional small molecule drugs. Companies cannot manufacture such complex proteins using conventional chemical synthesis. Rather living cells (e.g., a bacterial strain or animal cell line in culture) are genetically modified so that they manufacture therapeutic proteins.

The cell produces protein by transcription of the gene in DNA into RNA and translation from RNA into a protein. The cell may need to 'fold' this protein into a particular 3D shape or attach sugar and other groups to the amino acid backbone before it becomes active. Even under stringently controlled conditions, variations can emerge in the way that the protein is folded or in the groups attached. These subtle differences can affect efficacy, tolerability or both. For example, recombinant proteins with different formulations or manufactured by different processesⁱⁱ may differ in the likelihood that they will stimulate an immune reaction.

The usual protocols for assessing equivalence between generics and originator brands may not be applicable to biosimilars. (Obviously, the brand and the generic need to be equivalent to allow generic prescribing and substitution, otherwise the patient may receive a sub-therapeutic or toxic dose.) Conventional pharmaceuticals are considered bioequivalent if analyses show that the two drugs have the same chemical composition and pharmacokinetic studies demonstrate equivalent rate and extent of absorption. This assumes that the pharmacokinetic profile predicts the clinical

response. However, numerous factors compromise bioequivalence studies with biosimilars and mean that the principals that traditionally underpin generic substitution and prescribing probably do not apply to biosimilars ⁱⁱ:

- Biopharmaceuticals are large and complex molecules with complicated modes of action.
- The relationship between pharmacodynamics of biopharmaceuticals and the clinical effect is unclear. There are also few established efficacy markers.
- Biopharmaceuticals often have multiple targets of action
- Assays for biopharmaceuticals are often difficult to perform and the results can be ambiguous. For example, current analytical techniques may not be able to detect the structural differences responsible for the differences in clinical outcome. ⁱⁱⁱ

These differences form the heart of the controversy surrounding biosimilars and the barriers to entry, as these two examples illustrate:

- The innate variation and the lack of established methods to determine bioequivalence mean that regulators are likely to be much stricter when considering an application for marketing approval of biosimilars than they are with conventional generics. As a result, regulators will require more extensive clinical testing for biosimilars than for conventional generics.
- The cost of manufacturing a biopharmaceutical is much higher than that of a conventional generic. The estimated cost to develop a biosimilar is estimated to be in the range \$10-40 million, largely because of the need for extensive safety and efficacy testing. This compares with \$1-2 million for a traditional generic.

As discussed below, the pricing strategy for each biosimilar needs to balance two competing forces:

- The price will have to reflect the high investment in development and manufacturing and marketing. Therefore, price differentials between originator product and biosimilar can be much less than for traditional generics.
- A small price differential reduces the incentive to switch.

Furthermore, physicians will be cautious about the relative safety and efficacy of biosimilars in the short term at least. Therefore, the market may develop slowly, which is one reason why the commercial rewards are likely to be limited in the short term.

Biopharmaceuticals are expensive and marketers working in many branded companies can expect competition from biosimilars to emerge as health services worldwide struggle to contain spiralling healthcare costs ⁱⁱⁱ. Indeed, biosimilars are now a fact of pharmaceutical life:

- The EMEA had received three biosimilar applications by the end of 2005.
- The EMEA expects to receive eight more biosimilar applications during 2006.

- In December 2005, the EMEA reported that it had provided scientific advice about the development of 15 other biosimilars.
- The EMEA approved the first biosimilar, Sandoz's Omnitrope (somatropin; somatrophin) in April 2006.

Commercial drivers for biosimilars

Some of the world's most successful drugs are biologicals. Indeed, the market for erythropoietin, used to manage anaemia associated with cancer and renal disease, was worth nearly \$13 billion in 2005. This, arguably, makes erythropoietin the world's biggest product ahead of the lipid-lowering agent Lipitor (atorvastatin).

Biopharmaceuticals' commercial value derives from their ability to address otherwise unmet need. Genzyme's Cerezyme (imiglucerase) offers a case in point. Cerezyme treats Gaucher's Disease, which occurs because of an inherited deficiency in an enzyme called glucocerebrosidase. As a result, levels of a fat called glucosylceramide rise excessively, which grossly enlarges the liver, spleen, bone marrow and other organs leading to numerous potentially fatal complications and considerable morbidity among those who survive. Before imiglucerase, there were no effective treatments. Cerezyme markedly improves the prognosis of people affected by Gaucher's Disease. Cerezyme, which addresses this previously unmet need, is priced at around \$200 000 per patient per year.

