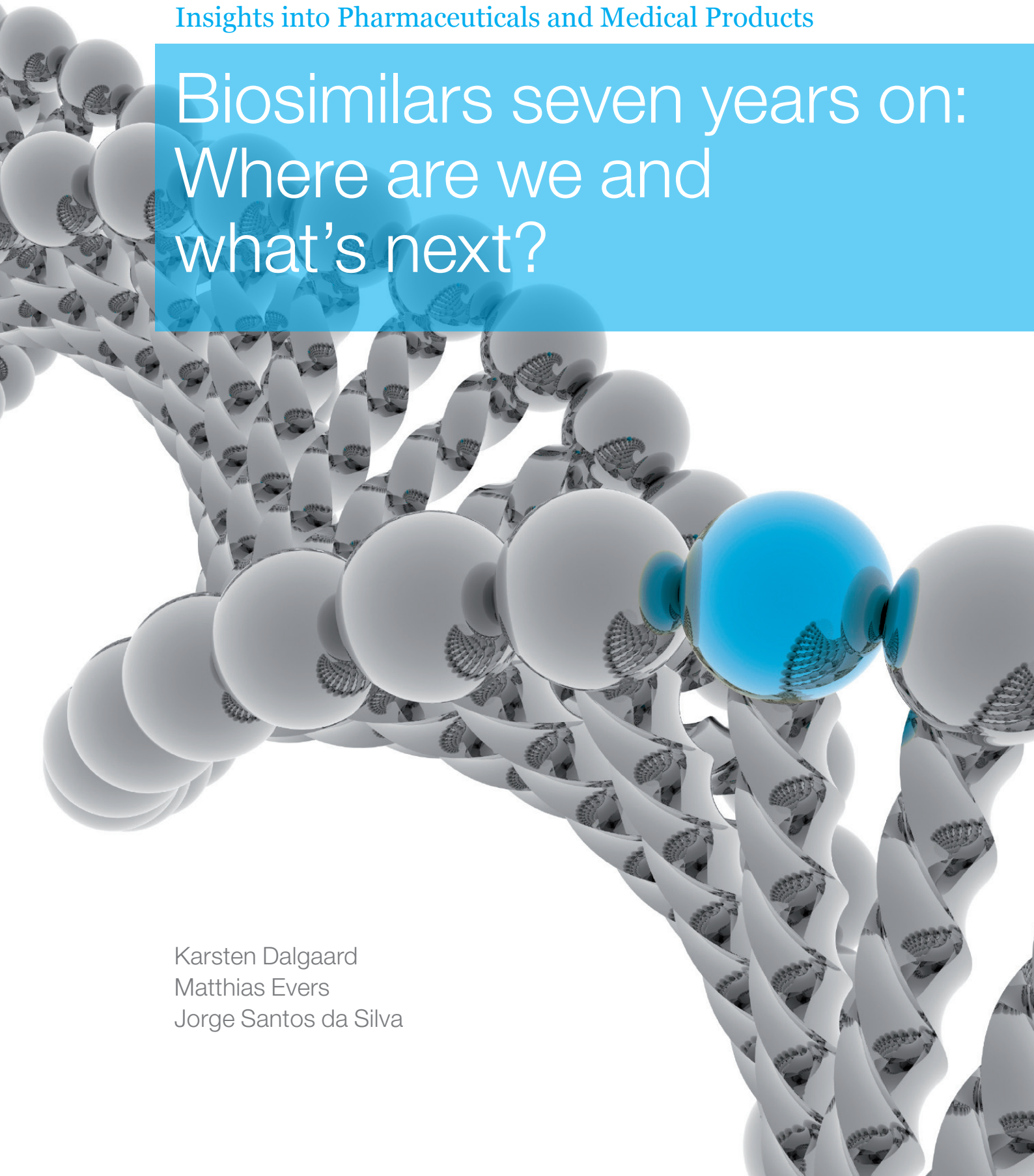
Insights into Pharmaceuticals and Medical Products

Biosimilars seven years on: Where are we and what's next?



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Biosimilars seven years on: Where are we and what's next?

