Original Article

Deciding between biobetter versus biosimilar development options based on net present value calculations

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ABSTRACT

The growing share of biopharmaceuticals is paralleled by an increasing interest in biogenerics, as blockbuster biologics are approaching their patent expiries. Companies need to make decisions whether to invest in biosimilars or in biobetters with enhanced properties, the latter enabling favorable differentiation vis-à-vis the original product on the one hand and biosimilars on the other hand. Net present value (NPV) modelling was applied to compare the financial value of two categories of biobetters with the value of biosimilars, proving superiority of truly innovative biobetters. Regardless of the high economic attractiveness of such products, engaging in such projects might not be appropriate for every company and recommendations are provided which options should be preferred depending on a company's scientific and technical capabilities and business model.

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INTRODUCTION

History and current status of biosimilars

The class of biologic drugs is increasingly gaining importance for the pharmaceutical and biotech industry. It is therefore obvious that there is a significant interest in developing and approving generic versions of such products after their patents expire.[1] Based on the significantly higher complexity of these products compared to small molecules, regulatory agencies request more than a pharmacokinetic study to demonstrate the safety and efficacy of such drugs. Special attention has to be given to the issue of immunogenicity of biologic drugs that is still not fully understood.[2] The European Medicines Agency (EMA) has published guidelines for different classes of biologic drugs that request phase III-like studies in all cases.[3] Another significant difference of biosimilars compared to small molecule generics is that, because of the higher molecular complexity of the earlier, the full identity of two biosimilar products can usually not be proven. This is why, by now, the term biosimilar is used instead of biogeneric.[4]

Over the past 15 years, many companies have been attracted by the new biosimilars business opportunity. In fact, both companies with generic and with innovative business focus are working in this sector today.[5] However, the significant investments have so far not paid off. The first approved biosimilars in Europe, i.e., the insulines, human growth hormone, and erythropoietin, are struggling to gain market share. The only advantage of biosimilar products compared to their innovative predecessors is their lower price. The high development costs and high cost of goods of biosimilars limit, however, the potential for price reductions. Opposite to small molecule originators it is now commonly believed that biologic originators will be able to keep 70-90 % of the total market.[6] These factors, combined with the need to promote biosimilars through a dedicated sales force,

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increase the investment per project and the risk of financial failure significantly.[7]

New hope: biobetters, talk of the town

Some years ago the term biobetter was introduced to describe a new type of projects that gain more popularity ever since. The term biobetter refers to a biological product that "is similar to an already approved biologic product, but is superior in one or more product characteristics".[8] Frequently targeted product improvements include longer half-life,[9] reduced immunogenicity,[10] higher potency,[11] and more convenient administration.[12] Currently, regulatory agencies have not yet issued guidelines for this new product category, but it can be expected that for biobetters a full development program will be required, at least when molecular changes have been introduced. When offering a meaningful advantage such products would have the potential to differentiate themselves not only from biosimilars but also from the original, potentially leading to significantly higher sales volumes compared to the latter. Indeed, most of the companies engaged in biosimilars as well as newly founded venture capital-backed biotech companies such as, e.g., Itero Biopharmaceuticals Inc., Femta Pharmaceuticals Inc., Glycotope GmbH, and PolyTherics Ltd., are currently developing biobetters.

Analytics for managers to select the most attractive projects

With the emerging concept of biobetters in addition to biosimilars, the number of potential projects is virtually unlimited, given the various approaches to create a biobetter. This article intends to provide guidance to decision makers how, for a given organization, value-creating projects with strategic fit can be selected. In a first step, the possible options of creating biobetters are categorized, and it is analyzed to which classes of biologics they may apply. In a second step, the concept of portfolio management will be applied, indicating the expected financial value for different classes of biologics. This will be done in light of the strategic options the originator companies have to defend their franchises.