Against this background, the potential savings for healthcare payers and consumers is, potentially, a huge driver of demand for biosimilars. Cheaper versions would result in greater utilisation of biological products, especially in Europe. In addition, some products may be used in indications where they are not currently considered cost effective. Nevertheless, in the short- to medium-term, the commercial opportunity for biosimilars will likely be limited to six product classes (discussed below). Table 2 summarises the current sales, growth, percentage of market share accounted for by the USA and predicted sales in 2010 for six leading biosimilar targets. The following sections briefly summarises some of the factors shaping the markets for each of these 'big six' products.

Drug	Global sales ¹	Growth ¹	Proportion of market in USA	Predicted biosimilar sales 2010
Erythropoietin	\$13 billion	7%	69%	\$701 million ²
G-CSF	\$5.6 billion	15%	63%	\$605 million ³
Interferon alpha	\$2.3 billion	6%	35%	\$188 million ³
Interferon beta	\$3.7 billion		55%	\$131 million ²
Human growth hormone	\$1.9 billion	2%	33%	\$442 million ³
Recombinant human insulin ⁴	\$8 billion			\$138 million ³

1 12 months to June 2006

2 EU markets – no sales predicted in the USA

3 USA and five major EU markets

4 Includes standard recombinant human insulin and insulin analogues

Source: IMS, Datamonitor

Table 2: Current sales, growth, percentage of market share accounted for by the US and predicted sales in 2010 for six leading biosimilar targets

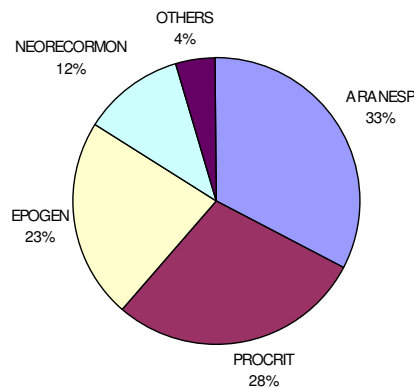
Pricing strategy

The pricing strategy for each biosimilar needs to balance two competing forces. On the one hand, the price will have to reflect the high investment in development and manufacturing and marketing, as well as pharmacovigilance commitments. These high barriers mean the competitive intensity will be weak, which translates into more pricing leverage. Therefore, price differentials between originator product and biosimilar can be much less than for traditional generics. On the other hand, a small price differential reduces the incentive to switch. The consensus seems to be that a 20-25% discount is optimum. Sandoz's Omnitrope was launched at a 20% discount compared to Eli Lilly's Humatrope in Germany. However, the discount is likely to increase when BioPartners' Valtropin is launched. Biosimilar human growth hormone in Australia costs 25% less than the brand. Originator products' pricing strategies will have a huge influence on the uptake of biosimilars. Many brands have raised the price of first-generation products to encourage switching to their second-generation products. The introduction of biosimilars may increase the cost differential and increase the switch back to first generation products.

Against this background, we believe that the biosimilar market will be characterised by price competition, even when there is only one or a very limited number of players for a given product. This will constrain the size of the commercial opportunity. As a result, in the short-term at least, the commercial benefits from biosimilars are likely to be small.

Erythropoietin

For many years, Amgen's Epogen (epoetin alfa) and J&J's Procrit dominated the market for erythropoietin (see figure 1), which is used to treat anaemia associated with malignancies, cancer chemotherapy and end stage renal disease, including people on haemodialysis. J&J licensed epoetin alfa from Amgen for most markets outside the USA and non-dialysis markets in the USA. Roche's NeoRecormon (epoetin-beta) is available in most European markets.



Source: IMS

Figure 1: Market share by brand for erythropoietin - \$13 billion global sales in 12 months to June 2006

In 2001, Amgen launched Aranesp (darbepoetin alfa), which differs from recombinant human erythropoietin by containing two additional sugar (oligosaccharide) chains attached to the amino acid backbone than recombinant human erythropoietin. These additional chains increase the molecular weight, which, in turn, changes the pharmacokinetics (absorption, distribution, metabolism and excretion). This allows clinicians to give Aranesp once every 2 to 3 weeks, compared to weekly dosing for Procrit. (As mentioned above, this example also underscores the sensitivity of proteins to relatively subtle changes in their structure.)

