



Shaping the biosimilars opportunity: A global perspective on the evolving biosimilars landscape

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After several years in the slow lane, important changes are driving new momentum in the market for biosimilars, paving the way for their accelerated growth over the next decade and beyond. Although currently small and narrowly focused on a few disease areas and countries, the biosimilars opportunity is set to expand as patents expire on leading biologics, US legislation comes into effect, and payers push for their wider adoption to manage burgeoning costs.

The signs are there, but questions remain. How will the commercial prospects play out? Where is the greatest potential? And what will be the optimal go-to-market model for entrants? Analysis from IMS suggests that companies looking to take advantage of the evolving landscape will need carefully planned strategies, strong commitment and the resilience to overcome some formidable barriers, especially in the short-term, to maximize return on investment.

By 2015, sales of biosimilars are expected to reach between US\$1.9-2.6 billion, up from US\$378 million for the year to the first half of 2011. Potentially, this market could be the single fastest-growing biologics sector in the next five years – albeit from a small base – spurred by the convergence of major dynamics that will see new biosimilars enter the US market by 2014, bring additional molecules to Europe through 2015, and open up oncology and autoimmune disease areas to biosimilars for the first time ever.

Cost pressures key

The changing outlook for biosimilars comes at a time when the global pharmaceutical market is feeling the combined impact of two key events: a period of unprecedented patent expirations on many of the world's largest pharmaceutical brands, and a financial crisis that has required healthcare systems to make significant and sustained cost reductions.

For payers in the advanced markets, limited economic growth and pressures on healthcare make the patent cliff a true generic dividend, enabling much needed savings to be realized. However, as potential savings from generics start

to decline in these countries over the next 5-10 years while the imperative to reduce expenditure continues to grow, payers face an urgent need to find new ways of rationalizing resources. Biologics – among the most expensive pharmacotherapies available and now approaching their own swathe of patent expirations – potentially represent the most lucrative source of savings on drug expenditure for Western nations after 2015. Biosimilars may be the key that helps them to realize this opportunity.

Biosimilars also bring clear potential for payers in the emerging pharmaceutical or “pharmerging” markets, such as Brazil, India and China. Here, the need to broaden healthcare coverage to large populations increasingly must be balanced against limited budgets and growing demand for innovative drugs. Biosimilars offer one way of widening access and enabling better value to be obtained from the money spent on healthcare. In some cases (such as South Korea, India and Brazil) they are seen as a key macroeconomic driver of growth, attracting foreign capital by creating manufacturing and R&D centers of excellence. →

Whether the US opportunity is realized is the single most important differentiator between success and failure for biosimilars in the next decade.

Growing demand for biologics

The imperative to find cost-effective alternatives to biologics reflects the growing demand for these specialty drugs. Since their origins in the 1980s, biologics have prospered into a US\$138 billion market (2010), fuelled by such key launches as recombinant insulins, human growth hormone (HGH), alteplase, erythropoietins (EPOs), granulocyte colony stimulating factors (G-CSFs) and then monoclonal antibodies (MAbs), among others. Currently accounting for 16% of global pharmaceutical expenditure and significantly outpacing total branded sales, biologics will continue to out-perform the global market as more innovative products deliver new treatment options for a growing range of indications.

Patent expiries driving new potential

A number of top-selling biologic brands, including Herceptin, Enbrel, Humalog, MabThera, Remicade and Aranesp, are due to lose product patent protection over the next five years, opening up a wealth of new possibilities for biosimilars players. Key therapy areas such as cancer, diabetes and rheumatoid arthritis (RA) will spearhead this new wave of biosimilars, with attention focused on the real prizes of anti-TNF MAbs, MAbs for oncology, and insulins (Figure 1).

Diverse competitive landscape

A diversified competitive arena for biosimilars is already emerging, with generics manufacturers, R&D-based pharma, and biotech companies

poised to compete: Teva is approaching the end of Phase II trials for a biosimilar version of Roche's rituximab (MabThera/Rituxan);¹ Pfizer recently signed a deal with Biocon (India) to manufacture biosimilar insulins;² AstraZeneca and Eli Lilly have both signaled intentions in this area;³ Boehringer Ingelheim is creating a dedicated division for developing and commercializing its own biosimilars;⁴ and a Merck&Co deal with CRO Parexel is expected to yield five late-stage biosimilars by 2012⁵.

Plans to develop biosimilars are also being mooted by leading innovator biotech companies, including Biogen Idec and Amgen – which has particularly called-out emerging markets in South America and Asia.⁶ Interest in the sector has even extended beyond the realms of pharma: digital technology leader Fujifilm and electronics giant Samsung have both now joined the race, securing biosimilar deals with Merck and Quintiles respectively. Samsung is planning to pursue further biotech ventures in its effort to achieve target revenues of US\$1.8 billion from biopharmaceuticals by 2020⁷. The entry of these players may not necessarily herald similar actions from more companies in other industries, but it does bring a fresh inflow of cash to fund development programs and atypical branding models that have already paid off in other industries (Figure 2). The commitment is clearly there, but how and where will the promise be fulfilled?