Seven years ago, on October 30, 2005 the "Guideline on similar biological medicinal products" came into effect in Europe, providing an overarching framework for obtaining approval for a biosimilar in the European Union. Having determined that the approach used for generic marketing authorizations is not scientifically appropriate for biologics, the guideline outlines a new approach for biosimilars. This paved the way for the subsequent launch of 14 biosimilar products in three molecule classes: human growth hormone (HGH), erythropoietin (EPO), and filgrastim.[1]

Below, we discuss where we are given the past seven years' development, where we are heading in the future, and what the important strategic questions are for stakeholders in this market.

Where are we?

One the one hand, regulatory pathways have now developed almost across the world, biosimilars are becoming more widely accepted (even by originators) and investments are at an all-time high. But, on the other hand, commercial success has so far been elusive. Biosimilars are at an important infliction point: can stakeholders create the conditions for future commercial success, or should they consider discontinuing their investments?

Regulatory pathways across the world have developed

The European Medicines Agency (EMA) was the first body to issue guidelines on biosimilars. The World Health Organization (WHO) and countries including Canada, Australia and South Africa have followed the EMA's lead soon after and adopted similar principles in their guidelines.

In the last two years, we have witnessed a range of new frameworks emerging in Latin America (LatAm). Brazil has created a "comparative pathway" that includes the need for pharmacodynamic and pharmacokinetic studies and phase III trials recognized by ANVISA, the local regulator. Specific trial demands will need to be worked out on a case-by-case basis but pharmacos will need to raise the bar to get biosimilars approved. The new guidelines in these countries will prevent entry of biosimilars without clinical data (e.g., current local "biocopies" in Mexico), but also trigger eventual re-certification of older, untested products (e.g., Argentina and Mexico[2]).

[1] For an overview of the products, see "Biosimilars approved in Europe," GaBI Online, July 8 2011, at http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe

[2] COFEPRIS, at www.cofepris.gob.mx; ANMAT, at http://www.anmat.gov.ar/principal.asp

Other countries have announced that they intend to follow suit on guidelines (e.g., Columbia, Venezuela and Mexico). This is a welcomed step for several global companies, as regional strategies become possible (some companies expect up to 30% of biosimilars revenue from LatAm in 2020-25). But even local champions are likely to evolve along with regulatory frameworks, as illustrated by the new biotech consortia among the largest Brazilian pharmacos[3], or the push by the Chinese government to nurture the emergence of large-scale generic drug companies and drive local companies to partner with multinationals, invest more in R&D, and produce a differentiated businesses in generics and biosimilars.[4]

Meanwhile, in the United States, the Food and Drugs Administration (FDA) developed an overall framework for biosimilars between 2009 and 2012, but it has still to decide on important questions such as the actual "ask" in clinical and scientific terms, substitution, interchangeability and indication extrapolation.

Acceptance is growing

Although biosimilars got a rather cool welcome from the innovative side of the business, several innovators have entered the market over the past two to three years.

In 2008, Merck & Co., Inc. was the first big pharma innovator to embrace biosimilars, with the formation of a separate business unit, Merck BioVentures (this unit was later made part of institutional R&D in 2012) and Boehringer Ingelheim started their biosimilar unit in 2011.[5] We have also seen large-scale partnerships announced by Samsung and Biogen Idec,[6] Pfizer and Biocon (discontinued in mid-2012)[7], Amgen and Watson,[8] and Dr. Reddy's and Merck Serono.[9]

A 2011 example of how the innovator side is warming up to biosimilars, is the Amgen-sponsored paper, "*Biosimilars 2.0 Guiding principles for a global "patients first" standard"*[10], where the authors take a balanced view on biosimilars, describing under what pre-requisites biosimilars can co-exist with innovator pharmaceuticals. This of course does not mean that now the doors are wide open, and there continues to be resistance from the innovator side, as seen in late 2012 with the Association of the British Pharmaceutical Industry (ABPI) position on biosimilar medicines[11]. Our observations on the ground, also suggest some companies will keep an overt strategy excluding biosimilars (e.g., Roche).