Scope and limitations of the investigation

The regulatory and economic environment for the development and commercialization of biosimilars and biobetters differs significantly in various regions of the world. The regulatory environment is certainly the most stringent and demanding in the US, Europe and some other developed countries, which leads to high development cost. In certain developing countries requirements are significantly lower for the local supply. The present investigation focuses on developed countries because the sales levels of biologics are highest in these territories (compare Table 1), and the analysis of the diverse regulatory environments in different emerging markets would go beyond the scope of this article.

DIFFERENT CLASSES OF BIOLOGICS AND TECHNICAL OPTIONS TO CREATE BIOBETTERS

The 10 bestselling biologic products in 2012 belong to two distinct categories, i.e., monoclonal antibodies and proteins. The present analysis focuses on these two classes of products because their economic potential is most attractive.

Three potential approaches for the development of biobetters will be discussed:

- Improvement of pharmacokinetic properties through pegylation / glycosidation
- Enhanced drug formulation
- Improvement of the benefit/risk ratio through deimmunization or through an increase of efficacy

These technical approaches give rise to two categories of biobetters that differ with respect to their benefits:

- Product modifications that reduce the application interval and/or improve compliance, such products are called "biobetterFORM" in this analysis
- Molecular modifications that improve the safety and/or efficacy of the drug, such products are called "biobetterADD"

The most widely used approach to improve protein drugs is to improve their pharmacokinetic properties. Initiatives to prolong the half lives of protein drugs have been pursued ever since this class of products entered the market. For example, pegylation describes the process of a covalent attachment of polyethylene glycol polymer chains to other molecules including proteins. Pegylation leads to product enhancements such as improved solubility, increased molecular stability, extended plasma half life, and reduced dosing frequency. Since the introduction of the first pegylated product, Adagen® by Enzon Pharmaceuticals in 1990, a total of 12 pegylated drugs

Table 1: The ten best-selling biotechnology drugs in the year 2012[13]

Name	Lead Company	Type of Molecule	Approved Indication(s)	World-Wide Sales (US$ million)
Humira (adalimumab)	AbbVie	mAb	Rheumatoid arthritis (RA), juvenile rheumatoid arthritis, Crohn's disease, psoriatic arthritis (PA), psoriasis, ankylosing spondylitis, ulcerative colitis (UC), Behçet syndrome	9,266
Enbrel (etanercept)	Amgen	Protein	RA, psoriasis, ankylosing spondylitis, PA, juvenile rheumatoid arthritis	7,967
Rituxan (rituximab)	Roche	mAb	RA, chronic lymphocytic leukemia/small cell lymphocytic lymphoma, non-Hodgkin's lymphoma, antineutrophil cytoplasmic antibodies associated vasculitis, indolent non-Hodgkin's lymphoma, diffuse large B-cell lymphoma	7,049
Remicade (infliximab)	J&J	mAb	RA, Crohn's disease, psoriasis, UC, ankylosing spondylitis, Behçet syndrome, PA	6,564
Herceptin (trastuzumab)	Roche	mAb	Breast cancer, gastric cancer	6,188
Avastin (bevacizumab)	Roche	mAb	Colorectal cancer, non-small cell lung cancer, renal cell cancer, brain cancer (malignant glioma; anaplastic astrocytoma, glioblastoma multiforme)	6,059
Neulasta (pegfilgrastim)	Amgen	Protein	Neutropenia/leukopenia	4,092
Lucentis (ranibizumab)	Roche	mAb	Wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion	4,003
Avonex (interferon beta-1a)	Biogen IDEC	Protein	Multiple sclerosis	2,913
Rebif (interferon beta-1a)	Merck Serono	Protein	Multiple sclerosis	2,408

have been approved by the FDA.[14] The sales of the two most successful pegylated products, Pegasys® (pegylated interferone alpha for the treatment of hepatitis C), and Neulasta® (pegylated GCSF for chemotherapy induced neutropenia) exceeded US$ 5 bn in 2011[15,16]. The pegylation of these two products led to a significant prolongation of their plasma half lives. As a consequence, Neulasta® requires only one application per chemotherapy cycle, while Neupogen® must be applied daily until a normalization of Granulocyte levels is achieved (which usually takes around 14 days after conventional chemotherapy).