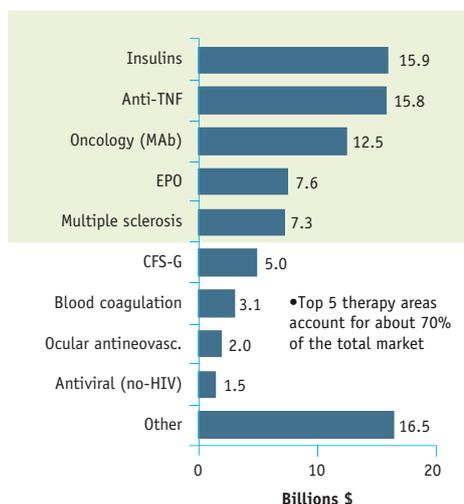
Defining the market

The biosimilars sector has reached very different stages of evolution around the world. Clarity of guidelines is variable and regulatory pathways diverse, leading to various definitions of biosimilars (or the broader group of follow-on biologics) across countries and regions. Europe has by far the best-established framework, with which the US is now more or less aligned. →

FIGURE 1: KEY AREAS SUCH AS CANCER, DIABETES AND RA WILL BE AT THE FOREFRONT OF THE NEW WAVE

Big PharmaCos, not only generics companies, are ready to compete

Core Therapy Areas for biologics (MAT 12/2010)



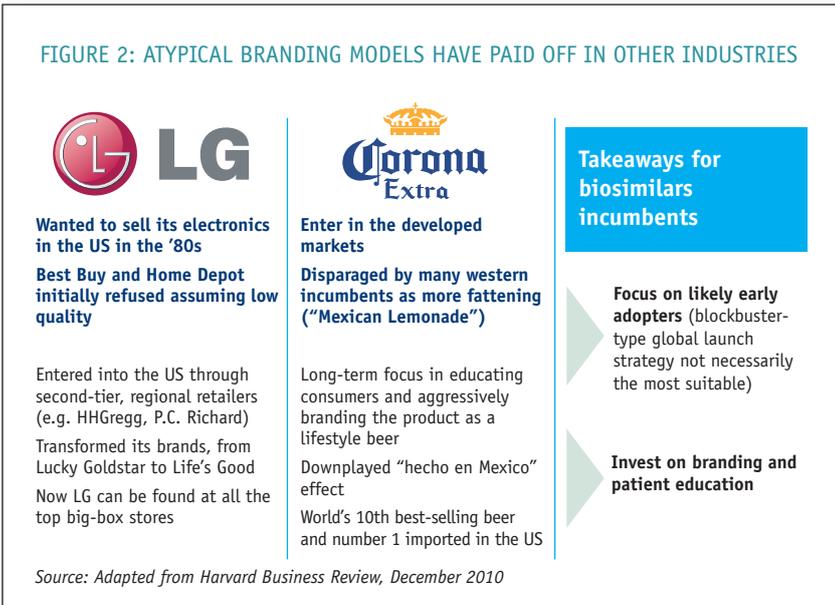
A diversified competitive arena is emerging

- Teva developing its first biosimilar version of rituximab (Mabthera/Rituxan)
- Pfizer recently signed a deal with Biocon (India) to manufacture biosimilar insulins
- Merck signed a deal with CRO Parexel to provide biosimilars to Merck BioVentures (5 late stage biosimilars are expected by 2012)
- Biogen Idec ready to enter the biosimilars arena as well ("the company is in the perfect position...biosimilars market as a low risk" Biogen's CEO Scangos)

Source: IMS Health

- 1 <http://www.tevapharm.com/en-US/Products/ProductsPipeline/Pages/default.aspx>
- 2 Pfizer to sell biosimilar insulins in Biocon deal. Accessed 3 Nov, 2011 at <http://in.reuters.com/article/2010/10/18/idINIndia-52267720101018>
- 3 Astra Zeneca eyes move into biosimilars. Accessed 11 Nov, 2011 at <http://www.ft.com/cms/s/0/9740a42e-d064-11dd-ae00-000077b07658.html#axzz1dO1hLirT>
- 4 Boehringer Ingelheim expands its business with biosimilars. Accessed 2 Nov, 2011 at http://www.boehringer-ingelheim.co.uk/news/press_release-Boehringer-Ingelheim-expands-its-Business-with-Biosimilars.html
- 5 Merck & Co in deal with Parexel to develop biosimilars. Accessed 3 Nov, 2011 at http://www.firstwordplus.com/Fws.do?src=corp_site&articleid=411CA68F1931475B92F0A475730DE0CA
- 6 Copying biotech medicine attracts more drugmakers. Accessed 3 Nov, 2011 at <http://uk.reuters.com/article/2011/01/13/healthcare-biosimilars-idUKN1313681520110113?rpc=401&feedType=RSS&feedName=governmentFilingsNews>
- 7 High-tech companies buy into biomanufacturing. Accessed 10 Nov, 2011 <http://www.genengnews.com/analysis-and-insight/high-tech-companies-buy-into-biomanufacturing/77899375/>

FIGURE 2: ATYPICAL BRANDING MODELS HAVE PAID OFF IN OTHER INDUSTRIES



Outside these markets, definitions of agents and pathways to approval are less precise. It is clear that follow-on or modified biologics already exist in China and India as well as in other countries. Some of these agents would fit the definition of existing biosimilars well; many are essentially copy versions of patented agents; others fail to meet either categorization, yet clearly are not original. For instance, Reditux, a copy of rituximab manufactured by Dr Reddy's, has been available in India since 2007, but its approval has been based on a smaller body of evidence than is likely to be required in Europe or the US.

To enable consistent analysis across geographies, therapies and manufacturers, IMS has established an industry-verified standard market definition for the biosimilars sector. This classifies biosimilars (also known as follow on biologics in

the US and subsequent entry biologics in Canada) as biologic products approved in a country which has an abbreviated approval process for biologic products that references an originator biologic in the regulatory submission. Products marketed in countries without a biosimilar approval pathway and for which the originator has not granted a license are not considered true biosimilars.