[3] "Orygem Biotechnologia - Brazil's newest biopharmaceutical company", Brazil Pharma News, May 2012, at http://www.brazilpharmanews.com/business-development/77-orygem-biotechnologia-brazil-s-newest-biopharmaceutical-company.html; "BioNovis: Brazil's giant biopharmaceutical company expects to release its first drug product by 2015, Brazil Pharma News, May 2012, at http://www.brazilpharmanews.com/business-development/66-bionovis-brazil-s-giant-biopharmaceutical-company-expects-to-release-its-first-drug-product-by-2015.html

[4] For more on the situation in China, see Healthcare in China: Entering uncharted waters, McKinsey & Company, July 2012

[5] Boehringer Ingelheim expands its Business with Biosimilars," Boehringer-Ingelheim Online, September 2011

[6] "Samsung makes biosimilars deal with Biogen Idec," GaBI Online, December 16 2011, at http://www.gabionline.net/Biosimilars/News/Samsung-makes-biosimilars-deal-with-Biogen-Idec

[7] The deal was subsequently called off in early 2012

[8] "Amgen finally jumps on biosimilars bandwagon," GaBI Online, January 13 2012, at http://gabionline.net/Biosimilars/News/Amgen-finally-jumps-on-biosimilars-bandwagon

[9] "Dr. Reddy's And Merck Serono Partner On Biosimilars," Seeking Alpha Online, June 10, 2012

[10] mAbs, volume 3, issue 3, May/June 2011 Pages 318 - 325

[10] ABPI Online, November 2012

R&D investments are at an all-time high

Numerous companies are pursuing biosimilar versions of blockbuster drugs. More than 20 companies are pursuing a biosimilar for trastuzumab (Herceptin) and several companies invest in molecules even further away from LoE (e.g., adalimumab).

A range of companies have biosimilars at different stages of development. In March 2012 there were 73 biosimilar mAbs under development.[12] Fifty-nine were in preclinical development, five in phase I or II, and nine in phase III. The number of biosimilar marketing authorization applications at the EMA is at its all-time high, with seven applications in 2012 (two for infliximab, three for human insulin, one for follitropin alfa, and one for filgrastim) compared with just one application in 2009 and none at all in 2010 and 2011.[13]

Given this unprecedented level of activity, it seems fair to conclude that expectations are running higher than ever before, and more products will be launched.

Commercial success has been disappointing

Overall, the financial results from biosimilars have been poor so far. Sales from the second half of 2010 to the first half of 2011 were about $400 million, with cumulative sales since 2006 of approximately $1.2 billion.[14] This must be seen in the light of R&D and manufacturing investments of approximately $1 to $1.5 billion across the seven biosimilar dossiers approved to date.[15] Only few, if any, have made a good return on investment yet.

However, there are promising signs. Although biosimilars' penetration rates, in general, have not been as high as those for small-molecule generics, nor as consistent across countries or molecules, they are improving. Growth and uptake rates and the number of countries with more than 50 percent penetration have improved for every new molecule class that has seen biosimilars. The filgrastim class has been the most successful so far, with average volume penetration rates of about 55 percent, and high numbers in many countries.

We should be wary of declaring failure too early; consider, for instance, how generics developed in the US in the 1980s and 1990s. It took almost 10 years for sales to pick up, and the concerns about safety and quality were remarkably similar to today's concerns about biosimilars.

[12] Fern Barkalow, Biosimilar monoclonal antibodies in the pipeline: Major players and strategies, Citeline, undated, at http://www.citeline.com/wp-content/uploads/Biosimilar-mABs-in-the-Pipeline.pdf

[13] "Biosimilars applications under review by EMA," GaBI Online, October 19 2012, at http://www.gabionline.net/Biosimilars/General/Biosimilar-applications-under-review-by-EMA

[14] McKinsey estimate based on IMS data released at 9th EGA International Symposium on Biosimilar Medicines, 14 – 15 April 2011, Millennium Hotel London Mayfair

[15] Seven unique dossiers have been approved by EMA; however, 14 marketing authorizations have been granted on this basis: for instance, the EPO alfas of Medice, Sandoz, and Hexal all derive from the same dossier. Each dossier or program is assumed to cost $100 to $250 million to develop and build.

Where are we heading?

Estimates of the future size of the biosimilars market range widely, from $2 billion to $20 billion by 2020. To date, entry has been relatively straightforward: only a few molecule classes have gone off patent, they have not been the biggest commercially, and they include only the simpler proteins. The question is what will happen once the real game begins, with biosimilars of more complex molecules, the entry of numerous molecule classes, and products worth more than $5 billion coming under pressure.