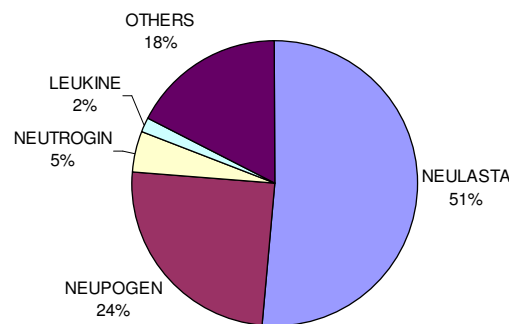
Over recent years, Epogen and Procrit have lost substantial global market share to Aranesp, the patent of which does not expire until 2014 in most territories. However, few patients switch from Epogen or Procrit to Aranesp – the more convenient dosing is not a significant differentiating factor for patients on the agent. However, it seems to influence the initial choice of treatment. Some companies have second-generation erythropoietin in early-stage development, but Amgen is likely to challenge the patents. Indeed, analysts Morgan Stanley described Aranesp as “the second best monopoly of our generation” after Microsoft’s Windows .

Despite strong competition, several companies are considering marketing biosimilar first generation erythropoietin biosimilars. In July 2006, Stada submitted the first application for a biosimilar erythropoietin (erythropoietin-zeta) to the EMEA, for oncology and dialysis indications. Stada believes the product could gain approval in 2007 and be on the market by the beginning of 2008. (Unlike other generic markets, the name given to a biosimilar may differ from the originator: epoetin alfa and erythropoietin-zeta. This potentially hinders generic substitution and prescribing.)

Granulocyte-colony stimulating factor (G-CSF)

Granulocyte-colony stimulating factor (G-CSF) stimulates production of white blood cells (eosinophils, neutrophils and basophils). Cancer chemotherapy can suppress production of these white blood cells (neutropenia), leaving patients vulnerable to potentially life-threatening infections and sepsis. G-CSF stimulates production of these immune cells, thereby reducing the risk of life-threatening complications.

Until recently, Amgen's Neupogen dominated the G-CSF market. However, a second-generation product from the same manufacturer, Neulasta (pegfilgrastim), cannibalised Neupogen's sales (see figure 2). According to IMS data, the conversion of Neupogen to Neulasta in Europe had reached 59% by early 2006.



Source: IMS

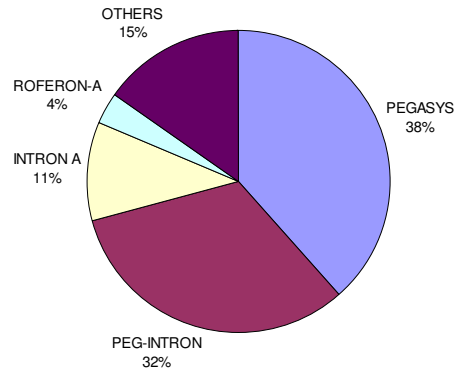
Figure 2: Market share by brand for Granulocyte-colony stimulating factor (G-CSF) - \$5.6 billion global sales in 12 months to June 2006

Developing biosimilar G-CSF is technically relatively simple, with few safety concerns and straightforward marketing. Nevertheless, Neulasta offers a tough competitor – once-weekly dosing fits better with most chemotherapy schedules than the daily dosing required with Neupogen. Furthermore, the pricing pressure among biosimilars is likely to be high, which will erode margins. Therefore, while G-CSF seems to be an obvious biosimilar candidate, the high level of competition

means that the already small market opportunity for first-generation products in the EU will rapidly decline.

Interferon alpha

Interferon alpha is used to manage several conditions including renal cell carcinoma, malignant melanoma, multiple myeloma and some leukaemias as well as patients chronically infected with hepatitis B or C virus. Sales of standard interferons are declining fast, attaining just \$330m in the 12 months to June 2006. Pegylated interferons now dominate the market (see figure 3).