Alternative strategies to prolong the half life of proteins are

- attachment to human serum albumin[17]
- attachment of hyaluronic acid[18]
- attachment of sugar molecules[19]

These methods have in common that the original protein is modified to create a new molecule with improved properties.

The majority of biologic drugs is administered either via the intravenous, intramuscular, or subcutaneous route. More convenient drug delivery might not only improve compliance but also lead to a more predictable release profile and thereby to a higher acceptance by physicians.

Examples for alternative drug delivery approaches are:

- pulmonary delivery[20]
- transdermal delivery[21]

Insulin was the first protein being investigated intensively for the pulmonary route of application. Of the several inhaled insulin devices that are in different

stages of development, the Exubera® formulation (Pfizer) was the first to achieve regulatory approval both in the US and EU,[22] proving technical feasibility of pulmonary delivery. Commercially, Exubera® never lived up to its expectations and was finally taken off the market.[23]

Transdermal delivery of proteins avoids the disadvantages of invasive parenteral administration. Since proteins are large hydrophilic molecules they cannot passively permeate through the skin. Enhancement techniques such as iontophoresis,[24] microneedles,[25] and others[21] are overcoming the skin barrier in different ways. These approaches do not require molecular modification of the biologic drug; only a suitable formulation and potentially a device are to be developed.

Alternatively, the original protein can be modified in order to reduce side effects and/or improve efficacy. Depending on the therapeutic context, biologics have proven to be surprisingly immunogenic. This is also the case for humanized or fully human monoclonal antibodies.[10] Different factors can contribute to clinically relevant immunogenicity, for example, molecular aggregation or the presence of epitopes in the molecule that attract a T-cell response. Various approaches have been developed to reduce the immunogenicity of protein drugs through reformulation[26] or protein engineering.[27]

For mABs, increasing the efficacy in a clinically meaningful way is an attractive option but not easy to accomplish. An impressive example for this approach is the second generation Anti-Her2 drug called Kadcyla® that was developed at Roche and recently approved by the FDA for 2nd line treatment of HER2-positive breast cancer relapsing after previous Herceptin-containing regimes. Kadcyla® is an antibody- drug conjugate consisting of the monoclonal antibody trastuzumab (Herceptin®) linked to the cytotoxic agent emtansine. Trastuzumab inhibits cellular growth by binding to HER2/ neu surface receptors, whereas emtansine is internalized and finally destroys the tumor cells by binding to tubulin.[28] In the Kadcyla® example the introduction of a cytotoxic mechanism has led to an impressive survival benefit of 5.8 months compared to standard therapy.[29] Another outstanding example for a biobetterADD is GA 101, also developed at Roche to enhance the activity of the CD 20 antibody Rituxan. Improved activity compared to the original molecule could be achieved by an optimization of the glycosidation pattern. The superiority of GA 101 was recently confirmed in a Phase III trial in which GA 101 had shown significantly higher efficacy than Rituxan in first line CLL (chronic lymphatic lymphoma) and might potentially lead to a paradigm change in the treatment of CLL.[30]

METHODS

Given the various options of developing biobetters, the present analysis focuses on the question under which conditions financial value creation can be expected. In addition, insights shall be generated how to make decisions with respect to biobetters on the one hand and biosimilars on the other hand.

