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Biosimilars Or Biobetters: Make Your Decisions Wisely

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Abstract:*There is an increasing interest in biosimilars and biobetters, with the total number of reported development candidates equaling the number of innovative development compounds. Even assuming attrition in development, the biosimilars market will suffer from significant competition in the future. The present article builds on a financial modeling approach that takes into account development cost and risk and minimum required sales to yield a robustly positive financial value. In reference to the commercial success of the originator, such models can facilitate portfolio decisions. Predictive success criteria for biosimilars on the one hand and biobetters on the other hand are presented.*

INTRODUCTION

Over the past 20 years, biologic drugs were among the most effective innovators in serious and life threatening diseases. Several of these drugs are now approaching patent expiry. Therefore, there is a significant interest in developing and approving generic versions of such products. However, based on the higher complexity of biologics compared to small molecules, regulatory requirements are more extensive to demonstrate their safety and efficacy. Special attention is directed to the issue of immunogenicity that is still not fully understood (Barbosa, 2011). The European Medicines Agency (EMA) has released guidelines for different classes of biologic drugs that demand phase III-like studies in all cases (http://www.emea.eu.int/htms/human/biosimilar/biosimilarfin.htm). Furthermore, because of the higher molecular complexity, the full identity of two biosimilar products can usually not be proven. This is why the term biosimilar is used instead of biogeneric (EU Guideline CHMP/437/04).

In spite of these challenges, many companies have been attracted by the new biosimilars business opportunity. In fact, both companies with generic and with innovative business focus are active in this sector today. 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 biosimilars compared to their innovative predecessors is their lower price. Unfortunately, the room for price reductions is much lower for biosimilars compared to small molecule generics because of their high cost of goods and higher development expenses. Furthermore, originator companies may defend their products by offering rebates or by bundling. Thus, the uptake of biosimilars has been slow or negligible in nearly all European countries, with a total market for all EU biosimilars of around US$ 400-500 million in the year 2013 (Rader, 2013). It is therefore commonly believed that biosimilars will by far not reach the market penetration of small molecule generics, and there are opinions that biologic originators may in fact be able to keep 70-90 % of their total markets (Belsey et al., 2006). These factors, combined with the need to promote biosimilars through a dedicated sales force, increase the investment per project and the risk of financial failure significantly (Nickisch & Bode-Greuel, 2013).

Several years ago the term ‘biobetter’ was introduced to describe a new product option whose popularity is growing. A biobetter is ‘similar to an already approved biologic product, but is superior in one or more product characteristics’ (Malkin & Wasson, 2011). Frequently targeted product improvements include a longer plasma half-life (Chapman, 2002), reduced immunogenicity (De Groot & Scott, 2007), higher potency (Platis & Labrou, 2008), and more convenient administration (Herwadkar & Banga, 2012). 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 not only against biosimilars but also against the original, potentially leading to significantly higher sales volumes than the latter. Indeed, most pharmaceutical 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. These developments lead to more optimistic expectations regarding the growth of the biosimilars/biobetters sector:

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whereas a recent study by Frost & Sullivan of January 2014 predicted the biosimilar/biobetter market to reach only US$ 23 billion in 2019, a new study published by Companiesandmarkets predicted a stunning US$ 167 billion market size already in 2017 (www.companiesandmarkets.com).

Given the significant investment needed for building a competitive infrastructure, the engaged companies realize the need to exploit synergies by building project portfolios. Consequently, there is a high number of reported biosimilar/biobetter projects. The Biotechnology Information Institute (BII) database currently includes 514 biosimilar projects and 402 biobetter projects (www. Biosimilars.com). The numbers appear even more impressive if they are compared to the (only) 907 originator products in clinical development, as reported by the Pharmaceutical and Manufacturer's Association (www.PhRMA.org). In particular, the number of biobetters is virtually unlimited, given the various molecular and technical approaches. This leads to an enormous economic potential but also creates significant challenges for decision makers to allocate the limited resources wisely, in view of the uncertain regulatory and commercial environment. It is the intention of the authors to provide guidance to decision makers how, for a given organization, value-creating projects with strategic fit can be selected. A detailed financial analysis of the opportunities and challenges associated with biosimilars on the one hand and biobetters on the other hand has been published earlier (Nickisch & Bode-Greuel, 2013; Bode-Greuel & Nickisch, 2014). In the following, the most relevant findings are summarized.