Source: IMS

Figure 3: Market share by brand for Interferon alpha - \$2.3 billion global sales in 12 months to June 2006

Pegylation adds a large water-soluble chemical (polyethylene glycol – PEG) to the amino acid backbone. This hinders excretion by the body and, therefore, increases the elimination half-time. In other words, the drug remains in the body and at therapeutic levels for longer. As a result, patients need treatment with pegylated interferons less often than is the case with the first generation form. This less frequent treatment regimen substantially lowers the cost, which erodes any potential price advantage associated with biosimilar interferon alpha.

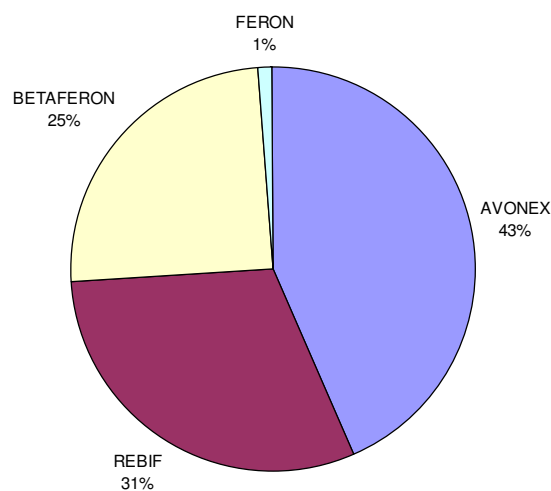
Several companies are developing biosimilar interferon alpha. However, GeneMedix deprioritized interferon development to concentrate on developing biosimilar epoetin. Furthermore, EMEA gave BioPartners' Alpheon, a recombinant standard interferon alpha, a negative opinion for chronic HCV infection, following concerns over quality, safety and efficacy. Many of the other potential biosimilar manufacturers are based in India and China, and it remains to be seen whether any of these products can be commercialised in the EU or USA. Against this background, a second-generation pegylated interferon alpha appears to offer a better commercial opportunity than the first generation product. However, full clinical trials will probably be required for approval of a second-generation interferon alpha.

Interferon beta

Interferon beta (there are two forms designated 1-a and 1-b) decreases the number of symptomatic episodes and slows the development of disability in patients with relapsing-remitting multiple sclerosis (MS). Schering AG's Betaferon (interferon beta-1b) was the initial product launched for MS. Biosimilar companies could develop novel non-infringing production processes for Betaferon relatively easily, by using microbial vectors instead of cell culture. As a result,

Betaferon will face loss of market exclusivity before 2010, although the patent position of all interferon betas tends to be complex.

Furthermore, the interferon beta 1-a brands Avonex and Rebif offer more convenient dosing schedules and have taken market share from Betaferon. Avonex is available in both a pre-filled syringe formulation as well as a dry powder form. Serono has launched auto-injection devices, most recently Rebiject II. This suggests that commercial success is likely to depend on developing competitive user-friendly delivery mechanisms as much as price. The importance of the delivery device is another characteristic of the biosimilars market that sets it apart from conventional generics.



Source: IMS

Figure 4: Market share by brand for Interferon beta - \$3.7 billion global sales in 12 months to June 2006

The reintroduction of Tysabri (natalizumab) complicates the market further. The FDA originally approved Tysabri in November 2004. The manufacturer, Biogen-Idec, withdrew Tysabri in February 2005 after three patients enrolled in clinical trials developed progressive multifocal leukoencephalopathy (PML), a serious viral CNS infection. In June 2006, the FDA re-approved marketing of Tysabri with a special restricted distribution program.^{iv} There are also potential oral treatments for MS in development, including Serono's Mylinax (cladribine) and Novartis' fingolimod (FTY720). As current medications are injected, oral formulations could radically alter the market.

Nevertheless, Betaferon presents a promising opportunity for biosimilars: it will probably lose market exclusivity before 2010; sales are almost \$1 billion; and the biopharmaceutical has a

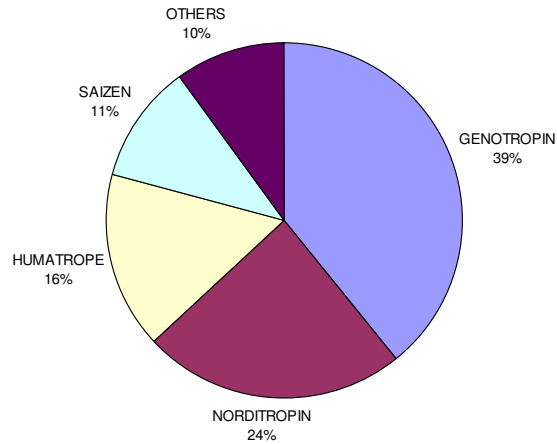
stronger position in Europe than the USA. Biopartners expects to submit a market authorization application to EMEA for its interferon beta in the first quarter of 2007.