In a previous analysis, net present value (NPV) modeling was applied to evaluate the financial attractiveness and business risk of different categories of biosimilars.[29] In the current analysis, the same methodological approach is applied to biobetterFORM and biobetterADD. In order to establish quantitative decision criteria for biobetterFORM versus biobetterADD, NPV analyses for both categories were conducted and compared to the analysis for biosimilars. It was investigated under which conditions a minimum acceptable NPV can be expected. General consensus is assumed that the minimum acceptable expected (risk-adjusted) NPV at project kick-off is around US$ 10 million. The applied NPV algorithm reflects the risk of development failure at each development milestone, while cost and revenue uncertainty was investigated in one-way sensitivity analyses. This methodology was preferred over Monte Carlo simulation because the intention was to demonstrate, for individual assumptions, at which level of deviation from the likely value the NPV falls below the comfort level for making a "Go" decision. The applied NPV model was described in detail previously.[31]

Table 2 summarizes the development assumptions that represent average values for biosimilars on the one hand, (compare 7), and the two categories of biobetters on the other hand. Regarding the probabilities of development success (PoS), it is assumed that a biobetterADD would be comparable to an average New Biological Entity (NBE), therefore the probabilities were taken from benchmark statistics for monoclonal antibodies[32] which represent, to our knowledge, the most recent publicly available source indicative of NBEs. PoS for biobetterFORM refer to the same benchmarks with the exception of the PoS for Phases II and III. For Phase II the PoS is increased from 37 to 80 % and for Phase III from 65 to 75 %, taking into account that the product's basic mechanism of action had already been established by the originator, leading to a significantly lower development risk. Timeline and cost assumptions were derived from information published by the Tufts Institute.[33] Sales, General and administration (S,G&A) costs were assumed to be 20% of sales, as reflected by data published in annual reports of companies marketing specialty products. Cost of goods sold (CoGs) are assumed to be around 30%. Efforts were made to establish plausible differences between the cost assumptions for the three project

Table 2: Assumptions applied for the valuation were taken from ref[29]. Alternative scenarios were also evaluated (see Tables 2 and 3)

	Biosimilar			BiobetterFORM			BiobetterADD		
eNPV: US$ 10 million	Probability of Success	Duration (years)	Cost (US$ m)	Probability of Success	Duration (years)	Cost (US$ m)	Probability of Success	Duration (years)	Cost (US$ m)
Process R&D	90%	2,5	12	90%	2,5	15	90%	3	15
Preclin Dev	85%		8	75%		8	75%		10
Formulation Dev	95%	1	5	90%	2,0	5	90%	2,0	5
Scale-up	95%		10	95%		10	95%		10
Phase I	90%	1	8	77%	1	8	77%	1	8
Phase II	100%	-		80%	1,5	10	37%	2	20
Phase III	75%	3	55	75%	3	55	65%	3	110
Registration	80%	1,5	2	95%	1,5	2	95%	1,5	2
Overall Probability of Launch	37%			25%			10%		
COGS (%of Sales)	30%			30%			30%		
Peak Sales (US$m)	**180**			**270**			**690**		

categories, driven by the focus and number of clinical trials. Overall, the figures represent base case assumptions. The impact of the ranges of uncertainty on value was investigated in the sensitivity analyses.

The NPV model includes all project related cash flows from the start of preclinical development (year 1) up to year 20. Cash flows are inflated by 2% per year. The discount rate is 8%, and the tax rate is 40%. Peak sales are achieved in year 5 on the market and are maintained for 2 years. Thereafter, a sales decline of 5% for the biobetterADD, 7,5% for the biobetterFORM, and 10% for the biosimilar is assumed. The sales decline reflects the impact of emerging new treatment options, which is expected to be less pronounced for a biobetter compared to a biosimilar, and to be lowest for the most innovative version. Cash flows beyond year 20 are modeled as terminal value, assuming a continuous decline at a yearly rate of 10%.

The influence of the different input parameters was investigated to understand the value drivers and to address the question under which conditions an expected NPV of US$10 million could be achieved. As indicated above, an expected NPV of US$ 10 million at project start was considered a minimum requirement to justify a "go" decision in the present analysis.