DECISION MAKING FOR BIOSIMILARS

Assuming an average biosimilar project with a considered marketing period of 12 years (assumptions see in Table 1), peak sales of around US$ 180 million would have to be

TABLE :1

Discount rate: 8% *Tax rate: 30%*	**Biosimilar**			**Biobetter Reformulation**			**Biobetter Molecular Modification**		
eNPV: USD 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%		
Mkt (% of Sales)	20%			20%			20%		
Peak Sales (USD m)	**180**			**270**			**690**		

Table 1: The table provides an overview of the assumptions applied in the financial valuation model for biosimilars and two categories of biobetters. The development assumptions reflect commonly accepted figures. Details of the methodology, the applied models and sensitivity analyses are provided elsewhere (Nickisch & Bode-Greuel, 2013; Bode-Greuel & Nickisch, 2014; Bode-Greuel & Greuel, 2005). In the valuation models, peak sales are reached in the year 5 after launch, maintained for 2 years, and thereafter impacted by innovative treatment principles, leading to a yearly sales decline of 10% for biosimilars, 7.5% for reformulated biobetters, and 5% for biobetters with molecular modifications. Overall, the product life cycle was modeled for 12 years. It is assumed that an expected net present value (eNPV) of US$ 10 million at project start would be considered sufficient for a 'go' decision. In view of the significant commercial risk, the present analysis focuses on the likelihood of achieving the necessary sales.

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predicted to yield a robustly positive expected net present value (eNPV) of US$ 10 million at the decision to start development (a detailed description of the valuation methodology is provided by Bode-Greuel & Greuel, 2005). Based on one-way sensitivity analyses for various development and market assumptions, the required peak sales for a robustly positive eNPV range between US$ 135 million and US$ 450 million. The required corporate capabilities for biosimilar development and marketing, as opposed to the requirements for small molecule generics, have been discussed earlier by Nickisch & Bode-Greuel (2013) and Bode-Greuel & Nickisch (2014). The following discussion focuses on the commercial success factors. In this context, the critical questions are at which circumstances it is reasonable to expect peak sales of US$ 180 million, and whether a product life cycle of 12 years after patent expiry of the originator can be maintained. The following success criteria can be derived from these questions:

- Market size of the originator product
- Total biosimilars share of originator market
- Number of biosimilar products
- Order of market entry of biosimilar products
- Impact of innovative treatment principles that may decrease the relevance of both originator and biosimilars

TABLE: 2

Overall 30% Biosimilars Share	OriginatorLOW OriginatorMEDIUM OriginatorHIGH	US$ 2,500 million US$ 5,000 million US$ 10,000 million				
	Share of					
Order of Market Entry	1st	2nd	3rd	4th	6th	7th
First	**100%**	-	-	-	-	-
BiosimLOW	750					
BiosimMEDIUM	1,500					
BiosimHIGH	3,000					
Second	**59%**	**42%**	-	-	-	-
BiosimLOW	428	303				
BiosimMEDIUM	856	607				
BiosimHIGH	1,711	1,214				
Third	**44%**	**31%**	**25%**	-	-	-
BiosimLOW	311	221	181			
BiosimMEDIUM	621	442	362			
BiosimHIGH	1,243	884	724			
Fourth	**36%**	**25%**	**21%**	**18%**	-	-
BiosimLOW	248	176	144	126		
BiosimMEDIUM	495	352	289	251		
BiosimHIGH	991	705	577	502		
Fifth	**31%**	**22%**	**18%**	**16%**	**14%**	-
BiosimLOW	208	148	121	105	94	
BiosimMEDIUM	416	296	242	209	188	
BiosimHIGH	832	591	483	419	375	
Sixth	**27%**	**19%**	**16%**	**14%**	**12%**	**11%**
BiosimLOW	179	127	104	91	81	74
BiosimMEDIUM	358	255	209	181	163	148
BiosimHIGH	717	509	417	362	326	297