A tale of three geographies

Geographically, the market for biologics and biosimilars falls into three distinct clusters: the US, the other advanced economies (Europe, Japan and Canada) and the pharmerging markets (Figure 3). The US accounts for most of the global spending on biologics and will be a key driver of long-term biosimilars market potential. The advanced economies have the advantage of an established framework for biosimilars but to date uptake has been slow; Europe is the most progressive. Some of the highest growth rates for biologics are currently seen in the pharmerging markets, where biosimilars already exist (albeit through a looser regulatory pathway) and where much of the immediate growth will be found. In Japan, biosimilars guidelines have been recently established and follow the principles of the EU Framework; biosimilar epoietin alfa has taken over a quarter of the market by volume in a period of 12 months, but somatropin has done less well.

US: The big opportunity

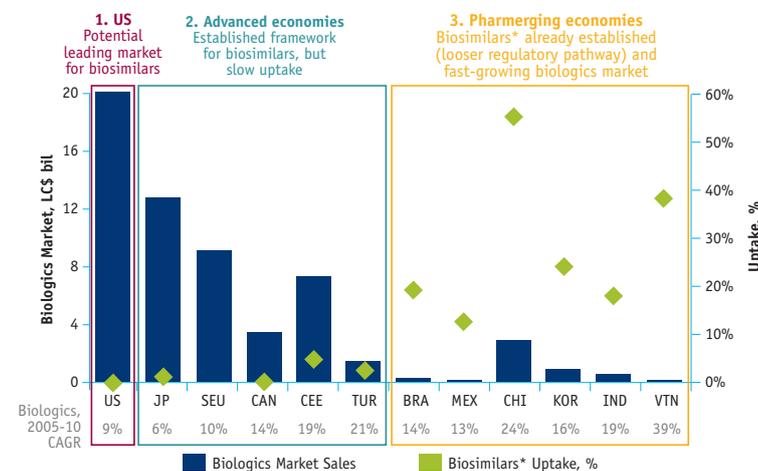
Devoid of a specific regulatory pathway, the US currently has no established industry for biosimilars. At present, there is only one product on the market that could potentially fit this description – Omnitrope (somatropin/HGH) which was launched by Sandoz in 2007 under a special ruling. However, all this is set to change in 2014 when the country's new framework for biosimilars, set out by The Patient Protection and Affordable Care Act of March 2010, comes into effect. With leading manufacturers including Pfizer and Merck already positioned to compete, and patients and health insurers stepping up the pressure for access to low-cost, high-value drugs, the US is forecast to be the single biggest opportunity for biosimilars by 2020. Whether this opportunity is realized is therefore the most important differentiator between success and failure for biosimilars in the next decade.

UNDERSTANDING THE ISSUES

The future market for biosimilars in the US will be shaped by a number of factors, not least the reaction of managed care and the play-out of pricing dynamics. While many of the uncertainties remain to be categorized, experience from analogous situations offers important pointers.

FIGURE 3: THREE GEOGRAPHICAL CLUSTERS ARISE, WITH US REPRESENTING A SIGNIFICANT PORTION OF MARKET POTENTIAL (~60%)

Pharmerging economies anticipated to be a potential growth driver



Source: IMS Health MIDAS, 2005-2010

* Biosimilars in Europe and Japan defined by regulatory pathway, in pharmerging markets looser approval processes apply for products that resemble biosimilars

Among the most interesting analogs for biosimilars in the US are the heavily contracted, narrow provider populations around erythropoietins and the G-CSFs where the influence of managed care is strong and payers have considerable sway over contracting and the defined treatment paradigm for a disease.

This set-up closely parallels, and is likely to mirror, the institutional contracting environment in Germany (the most advanced biosimilars market) where a very limited group of doctors administer erythropoietins in a small number of centers.

1 Price: For originator companies, one of the key challenges is to anticipate the way in which biosimilars will act on price. Heavy price discounting in the institutional sector provides a strong incentive for biosimilars to target a list price that is very close to the originator's and subsequently gain their advantage through contracts.

2 Established experience: In classes such as EPOs and G-CSFs, where there is general acceptance of high similarity between biosimilars and original brands, and established experience of their use in Europe, the technical bar is likely to be cleared relatively smoothly. Likewise, if there is a hospital network or relatively limited number of clinic/treatment centers, usage decisions will be faster.

By contrast, biosimilars targeting autoimmune diseases are likely to meet reticence in switching patients unless and until they fail on current treatment. Without a significant financial or co-pay advantage, there is likely to be little interest from managed care in starting new patients on these medicines – at least until the safety and substitutability of the biosimilars are demonstrated.

3 Duration of therapy: The nature of drug use will be also be a key consideration for the adoption of biosimilars in the US: those intended for chronic conditions such as RA and psoriasis, for example, may face particular scrutiny by payers in considering the impact of potential financial exposure to possibly lifelong therapy. Conversely, if the use of biosimilars were to enable significant savings in these areas, payers may be more favorably inclined towards them – provided of course that safety and efficacy are demonstrated. Much could depend on the relative influence of the prescribing physicians and the degree to which patients express a preference for a lower-cost therapy.

4 Familiarity and trust: Doctors are already familiar with the concept and cost benefits of initiating treatment with generic versions of non-biologic agents in such conditions as RA,

but they will need to trust and believe that biosimilars are an effective, safe and cheaper option to follow suit with biologics. Given that these biologics remain on the Tier 4 formulary level with 30% patient co-pay, this is likely to be a slow build.

5 Uncertainties: For US patients and payers, the key issues around biosimilars are the uncertainties. In large patient and provider populations, the level of co-pay will be crucial: unless they are significantly lower there will be little incentive for use. The possibility of moving biosimilars to a separate formulary tier is an option, but one that is likely to be heavily dependent on a stronger perception of safety around MABs. In the event that a track record of success is established in Europe before market entry in the US, and some form of medical consensus is reached on switching patients to biosimilars, this may change. The real key for biosimilar manufacturers within this broader provider community is that it will take longer to convince individual doctors one-by-one, versus contracting.