Human growth hormone

The pituitary gland secretes endogenous human growth hormone (hGH), which promotes growth during childhood and adolescence. The recombinant form (somatropin; somatrophin) offers an effective treatment for growth failure, growth hormone deficiency, short bowel syndrome and HIV-related weight loss or wasting.

The hGH market differs from that for other biopharmaceuticals in several ways:

- Somatropin is a relatively simple and well-characterised molecule that is associated with few safety issues. As a result, physicians may accept generic somatropin more readily than some other biosimilars.
- Unlike several other biosimilar markets, there are no second-generation hGH.
- Sales of most biopharmaceuticals are markedly higher in the USA than the rest of the world. However, Europe and Japan account for 39% and 21% of global sales of hGH.
- Numerous somatropin products are already on the market (at least seven in the USA and nine in the EU). In the US, Genotropin has by far the largest market share. In the EU, Genotropin holds the biggest market share but Norditropin, Humatrope and Saizen (see figure 5) also have substantial shares.
- Manufacturers have developed several user-friendly injection devices, such as needle-free devices and auto-injectors, for use with somatropin, which further differentiates the market. Again, commercial success is likely to depend on developing competitive user-friendly delivery mechanisms as much as price.

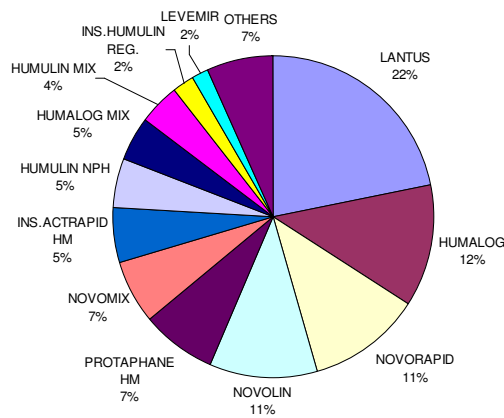


Source: IMS

Figure 5: market share by brand for Human growth hormone - \$1.9 billion global sales in 12 months to June 2006

Recombinant human insulin

The market for recombinant human insulin (Figure 6.) is heavily fragmented. For example, as well as insulin with variable durations of action, the industry markets 'mixtures' containing several products. These are designed to have a physiological profile that more accurately reflects endogenous basal and post-prandial blood sugar responses.



Source: IMS

Figure 6: Market share by brand for recombinant human insulin - \$8 billion global sales in 12 months to June 2006

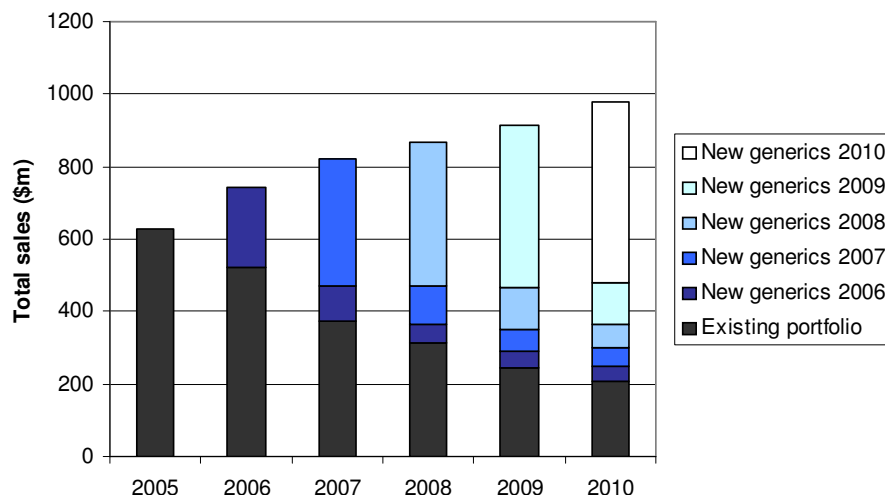
The domination of three companies (Eli Lilly, Sanofi-Aventis and Novo Nordisk) keeps prices relatively high. Furthermore, insulin analogs are patent-protected to 2013 and beyond in most

markets. These analogs are eroding the market for standard insulin, particularly in the USA. However, analogs have had a less marked effect on the EU market, which is likely to be the most important biosimilar market at least in the short- to medium-term. Nevertheless, insulin analogs still pose a barrier for standard insulin biosimilars.