Overall 10% Biosimilars Share	OriginatorLOW OriginatorMEDIUM OriginatorHIGH	US$ 2,500 million US$ 5,000 million US$ 10,000 million				
	Share of					
Order of Market Entry	1st	2nd	3rd	4th	6th	7th
First	**100%**	-	-	-	-	-
BiosimLOW	250					
BiosimMEDIUM	500					
BiosimHIGH	1,000					
Second	**59%**	**42%**	-	-	-	-
BiosimLOW	143	101				
BiosimMEDIUM	285	202				
BiosimHIGH	570	405				
Third	**44%**	**31%**	**25%**	-	-	-
BiosimLOW	104	74	60			
BiosimMEDIUM	207	147	121			
BiosimHIGH	414	295	241			
Fourth	**36%**	**25%**	**21%**	**18%**	-	-
BiosimLOW	83	59	48	42		
BiosimMEDIUM	165	117	96	84		
BiosimHIGH	330	235	192	167		
Fifth	**31%**	**22%**	**18%**	**16%**	**14%**	-
BiosimLOW	69	49	40	35	31	
BiosimMEDIUM	139	99	81	70	63	
BiosimHIGH	277	197	161	140	125	
Sixth	**27%**	**19%**	**16%**	**14%**	**12%**	**11%**
BiosimLOW	60	42	35	30	27	25
BiosimMEDIUM	119	85	70	60	54	49
BiosimHIGH	239	170	139	121	109	99

Annual peak sales 181≤ 250 US$ million

Annual peak sales ≤ 180 US$ million

Table 2: Expected annual sales for biosimilars depending on the sales of the originator and the overall share for biosimilars (assumption: 10- 30%, with the second and following product(s) launched, a price erosion of 2.5 % was assumed, respectively). Three categories of originators related to annual sales (LOW= US$ 2,500 million, MEDIUM=US$ 5,000 million, HIGH=10,000 million) were defined based on yearly sales. The companies' marketing capabilities were assumed to be equal. Calculated sales per market entrant, related to order of market entry, follow the rules published by Kalyanaram et al. (1995) and Urban et al. (1986).

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The analysis indicates that, if an overall biosimilars share of 10% were a likely scenario, biosimilars should only be developed for products achieving around US$ 10 billion annual sales. In fact, there is only one product of this category, i.e., Humira® (see Table 3). Enbrel® comes close with annual sales of US$ 8.8 million in 2013. For products with lower annual sales volumes, biosimilars would be at a high risk to make less than US$ 200 million per year, assuming several biosimilar competitors will reach the market (see Tables 2 and 3). If an overall share of 30% were a fair assumption for all biosimilars of a kind, the situation looked better. For products in the medium to high sales category, the sales risk for biosimilars will appear less threatening if the product is among the first four candidates launched. However, there are only 5 biologics with reported global sales of US$ 5-10 billion, and for these the number of biosimilars is highest.

In fact, competition among biosimilars evolves as a major threat for commercialization. Table 3 displays the top nine biologics in terms of sales and the respective biosimilars pipelines (www.fiercepharma.com/special-reports/10-best-selling-drugs-2013; www.MedTrack.com, July 2014). After application of appropriate attrition rates for the development phases (www.bioscience-valuation.com), 8 up to 18 launched biosimilars can be expected for each of the top 5 products. Although the originators' yearly sales range between US$ 6.5 to 11 bn, virtually all biosimilar candidates would be at risk to miss the US$ 180 million peak sales target in statistical terms, assuming that all of the expected 8-18 biosimilar products would be marketed both in Europe and in the USA.