There is also the potential in the US for greater biologic volume arising from the use of biosimilars – a phenomenon which has already been observed in Europe (see Figure 6, page 7). This could put at risk systemic “savings” with higher utilization, particularly if price discounting for biosimilars is only in the region of 20-30%.

6 Patient role: Increasing co-pays and the growing role of patients in treatment decisions will also be important for biosimilars: manufacturers may choose to differentiate their products through the use of patient assistance programs (PAPs) setting their list price at a similar level to the originator brand and offering co-pay assistance to the patient through social networking, thus bringing them into play into the decision making process.

SIGNIFICANT POTENTIAL – OVER TIME

Notwithstanding the significant potential for biosimilars in the US, their establishment in this market will be a slow process: stringent clinical requirements and an involved, potentially drawn-out procedure for resolving patent disputes are likely to delay the speed of uptake in the near future: behind every product patent there are several potential lines of defense for originator companies, including process patents, which may slow the entry of biosimilar versions when new markets open. Given the highly technical issues involved and lack of legal precedent to date, predictions are difficult to make and questions remain as to whether biosimilar versions of the more complex biologics (MABs) will reach the US market before 2015. →

It will also take time for the FDA and payers to build a learning curve on biosimilars and for physicians to overcome their concerns over safety and preferentially adopt these products: they will have to believe in the ability to technically, safely and consistently reproduce these molecules. The financial motivation for both payers and patients will also be crucial. However, even if technology regulatory barriers do hinder biosimilars take-off in the US until 2015, the financial incentives - for both public and private stakeholders - will ultimately drive uptake long-term, with the entry of leading US companies fostering credibility of the sector.

Europe: The first market

The EU presents the most advanced market for biosimilars, accounting for 80% of global spending on these molecules. However, despite a strong legislative foundation, to date only a few manufacturers have launched biosimilars in the region. These include a mixture of existing generics houses, the generics arms of major companies and new ventures, most notably Sandoz/Novartis, Stada, Hospira, Medice and Ratiopharma (Teva). Biosimilars are established in three therapy areas in Europe: EPOs for treating anemia caused by renal dialysis, G-CSFs for lowered white blood cell counts after chemotherapy, and HGH.

VARIED PENETRATION

The penetration of biosimilars varies by country, reflecting local pricing and reimbursement policies, stakeholder influence, and attitudes towards their adoption and use. Currently, Germany and France account for half the

biosimilars market by value in the region with a 34% and 17% share respectively across Europe, although uptake in Spain and the UK has started to increase.

Across markets, G-CSFs have generally achieved the highest penetration by value and HGH the lowest (25% and 4% class uptake respectively). The lower penetration of HGH has been largely driven by the greater element of patient choice and discrimination over devices and convenience. Original brand Genotropin, for example, is available in a form which does not require refrigeration, whereas this is a prerequisite for the biosimilar version. Cautious prescribing has also played a role, with physicians hesitant to use biosimilar HGH given the time it takes to show an effect: with G-CSFs, the impact of treatment is more readily apparent, enabling physicians to change course in a faster timeframe if required. In the case of EPOs, uptake is more driven by payer than patient concerns, given the lack of any discernible difference in the patient experience as a result of switching to a biosimilar.

Uptake also varies across countries when therapy areas are considered according to type (Figure 4), being significantly lower in differentiated markets where the stakeholder landscape is extremely complex, the value proposition is high and the market is driven by price (eg, somatropin) versus commodity markets where access is mostly controlled by payers and the product has limited intrinsic value (eg, G-CSF and the epoietins).

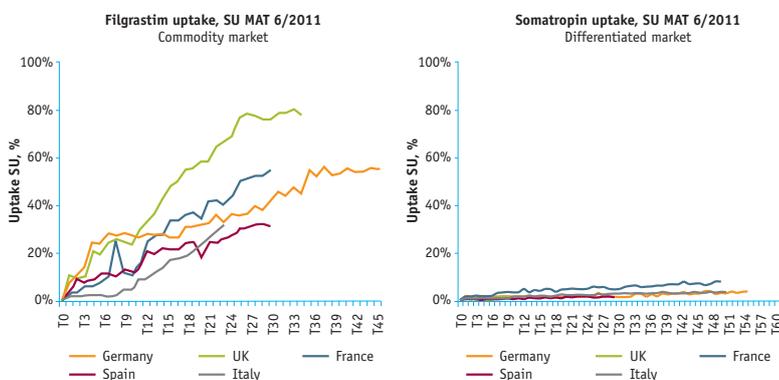
LIMITED SUCCESS

VERSUS SMALL MOLECULE GENERICS

To date, the first wave of biosimilars has met with limited success if compared to the uptake of small molecule generics. This can be partly explained by limited price reductions: average list (ex-manufacturer) price cuts in the region of 30% are considerably below those for generics which are typically around 70%-80%. However, the pattern is one of inconsistent uptake: while some countries in Europe with powerful payers and robust generics markets, such as Germany, have seen strong penetration, others such as the UK, which are also highly focused on generics and have strong payers, have seen low penetrations. Other countries with apparently high sales of biosimilars such as Greece are, in fact, most likely simply source countries for the burgeoning German market. →

FIGURE 4: OVERALL WE CAN IDENTIFY TWO UPTAKE PATTERNS FOR BIOSIMILARS, DIFFERENTIATED VS. COMMODITY

Differentiated markets will pose several challenges to biosimilars



Source: IMS Health

FUTURE EVOLUTION

The learning curve for biosimilars is essentially still building in Europe and the high clinical requirements of the new MAbs and anti-TNFs will present further hurdles ahead. In the meantime, small molecule generics continue to represent the main source of cost savings in the region. However, the clarity of EU regulation and the need for further cost-containment action in the unfavorable economic climate are likely to ease the uptake of biosimilars going forward, as payers become more familiar with their use, tendering processes are established and late-adopting markets such as Italy and Spain follow the leading countries.