RESULTS

On Tables 3 and 4, scenario 1 reflects the base case assumptions for biobetterFORM and biobetterADD, respectively, as indicated in Table 2. Taking into account these assumptions, required peak sales were determined to yield an expected NPV of US$ 10 million at development start. It turned out that, for BiobetterFORM, peak sales of US$ 270 million would be sufficient to achieve that goal, US$ 90 million above the sales level required for biosimilars.[30] This is mostly driven by the higher development risk and longer development time of biobetterFORM compared to biosimilars (overall PoS 25% versus 37%, development time 11,5 versus 9 years, respectively). In contrast, the profile of a biobetterADD more closely compares to the profile of New Biological Entities (NBEs), with peak sales of US$ 690 million being required for an expected NPV of US$ 10 million at project start, and a development time of around 12,5 years. Since regulatory agencies will not require a biobetterADD to closely resemble the innovator molecule regarding, e.g., pharmacokinetic profile, efficacy and safety, biobetterADDs are considered comparable to NBEs and may therefore benefit from their higher probability of approval compared to biosimilars.

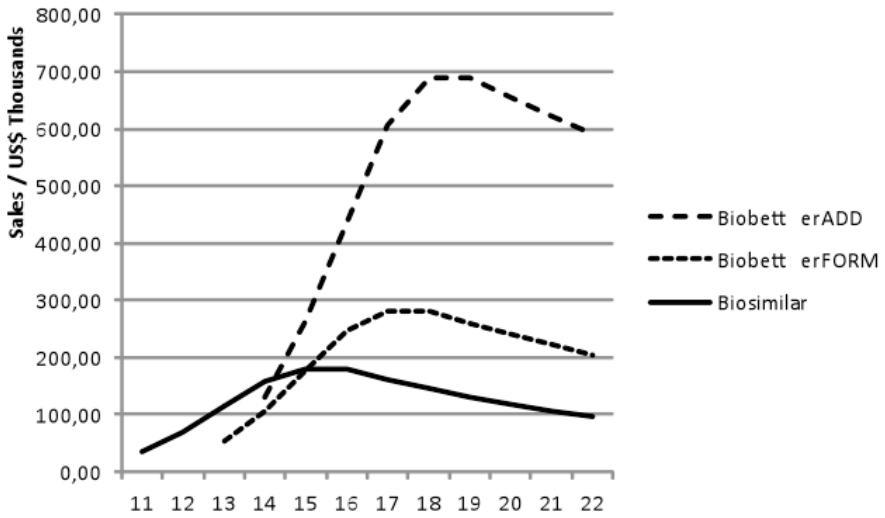

Figure 1: Expected life cycle curves for BiobetterADD and BobetterFORM, in comparison to a biosimilar. In the base case it is assumed that, after 6 years of marketing, sales will be impacted by innovative treatment alternatives. However, the impact will likely vary depending on the degree of innovativeness of the respective product category: the decline of sales is expected to be 10%, 7.5% and 5% for biosimilars, BiobetterFORM, and BiobetterADD, respectively.

In Scenarios 2 and 3 the influence of higher discount rates was investigated. While in the base case scenario a discount rate of 8% is applied, which appears appropriate for established pharmaceutical companies, higher discount rates are used in smaller corporations (10%) and biotech companies (15%) based on their higher cost of capital. At a rate of 15%, however, both biobetterFORM and biobetterADD run into negative NPVs (below US$ -10 million), at a rate of 10% NPVs are virtually zero. For a BiobetterADD, forecasted peak sales would actually have to be at a level of US$ 2,3 billion to achieve the target NPV of US$10 million (Scenario 4, Table 4).