Once again, most companies invest heavily in delivery devices to aid differentiation. This will complicate the development of biosimilars. On the other hand, the need for innovative devices should keep competition low, and prices high. Inhaled insulin (e.g., Exubera) could move the rapid onset of action section of the market away from standard insulin. However, reimbursement of inhaled insulin is an issue in some countries.

Which country markets offer the best opportunity for biosimilars?

To make the most of these opportunities, generic companies will have to change their business model. The current model depends on regular product launches to maintain growth. Severe price competition, which reduces sales significantly after the first year on the market, constantly erodes the product portfolio (see Figure 7). Analysts SG Cowen estimate, for example, that Teva is expected to book \$350m of generic simvastatin sales in 2006. This will fall to \$105m in 2007 and \$40m in 2010. However, there are not enough possible biosimilars for a company to rely on these alone to launch a new product every year. Therefore, stand-alone biosimilars companies will find life very difficult. The economics of the generics markets and the issues specific to biosimilars suggest that larger players are likely to be those that will succeed in the sector.



Source: PwC analysis

Figure 7: Revenue trend for typical generics company

In the short- to medium-term, biosimilar players will need to have a presence in the EU. The USA has a much larger potential addressable market than that in Europe in almost all product classes. However, there is unlikely to be a regulatory pathway for most biosimilars in the USA until after 2010.

Even once the pathway is in place, the risk of failure to enter may be considerable and unpredictable. The commercial decision about which products to develop will depend, in the first instance, on what level of sales a biosimilar can generate in Europe, although the EU, despite European Commission regulation, is not yet homogenous. For instance:

- Germany has a very well developed generics market, high prices and high biopharmaceuticals usage. Germany is, therefore, probably the most attractive European market for biosimilars.
- The UK, on the other hand, also has a well-developed generics market and high prices. However, the lower use of biopharmaceuticals makes it a much less attractive market.

Germany

Currently, German doctors write around half of their prescriptions generically, although the government has a target of 70%. Germany's reference pricing system, which removes the incentive to reduce prices, and a dearth of physician incentives to contain costs make the German generics market second only to the USA in terms of value. Indeed, Germany is a relatively high price market even for generics. According to BKK Bundesverband, one of the organisations that fund German health care, the generic discount is just 20-25% compared to the branded product following patent expiry.

The branded generic market is strong in Germany and most generics players already promote to physicians. This is a key advantage for generics firms already in the German market: promotion and detailing is expected to be crucial to success in the biosimilars market. In summary, high biologicals use, high prices, high growth and widespread acceptance of generics make Germany a very attractive market for biosimilars.

United Kingdom

The generic culture is probably stronger in the UK than in any other EU country. Four years after launch, generics attain an average penetration of 55%; compared to 45% in Germany and 35% in the Netherlands. Nevertheless, the UK imposes considerable downward pressure on prices and the value of generic sales declined in 2005. On the one hand, the cost pressures and a well-developed existing generics market mean that the UK is likely to be a fast-adopter of biosimilars. On the other hand, relatively low usage of biologicals reduces the UK's attractiveness as a biosimilars market.

France

Traditionally, generics do not account for a significant proportion of the French pharmaceutical market. However, government policies to reduce the healthcare budget deficit provided new impetus to the generic sector in the last few years. Nevertheless, the government has introduced few incentives to encourage generic prescribing. The main impetus has come from pharmacy substitution, driven by higher margins obtained on generic products and discounting by manufacturers. Generics entering the market from 2006 onwards must be priced 50% below the original brand price. This makes the French generics market less lucrative than that in, for example, Germany. In summary, companies considering entering the French market need to balance the high biologicals use and high generic market growth, against low prices and low acceptance of generics.