Pharmerging economies: On a fast track

Most of the pharmerging markets, including China, India, Brazil and Mexico, have developed their own regulatory pathway to manage the approval of biosimilars. While often drawing on the European framework, these generally set a lower barrier in terms of clinical trial requirements and regulatory control. This enables local manufacturers to enter the pharmerging markets on a more level playing field, but it also potentially provides a lower cost entry point for international players. Such a looser structure has already fuelled the launch of modified biologics within the oncology and EPO markets in key countries such as China.

Going forward, government initiatives are anticipated to boost the biosimilars market in

south-east Asian countries, principally as a means of sustaining their domestic industry. Within the concentrations of biopharmaceutical manufacturing globally, bio-clusters are already emerging in this region, some of them matching the quality standards of advanced economies. South Korea in particular, with plans to become a leading biosimilars player, is actively expanding its world-class clinical trials and production infrastructure, cultivating bio-specialized manpower, reinforcing global export capability, building R&D, legal and system support strategies.

Although the biologics market is still at an early stage in the pharmerging economies it is expanding fast and biosimilars will play a key role in its future growth. However, the unique nature of these countries may see a market that evolves over time in an entirely different fashion. Whether European and US manufacturers of biosimilars will be able to enter more easily or find themselves locked out by local competition is currently an open question.

2020 outlook

Within the three main geographic clusters, a number of differentiating factors will impact the value generation opportunity for biosimilars, including ease of access in the short term, speed of uptake, clarity of regulation and, particularly, the role of public and private stakeholders.

Accordingly, most of the immediate value will be sourced from the pharmerging markets, spurred by the anticipated flow of new patients. However, in the long-run, the US will be the cornerstone of the global biosimilars market, powering a sector worth between US\$11 billion and US\$ 25 billion in 2020 (Figure 5) representing a 4% and 10% share respectively of the total biologics market. The overall penetration of biosimilars within the off-patent biological market is forecast to reach up to 50% by 2020, assuming a price discount in the range of 20-30% (or 40-50% with tender discounts included).

Underlying this forecast are six core drivers with the potential to spur or curb future growth of the biosimilars market: the US uptake, the spread of biosimilars in pharmerging markets, the continued pattern of evolution in Europe, technology and the second wave of biosimilars, volume effect and the competitive landscape. →

FIGURE 5: US WILL REPRESENT THE CORNERSTONE OF THE BIOSIMILARS MARKET IN THE LONG RUN, WITH AN UPSIDE POTENTIAL OF UP TO 25 BIL US\$ IN 2020

Biosimilars not a short-term game

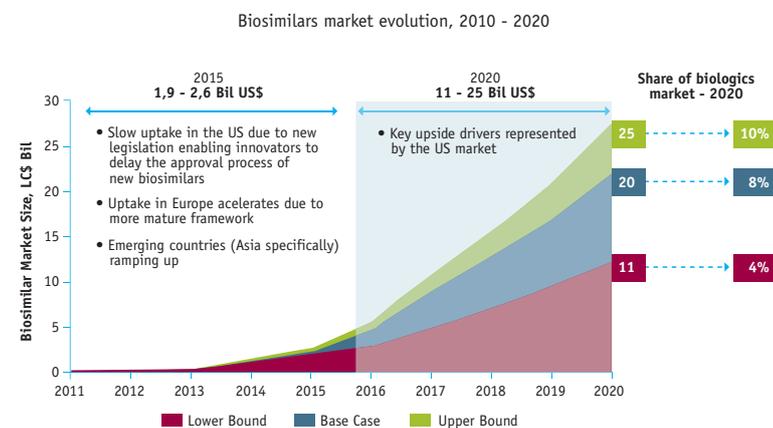
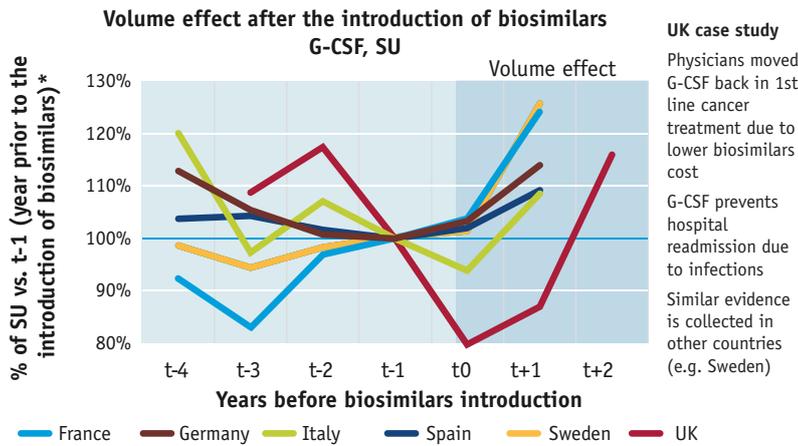


FIGURE 6: AS SHOWN BY G-CSF, THE INTRODUCTION OF BIOSIMILARS CAN GENERATE A SPILL-OVER EFFECT ON OFF-PATENT BIOLOGIC MOLECULES
Opportunity for biosimilars players only or also for innovators?