We will soon see biosimilars of highly complex monoclonal antibodies. Measured by their chemical structures, mAbs are 10 to 15 times larger than simpler proteins such as hGH and EPO, and 100 to 1,000 times larger than small molecules. Copying them is inherently more complicated, and there will be greater uncertainty over whether small deviations will have any meaningful clinical effect. The probability of success in developing these molecules is also likely to be lower. Both Teva and Samsung have recently had difficulties in developing biosimilar rituximab.[16] Deep expertise and talent in biologics technical development and manufacturing scale-up will be critical, resulting in an increasing competition for talent in this area.

In addition, much more value is at stake now. The five largest mAbs will go off patent before the end of the decade, and each has global sales above $6 billion. The first mAb to see competition will be infliximab, a biosimilar of J&J's Remicade, which has an annual turnover of $8.5 billion. Korea's Celltrion got their biosimilar infiximab approved in South Korea and have submitted an application to the EMA in 2012.[17]

More over, emerging markets are candidates to becoming competitive testing grounds in the near- and mid-term. Since patents are several times not in force in these countries (e.g., Remicade, Enbrel or IFNß1A in Brazil), originators can opt to move into a biosimilar play or lower the price of their current product, while competitors might persuade governments to move into exclusivity deals (e.g., Brazil) or into tender lists (e.g., China, Mexico). Getting rapidly into Emerging Markets is an intriguing possibility as it can provide early revenue streams, local clinical trial options and the subsequent increase in in-market data ahead of 2018-2020 submissions in mature markets. In itself, sales opportunities can be significant (often more than $100 million), as current therapy penetration is extremely low compared to mature markets (e.g., MabThera treatment rates in Brazil are three times lower than in UK and six times lower than in the United States). This is especially true in Brazil, where the local near-term economic momentum creates very large opportunity if the bulging middle-class can be targeted. This creates opportunities that might be larger than previously thought, though success will be the game of few since access will be exclusive or semi-exclusive under the new PDP[18] framework.

[16] "Teva halts phase III biosimilar rituximab trial," GaBI Online, October 12 2012, at http://gabionline.net/Biosimilars/News/Teva-halts-phase-III-biosimilar-rituximab-trial; "Samsung halts biosimilar rituximab development," GaBI Online, October 19 2012, at http://gabionline.net/Biosimilars/News/Samsung-halts-biosimilar-rituximab-development.w

[17] "EMA receives another infliximab biosimilar filing," Biosimilar News, September 21 2012, at http://www.biosimilarnews.com/ema-receives-an-another-infliximab-biosimilar-filing.

[18] Product Development Partnerships

In our view, there are four swing factors that could take biosimilars to the tipping point in the next few years: their acceptance in the US, automatic substitution and interchangeability, indication extrapolation, and payor involvement.

Acceptance of biosimilars in the US

About half of all global branded biologics sales, amounting to some $160 billion in 2012, are in the US.[19] Success in the US will make or break most entrants' business cases. So far, no biological product has been approved through the new abbreviated biologic license application (aBLA) pathway. Moreover, the FDA has been vague about some aspects of regulatory approval such as indication extrapolation and interchangeability. As a consequence, companies are pursuing the regular biologic license application (BLA) route, as seen recently with Teva's tbo-filgrastim.

Three factors that suggest biosimilar penetration may eventually reach high levels in the US are the price of its pharmaceuticals (including biologics) – almost twice the average price in the rest of the world[20] – the scale of its healthcare spending, the highest in the world at 18 percent of GDP – and, the new healthcare legislation to be enforced in 2014. In other words, there should be plenty of room to undercut current prices, and the healthcare system simply cannot afford not to embrace biosimilars.

Automatic substitution and interchangeability

EU legislation demands that 'each biological medicine including biosimilars has a distinct name that clearly distinguishes it from other biological medicines in order to facilitate compliance with the patient safety and pharmacovigilance identification and traceability requirements. In addition, countries create further distinction from the originator products, e.g., the black triangle symbol introduced by the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, which requires biosimilars to have this symbol on the package and to be monitored intensively for safety and efficacy.

Attempts to allow substitution have been seen already, as with the Norwegian Medicines Agency's inclusion of filgrastim on the substitution list ("byttelisten") in June 2010. After a lawsuit, the Oslo court ruled the decision invalid in 2011, as the prerequisite for a drug to be on the substitution list is that it is "generically equivalent," which biosimilars are not, being only similar.[21] In few countries, substitution is already allowed (e.g., Mexico where a patient might be given an originator or a "biocopy" depending on time and location, since prescriptions are made with INN rather than brand).