Italy

Brands dominate the Italian market and the generics market is poorly developed. Despite the absence of strong pro-generic policies and negative attitudes to generics among doctors, (branded generics helped boost generics' share of the Italian market in recent years. Furthermore, the Italian medicines agency, AIFA, embarked on an information campaign that aims to increase generics' share of the market to 20% by 2008. In summary, the Italian market is characterised by high use of biologicals, rapid uptake of new products, acceptance of branded generics and medium growth.

Spain

The legacy of counterfeit products and low medicine prices impeded the development of the Spanish generics market. Reference pricing, which erodes price differentials between off-patent brands and generic versions as well as the few incentives for doctors to prescribe generics or for pharmacists to dispense cheaper alternatives, undermine the market. Because of these factors, generic consumption in Spain remains among the lowest in the EU, although the Spanish market is characterised by high use of biologicals and a rapid uptake of new products.

United States

The USA is the world's most dynamic generics market. However, the US market is also one of the toughest, with strong competition exerting considerable pressure on margins. The lack of a regulatory pathway means a market for most biosimilars will not develop before 2010.

Developing new competencies

Obviously, companies need to balance the risks and rewards when considering whether to enter the biosimilars market. Unfortunately, much of the market represents unknown territory. The risks in the biosimilars market fall somewhere between those of standard generics and New Chemical Entities. Companies who wish to market biosimilars will require a different business model for traditional generics. Figure 8 shows the different skills that generic companies will need to build or acquire.

Setting up a new business model and transitioning to it is always fraught with implementation risks requires getting the right skills in place:

- Regulatory expertise to navigate the evolving regulatory pathways in Europe and in the US. The innate variation and the lack of established methods to determine bioequivalence mean that regulators are likely to be much stricter when considering an application for marketing approval of biosimilars than they are with conventional generics. As a result, regulators will require more extensive clinical testing for biosimilars than for conventional generics
- Product development and clinical trials expertise to demonstrate bioequivalence and develop new delivery devices. A biosimilar can add significant value and enhance product differentiation by using an improved delivery device. The method of delivery already differentiates products in the insulin and human growth hormone markets.
- Sales and marketing expertise to develop a brand without the backup of an INN (International Non-proprietary Names) that is used by prescribers and to compete effectively with strong market defence strategies from the branded players. Many leading generics players already have experience in marketing their products, especially in Germany. Those that do not already have this infrastructure will need to set up a sales team, either fully in-house, using a contract sales force or both. They could also partner with a bigger pharmaceutical or generic company. The choice may depend on the biosimilar. Most - e.g. erythropoietin and human growth hormone - are specialist drugs so sales forces can be relatively small. Promoting insulin, on the other hand, will require a huge marketing effort. Thus, PricewaterhouseCoopers expects to see increased partnering for R&D, manufacturing and sales and, therefore, increased supplier power. The manufacturer of the branded product is likely to use sophisticated defensive tactics - legal issues, doubts about bioequivalence, switching to second-generation products, authorised generics, patent withdrawal, aggressive pricing.
- Post-approval safety monitoring skills. Post-approval safety monitoring is expected to be compulsory, at least for the first few biosimilar products approved. European guidelines state that prescribers should specify the product (either using the INN or brand). This is, partly, in response to the innate variation in biopharmaceuticals noted above and, partly, to accrue

distinctive safety data. While the practicalities of setting up this post-approval monitoring are achievable, they represent a barrier to entry. As most biosimilars will have different INN to the originator, drugs cannot be prescribed generically or undergo generic substitution.

- A financial structure capable of making investments in manufacturing assets or securing third party manufacturers before the product is launched. For example, cell culture facilities (required to manufacture erythropoietin and interferon beta) require sizable capital and labour investment, taking, on average, three to five years to construct and costing \$250–\$450 million.