Source: IMS MIDAS, MAT Q4 2010, NHS. *t-1 =100%, t0 = year of biosimilars introduction

Source: IMS Health

1 US uptake: The core upside driver of biosimilars value in 2020 is uptake in the US long-term (2014-15), unlocking market potential and economies of scale. Any limitations on this, for example due to regulations favoring innovator companies, will drive down the likelihood of significant growth.

2 Pharmedging markets: Growth is also dependent on the pharmedging countries becoming a key biosimilars player in terms of both manufacturing and market size. The more moderate spread of biosimilars in developing markets and any shortfall in quality standards that prevents these countries from materializing as leading exporters could impact overall potential.

3 Europe: Late-adopting major EU markets such as Spain and Italy will need to follow Germany in terms of biosimilars uptake to maximize prospects for growth; it is possible that physician and payer resistance may impede this, negatively impacting the 2020 outlook.

4 Technology: If the US is the key driver of upside potential, the higher complexity of future biosimilar targets may be the barrier that hinders future growth. Technical hurdles, particularly devices in the case of anti-TNFs, will be a challenge for manufacturers and one that may not be overcome by several companies at once. These issues could prevent biosimilars tapping into all therapy areas where biologics are off-patent, curtailing the number of successful launches across therapy areas.

5 Volume effect: There is potential for a significant volume effect on biologics consumption, as observed with G-CSF in the UK

and Sweden (see Case in Practice: G-CSF - Figure 6). This could drive up biosimilars market growth considerably or equally constrain it should uptake be insufficient to generate a spill-over incentive.

6 Competitive landscape: The forecast assumes that major markets will drive positive financial returns and biosimilars growth, enabling a good degree of competition. Should financial barriers and poor uptake in major markets yield a limited number of competitors, growth prospects will be similarly reduced.

Against this background, how will the competitive landscape for biosimilars evolve going forward?

Stakeholder moves

To date, one of the main challenges for biosimilars has been the reluctance of payers, prescribers and patients to accept these products in place of the original brands. Going forward, the reaction of these stakeholders and the chosen strategies of aspiring players, and particularly innovators, will be key to their speed of uptake:

- **Payers:** As yet, biosimilars have not been a key priority for payers and there has been little, if any, top-down pressure urging a move to extensive biosimilar prescribing. Limited price discounts, sophisticated products and lack of familiarity with their use has perhaps made the decision less clear cut than for small molecule generics. Going forward, however, this is likely to change as biosimilars move into the higher cost areas of oncology and autoimmune diseases and efforts to rationalize healthcare intensify. Emphasis will be placed on the strongest assurances of clinical safety and efficacy.
- **Patients:** Increasingly vocal in their treatment decisions, patients are also becoming more focused on broader and affordable access to treatment. However, it is likely that they will be heavily influenced by physician guidance on administration of biosimilars and they may not even be aware whether they are being treated with a biosimilar or an originator product.
- **Physicians:** Lack of experience with biosimilars and the newness of the regulatory pathway have led to a natural conservatism in prescribing approach among many physicians. The learning curve has yet to be built and overcoming safety and efficacy concerns will be paramount to their acceptance of biosimilars. Usage will vary by therapy area but it is likely to be contained to small groups of new patients initially, with close monitoring of outcomes before considering more widespread use. →

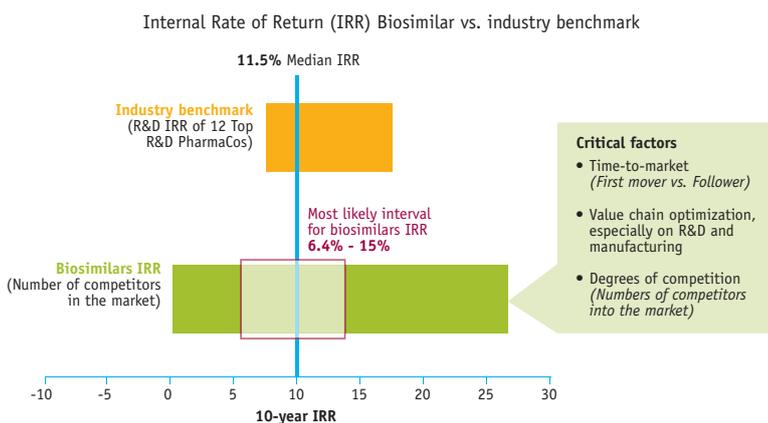
- **Aspiring players:** With significant capital invested in biosimilars, the entry of branded players bringing R&D capabilities, and biosimilars addressing multiple areas of the strategic agenda, would-be entrants are clearly key to the sector's success going forward.
- **Originators:** The lifecycle management strategies of the originator companies have an important role to play in driving volume expansion, with the power to limit uptake opportunities in advanced economies whilst growing penetration in pharmerging markets. To date, many originators have chosen to develop biobetters or functionally enhanced biologics, such as pegylated, long-acting formulations, and have sought to establish these newer versions as the standard of care. This has met with some success in certain areas – most notably with Amgen's launch of Aranesp and Neulasta, second generation versions of Epogen and Neupogen respectively. More sustainably, originators have established extremely strong relationships with prescribers, KOLs and patients, based on services, clinical development and investment, which biosimilars may struggle to replicate. Patent disputes, especially in the US, where the legislation requires disclosure of patent information by the biosimilar manufacturer, may also delay or prevent the entry of some biosimilars.