CoGs strongly influence the value of pharmaceutical products. Therefore, CoGs are a relevant uncertainty for biobetterFORM at development start. The reason is that biobetterFORM may only enjoy a moderate price premium compared to biosimilars, ranging around 15%. The sensitivity analyses in Scenarios 4-6 (Table 3) indicate that an increase of CoGs from 30% to 43% results in an expected NPV of US$ -15 million, which could potentially be compensated by an increase in peak sales from US$ 270 million to US$ 775 million in order to get back to the targeted NPV level of this analysis. In order to achieve improvements in a product's pharmacokinetic profile or application mode, increased CoGs are not uncommon which need to stay in balance with realistic sales expectations. For biobetterADDs, product prices are assumed to reflect the more innovative product properties; therefore, CoGs beyond 30% are considered unlikely. There may rather be room for a value increase through lower CoGs, as indicated in Scenario 6 (Table 4).

The impact of higher development costs was also investigated. If a second Phase 3 where required for a biobetterFORM (Scenarios 7 and 8, Table 3), development costs could increase by US$ 55 million. This would reduce the project's expected value by US$ 7 million. In order to compensate for this effect, peak sales would have to be forecasted at a level of US$ 320 million. In order to have a similar impact on expected NPV, cost for a biobetterADD would have to increase by US$ 75 million. This could occur if one additional Phase II and III trial, respectively, or one additional large Phase III trial, were required. The value impact of the additional expense would be compensated by an increase in expected peak sales to US$ 811 million (Scenarios 7 and 8, Table 4).

The sensitivity to overall development risk was also investigated. For example, the development risk for a BiobetterADD could be exceptionally low if an innovative route of administration did not (only) lead to improved convenience, but also to significantly enhanced efficacy. In certain cases, e.g. neurodegenerative diseases, constant plasma levels brought along by a sustained release formulation could induce a quantum leap in benefit. Such a case could be reflected by Scenario 9 (Table 4), with an increase of PoS from 10% to 25%. This would increase the value of the project from US$ 10 million to US$ 61 million. Also a biobetterFORM could potentially benefit from a reduced development risk if a Phase II had virtually no risk to fail based on information generated in Phase I and the knowledge generated by the innovator. This may increase overall PoS from

Table 3: BiobetterFORM: Major value determinants for the base case scenario (1). A peak sales level of US$ 270 million (and total life cycle sales according to the graph indicated in Figure 1) would be required to achieve an expected NPV of US$ 10 million. Scenarios 2-14 demonstrate the sensitivity of the base case NPV to variations of individual parameters that are within common margins of market, development, and financial uncertainties.

Scenario	Development Time (years)	Development Cost (US$ million)	PoS	Peak Sales (US$ million)	Yearly Sales Decline after Year 6	Discount Rate	CoGs (% of Sales)	SG&A Cost as % of Overall Slaes	Risk-adj. NPV (US$ million)	NON Risk-adj. NPV (US$ million)
1	11,5	113	25%	270	7,5%	8%	30%	20%	10	101
2	11,5	113	25%	270	7,5%	10%	30%	20%	0	59
3	11,5	113	25%	270	7,5%	15%	30%	20%	-10	8
4	11,5	113	25%	270	7,5%	8%	17%	20%	35	159
S	11,5	113	25%	270	7,5%	8%	43%	20%	-15	3
8	11,5	113	25%	775	7,5%	8%	43%	20%	10	100
7	11,5	168	25%	270	7,5%	8%	30%	20%	3	80
8	11,5	168	25%	320	7,5%	8%	30%	20%	10	108
9	11,5	113	31%	270	7,5%	8%	30%	20%	18	101
10	11,5	113	25%	270	7,5%	8%	30%	30%	-10	21
11	11,5	113	25%	575	7,5%	8%	30%	30%	10	101
12	11,5	113	25%	242	5%	8%	30%	20%	10	100
13	11,5	113	25%	200	0%	8%	30%	20%	10	101
14	11,5	113	25%	480	20%	8%	30%	20%	10	101

Table 4: BiobetterADD: Similar to Table 2, Table 3 indicates the major value determinants for the base case scenario (1). A peak sales level of US$ 690 million (and total life cycle sales according to the graph indicated in Figure 1) would be required for a BiobetterADD to achieve an expected NPV of US$ 10 million. Scenarios 2-14 demonstrate the sensitivity of the base case NPV to variations of individual parameters.