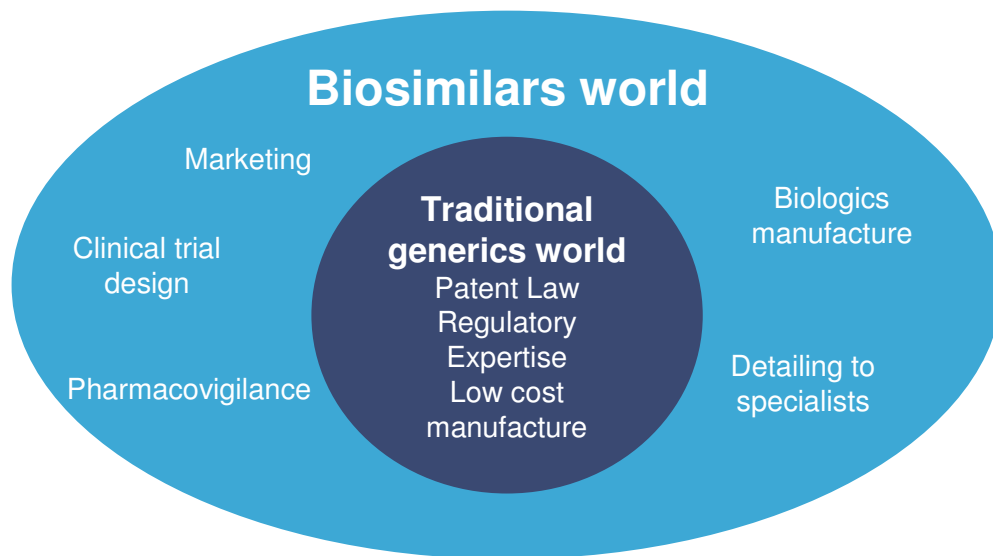


Figure 8: Core competencies that biosimilar companies need to survive

Summary

Biosimilars represent, potentially, an attractive market, although there are significant regulatory and commercial hurdles to overcome. Briefly, however, these include:

- The manufacturer of the branded product is likely to use sophisticated defensive tactics, including the development of complex biopharmaceuticals to maintain share.
- Several potential biosimilars face competition from second-generation products with more convenient administration schedules. In many cases, the same companies market the original and second-generation products.
- The required capital investment in property, plant, and equipment and the costs of manufacturing will be much higher for biosimilars than for generic drugs. Furthermore, materials used to manufacture biosimilars can cost up to 100 times more than those used for drugs.

- Post-approval safety monitoring is expected to be compulsory, at least for the first few biosimilar products approved.
- European guidelines state that prescribers should specify the International Nonproprietary Names (INN) or brand. This hinders generic prescribing and substitution.
- Brand development will be very important and direct marketing to small numbers of specialists is likely to be highly competitive.
- Physicians will be cautious about the relative safety and efficacy of biosimilars in the short term at least and so high promotional investment will be required. Companies without a sales infrastructure will need to set up a sales team, either fully in-house, using a contract sales force or both. They could also partner with a bigger pharmaceutical or generic company.
- Improved delivery devices can add significant value to a biosimilar and enhance product differentiation. There are, however, a finite number of drug delivery companies, many of which are already working exclusively with the branded incumbents.
- Sales of most biopharmaceuticals are markedly higher in the USA than the rest of the world. However, there is unlikely to be a regulatory pathway for most biosimilars in the USA until after 2010. The commercial decision about which products to develop will depend, in the first instance, on what level of sales a biosimilar can generate in Europe. However, the EU generic and biopharmaceutical markets are not yet homogenous.
- The biosimilar market will be characterised by price competition, even when there is only one or a very limited number of players for a given product. This will constrain the size of the commercial opportunity. A small price differential reduces the incentive to switch. The consensus seems to be that a 20-25% discount is optimum.
- Originator products' pricing strategies will have a huge influence on the uptake of biosimilars. Many brands have raised the price of first-generation products to encourage switching to their second-generation products. The introduction of biosimilars may increase the cost differential and increase the switch back to first generation products.

To make the most of these opportunities, generic companies will have to change their business model: there are not enough possible biosimilars for a company to rely on these alone to launch a new product every year. Initial success will probably result mainly from speed to market and successful marketing and promotional strategies. Only later, as biosimilars become more widely accepted, will lower-cost players begin to dominate.

In conclusion, companies likely to succeed in the biosimilar market need to have an appropriate marketing structure as well as the financial resources to develop the products and to accept higher upfront risks in development, commercialisation and capital investment, a major shift in skills for most generic players. This skills shift means that biosimilar players will need to evaluate their

strategic options and to adopt different business models and skill sets to conventional generics companies. This is new territory for most generic players and the likely commercial rewards of entering most biosimilars markets, in the short-term at least, will probably be small.

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