Challenging arena

For new entrants, biosimilars pose very different challenges to those presented by small molecule generics, with more demanding requirements in terms of clinical development, market access, manufacturing and sales and marketing capabilities:

- **High development costs:** Developing a biosimilar is not a simple process but one that requires significant investment, technical capability and clinical trial expertise. Average cost estimates range from US\$100-250 million (various industry sources) if plant development is included (or US\$20-100 million for non-plant cost). Whilst lower than the costs of developing a small molecule NCE, they are nevertheless orders of magnitude higher than the costs associated with developing traditional generics, which are typically around US\$1-4 million.
- **Fledgling regulatory framework:** In most markets apart from Europe, the regulatory framework for biosimilars is generally still very new compared to the well-established approval process for NCEs and small-molecule generics; in some cases it is non-existent, making global investments risky.
- **Manufacturing issues:** Barriers to developing a biosimilars manufacturing capability are not prohibitive, but the development of biosimilars involves sophisticated technologies and processes, raising the risk of the investment. In the near term, entrants face limited benefits of scale, relative to incumbents, and in specific areas such as insulins, strict requirements for compatibility with existing devices will apply.
- **Branded mentality:** Winning the trust of stakeholders will call for many of the skills, resources and branded mentality of a conventional innovative pharmaceutical company – potentially involving changes to commercial models. Initiatives to allay safety concerns among physicians and patients will be particularly important, supported by sales teams with deeper medical and technical knowledge. This will mean significant investment in sales and marketing – initially at least – using either internal commercial capabilities or by sourcing these from branded companies. Investment in pricing and market access will also be increasingly important: post-marketing surveillance is already mandatory in Europe and the US is likely to follow. →

FIGURE 7: ALTHOUGH RISKY, THE EXPECTED PRODUCTIVITY OF INVESTING IN BIOSIMILARS MATCHES OR OUTPACES BENCHMARK RETURNS FROM R&D



Source: IMS analysis. Benchmark from Deloitte & Thomson Reuters Research 2010 (publicly available document)

The higher break-even requirements and technology barriers associated with biosimilars are likely to make the competitive arena less crowded than generics. However, the ability to build the right commercial capabilities will be key to ensuring a successful go-to-market strategy.

Compelling returns, wide appeal

Despite the inherent risk, the expected productivity of investing in biosimilars could match or exceed benchmark returns from R&D. In fact, simulating the potential internal rate of return (IRR)⁸ of a biosimilar investment compared to an industry benchmark shows that it could actually yield a higher IRR than developing a brand new biologic (Figure 7).

Furthermore, biosimilars can fit within the strategic agenda of various company profiles – as demonstrated by the eclectic mix of innovator manufacturers, generics houses and players from other industries that are already entering the sector. They offer a source of long-term financial returns, an opportunity to address diminishing pipeline productivity and a basis for building an R&D platform for the future. Importantly, too, they provide access to the fast-growing pharmerging markets where critical new patient segments are easier to penetrate. The enormous potential of the pharmerging markets is a key upside driver and for many companies a principal reason for investing in biosimilars despite the high financial barriers short-term.

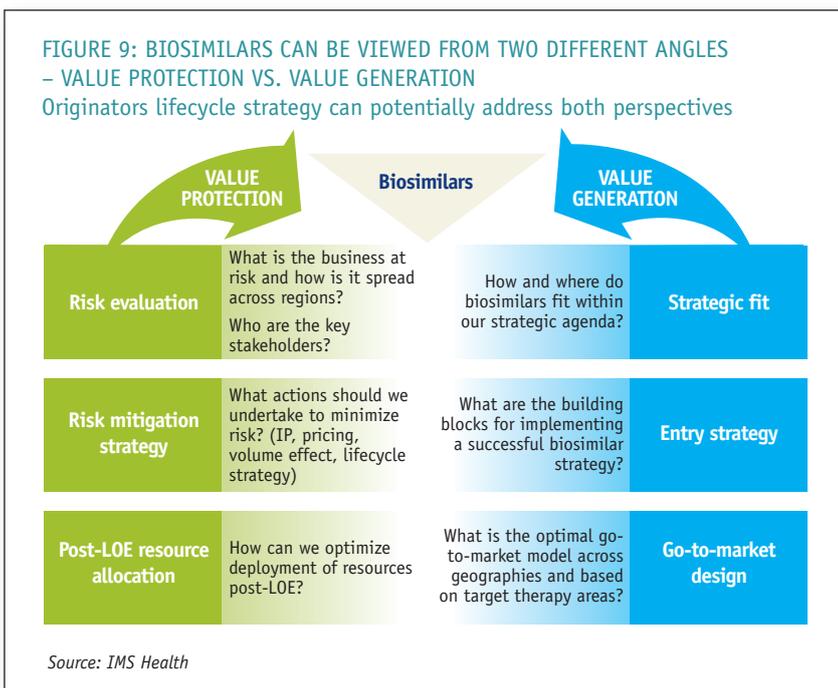
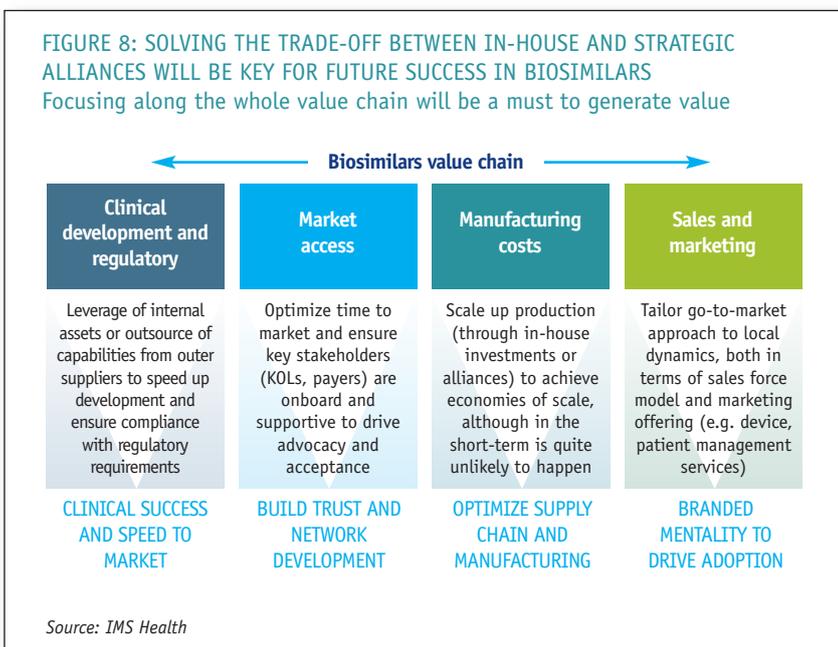
A further key attraction of biosimilars for R&D-based companies is the opportunity to develop biobetters or biosuperiors – ie, improvements to originator biological molecules as opposed to structural imitations of the originator. For manufacturers, a major advantage of biobetters is their lower early-stage R&D costs compared to originator drugs.