[19] *Biosimilars: US and International Update*, Elsevier, October 10 2012
[20] Barry Ritholtz, "A look at absurd US healthcosts (vs. rest of world)," April 21 2011, at http://www.ritholtz.com/blog/2011/04/us-healthcare-vs-rest-of-the-world/
[21] "Oslo District Court rules for Amgen," AmCham Norway website, April 13 2011, at http://www.amcham.no/oslo-district-court-rules-for-amgen/437

Another challenge concerns what is required to demonstrate interchangeability. The FDA's guidance says that an interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient" and that if the patient takes it more than once, "the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."[22] The reward for being recognized as interchangeable is considerable – in addition to achieving substitution, the first interchangeable biosimilar also gets one-year exclusivity – but so are the risks. If a trial fails to show interchangeability, it will undermine beliefs about similarity.

Indication extrapolation

According to the EMA and the FDA, indication extrapolation is possible provided there is evidence of biosimilarity from the comparability exercise and adequate clinical and scientific justification.

This is an important issue, since the lack of indication extrapolation will lead to a more expensive development program or a smaller addressable market for the biosimilar. However, the importance of extrapolation is exaggerated from a financial perspective. If we examine sales by indication, most of the large biologics have 55 to 65 percent of sales in their largest indication; in some cases, such as insulin, the share is 100 percent. There should thus be plenty of originator sales to penetrate. The second- largest indication typically has another 15 to 25 percent of sales, so doing trials in two indications will typically cover 80 to 90 percent of the potential.[23]

From a marketing and sales perspective, indication extrapolation can be more tricky. If a product is indicated for one but not all indications, it could add to the perception that it is not really similar and thereby damage sales.

Payor involvement

Although biosimilars can lead to significant cost savings for the payors, not all payors are playing an active part in making biosimilars a commercial success.

Payor involvement can take place at two levels. At an international level, payors could push for the acceptance of global development programs that would make biosimilars less expensive to develop. At a national level, payors could push for making substitution and interchangeability possible, provide minimum prescription quotas, introduce price tiering, or tender similar molecules (such as all EPOs instead of only EPO alfas), and so on. There have been examples of these actions already, but the extent could be much more significant.

[22] "Guidance for Industry: Quality considerations in demonstrating biosimilarity to a reference protein product," FDA, February 2012
[23] Evaluate Pharma, November 2012

How the swing factors could play out

The main question left is if and when these swing factors might come into play.

If they don't materialize, or not in a significant way, the biosimilar market is unlikely to develop much further. There will be a strong need to explain the differences between biosimilars and their reference products, and marketing and sales activities will resemble those for me-too drugs and branded generics. This commercial model is more costly to operate and markets are harder to penetrate, so entrants will face extra costs and lower sales which they will need to recoup through pricing, reducing the price difference between originators and biosimilars.

However, if some or all of these swing factors do come into play, biosimilars are likely to behave in much the same way as the generics market. We believe that regulators, governments, and payors will be reluctant to go all the way and allow indication extrapolation and automatic substitution during this decade. However, these limitations could be loosened once good in-patient experiences have been established. In such a market, cost will become the main competitive battleground. Choices made now in R&D (such as choice of trial design) and manufacturing (such as fixed or disposable capacity) will play an important role in the economics of biosimilars. In the interim, striking a balance between R&D investment and privileged partnerships for access can support the "implementation" of biosimilars – e.g., PDP contracts in Brazil or tender differentiation groups in Mexico or China

Naturally, the timing of these developments will depend on how stakeholders' efforts play out and who takes the lead. The early entrants have been active in shaping the development, but need to engage payors and regulators further to really pick up momentum. Institutional payors, regulators and the flexibility and prescriptiveness of their guidelines (i.e., how high the bar is set), will be key to determining the levels of competition and economic gains to be made on biosimilars.

What are key questions for players going forward?

We tend to think of three main stakeholder groups in biosimilars: the large generics companies with marketed biosimilars and pipelines; the many smaller entrants with pipelines but no marketed products; and the originators. However, given their potential importance in the development of the biosimilars market, we have also included payors.