Scenario	Development Time (years)	Development Cost (US$ million)	PoS	Peak Sales (US$ million)	Yearly Sales Decline after Year 6	Discount Rate	CoGs (% of Sales)	SG&A Cost as % of Overall Slaes	Risk-adj. NPV (US$ million)	NON Risk-adj. NPV (US$ million)
1	12,5	180	10%	690	5%	8%	30%	20%	10	316
2	12,5	180	10%	690	5%	10%	30%	20%	-1	193
3	12,5	160	10%	690	5%	15%	30%	20%	-12	50
4	12,5	160	10%	2260	5%	15%	30%	20%	10	271
5	12,5	180	10%	515	5%	8%	30%	20%	0	218
6	12,5	180	10%	690	5%	8%	17%	20%	35	566
7	12,5	255	10%	690	5%	8%	30%	20%	3	288
6	12,5	255	10%	811	5%	6%	30%	20%	10	356
9	12,5	180	25%	690	5%	8%	30%	20%	61	316
I0	12,5	180	10%	690	5%	8%	30%	30%	-9	133
11	12,5	180	10%	1305	5%	8%	30%	30%	10	316
12	12,5	160	10%	588	0%	6%	30%	20%	10	315
13	12,5	180	10%	810	10%	8%	30%	20%	10	316
14	12,5	180	10%	1203	20%	8%	30%	20%	10	316

25% to 31%, increasing the expected NPV from US$ 10 million to US$ 18 million.

In highly competitive markets, overall SG&A cost may exceed the 20% reference to overall sales. The impact on value is comparable to the effect of CoGs. For a biobetterADD, an increase of SG&A to 30% of sales would reduce the expected NPV to US$ -9 million. Peak sales estimates would have to be as high as US$ 1,3 billion to get back to the target NPV of US$ 10 million (see Scenarios 10 and 11, Table 4). The effect of high SG&A cost would be comparable, in relative terms, for biobetterFORM (Scenarios 9 and 10, Table 3): increasing SG&A to 30% of sales reduces the NPV to US$ -10 million, peak sales estimates of US$ 600 million instead of US$ 280 million would compensate for this effect.

The late phases of the product life cycle are generally difficult to predict. In particular, it is uncertain to what extent innovative treatment paradigms will affect the sales of product classes with a longstanding history. The last three scenarios of the sensitivity analysis focus on this issue. For example, if there were no sales decline for a biobetterADD over a prolonged time period (Scenario 12, Table 4), expected peak sales could stay below US$ 600 million to yield the target NPV. If, however, the sales decline would aggravate to 10% or 20% per year, expected peak sales would have to achieve US$ 810 million or US$ 1,2 billion, respectively, to compensate for the losses in the later years. Applied to biobetterADD, a prolonged period without sales decline would reduce the peak sales level required to achieve the target NPV down to around US$ 200 million, while a strong competitive impact leading to 20% decline per year increases required peak sales to US$ 480 million.

The results suggest that the market size of the pioneer, a strong competitive profile vis-a-vis the pioneer/biosimilars, low to moderate biobetter and/or innovator competition, and only moderate CoGs and/or favorable pricing opions represent the strongest driver for value creation. However, the two categories of biobetters are impacted differently by these factors.

DISCUSSION AND RECOMMENDATION

The critical success factors for the development of biosimilars have been described earlier.[7] Besides establishing the required infrastructure for a cost-effective commercial production and the sales force for detailing the product, it is of utmost importance to be the first or second market entrant, because the market share of generics is depending on the number of competitors and the order of market entry (34, 35; see also discussion in 7).