In reality, regulatory pathways in the EU and US could encourage the development of biobetters rather than biosimilars. These biobetters would use the standard biological approval route, rather than the abbreviated pathway used by biosimilars. This would mean that biobetters, as ‘new drugs’, would benefit from market exclusivity.

Tapping the potential

Unlocking the potential of biosimilars will require a focused strategy along the whole value chain, from optimizing the clinical development program through developing the most suitable strategy for commercialization. Balancing the trade-off between in-house versus strategic alliances will be essential for achieving cost efficiencies and speeding up time to market, with further tailoring by geography to cope with a heterogeneous landscape (Figure 8). Entry into pharmerging markets, for example, will be strongly governed by partnerships with local players.

The opportunity afforded by biosimilars can be considered from two different standpoints: either as a means of protecting current value or as a source of new value generation. For companies focused on value protection, evaluating and mitigating risk will be key with a view to optimizing resource allocation post-LOE; those looking to join the biosimilars journey will need to thoroughly assess their strategic fit, the building blocks for successful entry and the optimal go-to-market model design (Figure 9). →



⁸ IRR is used in capital budgeting to measure and compare the profitability of investment options (also known as discounted cash flow rate of return)

Summary

To date, limited experience with biosimilars captures only a small portion of their anticipated future potential, as powerful economic pressures increase their appeal to payers in mature and pharmerging markets. Nevertheless, there are major barriers in place which mean that it may be challenging to be successful. The biosimilars sector is also at very different stages in each of the major regions and will likely take a different course. Ultimately, from the heterogeneous group of biosimilars entrants and would-be players, the number of winners may be small.

Companies looking to take advantage of the biosimilars opportunity will need to be clear of their strategic relevance within the organization, in terms of portfolio fit, financial suitability and synergies within the value chain, bearing in mind that this may be an established or pharmerging markets play. A full understanding of the financial upsides and risks of the investment will be critical, based on realistic scenarios of the size of the potential, the therapy areas where it will be found, and whether collaboration and alliances are required to access the necessary skills. An effective market access strategy will be vital for successful entry: the value proposition is complex and will need to address the full range of stakeholders – including payers, physicians and patients whose opinion will be critical. Robust, up-to-date intelligence will also be key: competitors will be diverse and their quantity unknown. Above all, companies will need commitment: the prospects are good and growing but biosimilars will likely be a long-term game. •

FOR FURTHER INFORMATION, SEE OVERLEAF...

Working with IMS in biosimilars

We work closely with clients and leading industry groups to keep pace with market changes. Our highly relevant, consistent metrics cover the trends driving global change and innovation — from new distribution channels and emerging markets to generics, biologics and biosimilars — and help clients successfully adapt to new realities. Our key approach to supporting organizations in addressing the key issues to successfully exploit the biosimilars opportunity is highlighted below.

FIT WITHIN STRATEGIC AGENDA	NEW GEOGRAPHIC OPPORTUNITIES	NEW THERAPEUTIC OPPORTUNITIES	INVESTMENT AND INFRASTRUCTURE FOR SUCCESS
<ul style="list-style-type: none"> • How do biosimilars fit within a company strategic agenda? <ul style="list-style-type: none"> - Portfolio synergies - Financial suitability - Synergies within the value chain (R&D, manufacturing, sales & marketing) • What are the financial upsides and risks of investing in biosimilars? • In which therapy areas to pursue this strategy? • How to develop a successful biosimilar entry strategy? 	<ul style="list-style-type: none"> • The US is the biggest biologics market: how to enter it successfully when the biosimilar opportunity opens up? • What other countries offer new opportunities for biosimilar markets, and how to enter? • How to maximize uptake in the EU landscape? • What are the likely competitive scenarios (originators/other biosimilar competitors)? • What are key drivers and barriers to manage stakeholders across geographies and how to deal with them (e.g. Branded approach, DTC)? 	<ul style="list-style-type: none"> • Which biosimilar therapeutic markets will be the most attractive? • What are the likely barriers to entry? <ul style="list-style-type: none"> - Investment levels (e.g. Marketing capabilities, device)? - Stakeholder management? - Market access approach? (e.g. Pricing, development of the appropriate clinical package) - Launch preparation? 	<ul style="list-style-type: none"> • What is the optimal go-to -market model for a successful biosimilars business? <ul style="list-style-type: none"> - Integration and synergies with existing business - Partnership and strategic alliances • What skillsets and resource levels will be needed, internationally and locally, to address new geographic and therapeutic markets? • What Key Performance Indicators should be used to manage and measure the business?
<p>GO OR NO-GO?</p>		<p>WHAT IS THE OPTIMAL APPROACH?</p>	

FOR FURTHER INFORMATION

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