Let's look at each of these in turn. First, l*arge generics companies with marketed biosimilars and pipelines* may want to think about the following questions:

- What is our optimal go-to-market model? Given the lack of substitution and indication extrapolation, biosimilar products need to be marketed differently from generics, using some elements of the branded drug model, such as market and customer insights, detailing, and a sizeable field force. On the other hand, biosimilars are sold at a discount to the originals and cost is the most important differentiator, so the closer a company can keep to the generics model, the better.
- What role should emerging markets play in forming our global programs? Given the differences in regulatory pathways vs. EMA and FDA, the possibility of earlier launch and build up of in-patient data, emerging markets could perhaps have a larger role than what their sales potential alone would indicate.
- How many indications should we pursue? It is worth considering pursuing all major indications regardless of whether extrapolation will be granted, simply to avoid additional hurdles to commercialization.
- How can we create the optimal conditions for biosimilars? Answering this question involves identifying the most important stakeholders and forming views on the swing factors above. For instance, payors could be pushing for biosimilars to save money in already strained budgets, but how do we engage them effectively?
- Should we go after interchangeability? If yes, when? Is it worth the risk? In-patient data of successful interchangeability could be a powerful argument in the substitution debate. A company could, for instance, try to make a case from real-world evidence for insulin or EPO, drugs where some large payors change suppliers on a regular basis through tenders.

Second, the following strategic questions could be important for *smaller entrants with a pipeline but no marketed product*:

- Who should we partner with and when? The consolidation of pipelines seems inevitable. As a host of companies try to get to market through investments in excess of $100 million, several will give up or look for partners. However, many options are already closing as top-tier originators form partnerships with biosimilar entrants. To avoid being left with an asset but no interested partner, smaller companies in weaker positions should consider speeding up their partnering efforts.
- What does a cost-minimizing strategy look like? Work out how to create the cheapest possible characterization and development program to achieve the lowest cost position in the market without losing valuable time. In addition, consider exploring how to use the latest manufacturing technologies to achieve the lowest cost of goods sold, which may well be the winning strategy in the long run.
- Should we follow the BLA or aBLA route in the US? There is a clear trade-off between risk, speed, and cost.

Third, *originators interested in biosimilars* should consider:

- How can biosimilars complement our portfolio and strengthen our offering for a therapeutic area? For example, if we have a small-molecule diabetes portfolio, could a biosimilar insulin addition be relevant? There would be obvious salesforce synergies that other biosimilar entrants would find hard to match.
- Under what conditions should biosimilars be allowed? Most originators have strongly opposed biosimilars, but will find this stance harder to maintain if they invest in biosimilars themselves. They will need to shift their emphasis to defining the circumstances under which biosimilars can be accepted, which will involve making a trade-off between defending their existing business and pursuing new opportunities.

Fourth, the strategic questions for *originators with no stated interest in biosimilars* include:

- How can we lead the debate on outstanding regulatory questions? There are valid reasons why indication extrapolation is not granted automatically and originators have a role in determining where the limit should be set.
- How should we respond to increased competition? Is a second brand an option? What pricing strategy should we adopt? Given that fewer companies will enter the biosimilar market, it is likely that the dynamics will be closer to an oligopoly than perfect competition.
- How should we adapt our operating model? Once biosimilars are in the market, should we move toward a leaner commercial model and more payor interactions? Our messaging and key opinion leaders will change. To differentiate our offering, can we offer services in addition to the drug?

Finally, the key questions for *payors*, who will ultimately benefit from a lower cost of treatment, are:

- How can we optimize cost savings? Payors need to think through their role in creating a good environment for biosimilars nationally and internationally.
- How can biosimilars improve patient health? As they offer lower costs, the cost/benefit analyses included in health technology assessments will need to be revised, and broader access may need to be granted for patients. Only half of severe rheumatoid arthritis patients are currently treated with biologics, for instance.[24] This could change as prices fall. Biosimilars have the potential to bring substantial improvements in patients' quality of life.

Although the future of biosimilars is still uncertain, several developments give reason to believe that they are here to stay and that some companies will eventually make reasonable returns on their biosimilar programs. However, the range of outcomes is still wide, and depends heavily on which stakeholders make the first moves.

[22] Ameet Malik, "Biosimilars by Sandoz: Capturing the future opportunity," November 14 2012

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