A true biobetter, exhibiting a superior benefit/risk profile compared to the originator, is an alternative with the option to create more financial value compared to biosimilars. There is a significant chance that the higher investment for biobetters would be balanced favorably by higher sales compared to the respective biosimilars. In particular, an extended label may enable market and value expansion by increasing the patient pool and by maintaining a favorable price. In addition, new patents guarantee exclusivity for many years and a significantly improved standard of care will minimize the impact of potential competition from biosimilars. Therefore, biobetters are highly attractive projects

However, the biobetter strategy demands particular skills from the organization that go beyond process development. Analyzing potential options for the improvement of the originator product early on, combined with access to the required technologies to execute the ideas, requires strong capabilities in discovery research and development. Innovation capabilities resulting in products such as, e.g., Kadcyla® and GA 101 developed at Roche, might only be available at very few research based companies and not at the standard generic companies that are attracted by the biosimilars market. As a case in point, Roche has established a noteworthy strategy for defending its HER2-franchise by elevating the therapy standard in breast cancer in two steps.[36] In step one, the antibody Perjeta® (pertuzumab, a HER2 dimerization inhibitor that works complementary to Herceptin®) was developed for 1st line therapy in combination with Herceptin®. Combination therapy increases progression-free survival by more than 6 months compared to Herceptin® alone. It can therefore be assumed that, by the time of launch of Herceptin® biosimilars, combination therapy will have become treatment standard, giving Roche the opportunity to generate significant profits with Perjeta® on the one hand and still benefit from Herceptin® on the other hand, while pricing can be adapted flexibly to the future biosimilars environment. Purchasing the overall treatment package from one provider could then become the preferred option for oncology centers, reducing the commercial opportunity for Herceptin® biosimilars. In step two, Kadcyla® has been developed successfully for 2nd line therapy for patients relapsing after previous Herceptin®-containing regimens, again yielding an outstanding survival benefit.[37] This further expands the HER2-franchise and opens the option of positioning Kadcyla® in 1st line therapy. In fact, Roche is currently investigating a combination of Kadcyla® and Perjeta® in 1st line treatment in the ongoing MARIANNE study[37] which, if showing superiority of the combination over current standard therapy, could significantly reduce the role of trastuzumab in breast cancer therapy in the future. Overall, Roche's strategy

outlines that originator companies may successfully defend their commercial position vis-à-vis biosimilars by outperforming competition with innovative biobetters, leading to more volatile commercial scenarios for biosimilars today compared to previous years. In conclusion, any company considering biosimilar (and biobetter) approaches needs to be aware that most likely the innovator company will evaluate all potential options to protect and potentially expand the existing franchise by investigating second generation products with improved properties.

Regarding development requirements, biobetterFORM projects are in between biosimilars on the one hand and biobetterADDs on the other hand. The investments for biobetterFORMs are not significantly higher than for biosimilars. To create enough differentiation over biosimilars, however, an advantage for patients and payers has to be demonstrated. This could, for example, be achieved by an improved benefit/risk ratio through a more sustained Pk profile. In such cases, preferring a biobetterFORM approach over a biosimilar approach might make sense because it would lead to a differentiated product. Such product opportunities are particularly valuable in therapeutic areas where a substitution therapy requires long-term therapy and continuous drug exposure, such as, e.g. factor VIII deficiency or other genetic disorders like Gaucher disease.

In summary, each company engaged in the biologics or biosimilars business needs to establish a systematic evaluation process in which new product opportunities are reviewed on a regular basis and the different approaches ranging from biosimilars over biobetterFORM to biobetterADD are compared and prioritized. The final decision should be based on a realistic attitude towards the capabilities and the competitive strength of the own organization. For companies with a generic background the decision will likely be between pure biosimilars and biobetterFORMs. In contrast, for originator companies and for companies with significant research capabilities in the required areas biobetterADDs might be the most appropriate alternative.

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