So far, the conclusions drawn from the competitor pipeline were based on global sales. However, it cannot be deduced with certainty from public information which territorial development and launch strategies the respective companies will pursue. Furthermore,

TABLE :3

Originator Product	WW Sales 2013 (USD bn)	Cumulative probability of success	Preclin 37%	PhI 49%	PhII/Ph III 60%	Reg 80%	Launched 100%	Expected number of launched products
Humira	11.02	Number of	12	3	4	0	0	**8**
Enbrel	8.78	biosimilars	13	1	6	0	7	**16**
Rituxan/MabThera	7.5	in development	14	3	9	1	5	**18**
Avastin	6.75	per stage	15	1	3	0	0	**8**
Herceptin	6.56		9	2	7	1	1	**10**
Neulasta	4.39		4	2	3	0	5	**9**
Lucentis	4.21		3	0	1	0	0	**2**
Avonex/Rebif	3.01		0	2	1	0	5	**7**
Remicade	2.48		7	2	3	1	1	**7**

Table 3: There is a high number of biosimilars in development, and based on the favorable probability of development success compared to new molecular entities, many of them will be launched. In the assumed launches are compared to the expected sales related to order of market entry, in can be concluded that products currently in Phases I and II are at risk to miss their sales targets.

it cannot easily be assumed that all biosimilar products will be approved both in Europe and in the USA because of the different attitudes of regulatory agencies. It may in fact be challenging to achieve value creating sales levels only in one territory while development cost and risk remain the same. To what extent this effect will be balanced off by a lower number of competitors in a given territory remains uncertain, because it is not known which territorial strategies individual companies pursue. In any case, Europe will probably become a highly competitive market for biosimilars in the future.

Physicians hesitate to switch among biosimilar products because of the risk of immunogenicity. Therefore, the market uptake of biosimilars will mostly be driven by patients starting biologics therapy or requiring therapy

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change, which may lead to a slower uptake of biosimilars compared to that of ordinary generics. Among the commercial success factors for biosimilars mentioned above, being the first or second market entrant is therefore of utmost importance. The chance to win the race should be evaluated before decisions on major investments, such as, e.g., upscaling to commercial production or initiation of expensive clinical trials, are due.

DECISION MAKING FOR BIOBETTERS

A biobetter, exhibiting a superior benefit/risk profile compared to the originator, may be an attractive alternative to biosimilars with a larger commercial opportunity. There is a significant chance that the higher investment for biobetters (see Table 1) would be balanced favorably by higher sales compared to the respective biosimilars. In particular, an extended label may facilitate 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. For biobetters based on reformulations, financial analytics suggest that with an annual sales volume of US$ 270 million an expected NPV of US$ 10 million would be achieved at project start. For biobetters with molecular changes, which are most common in oncology, a more expensive and more risky full development program would be required, leading to a higher sales demand of around US$ 690 million at peak, to obtain a robustly positive expected NPV to substantiate the project decision.

In any case, the biobetter strategy demands particular skills from the organization that go beyond process development. The analysis of potential options for an improvement of the originator product, 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® 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, thereby securing competitiveness for three of its products. Perjeta® (pertuzumab, a HER2 dimerization inhibitor that works complementary to Herceptin®) is used in combination with Herceptin® as first line therapy, and the Herceptin®-biobetter Kadcyla® is positioned as second line therapy, with an option to move the latter to the first line position later on (King, 2012, see also Bode-Greuel & Nickisch, 2014). 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 even more volatile commercial scenarios for biosimilars today compared to previous years. In conclusion, any company considering biosimilar (and biobetter) approaches should be aware that most likely the innovator company will evaluate all potential options to protect and potentially expand the existing franchise by investing in second generation products with improved properties.

Regarding development requirements, biobetters based on reformulations lie in between biosimilars on the one hand and biobetters with a new molecular composition on the other hand. The investment for the earlier is not significantly higher than for biosimilars (see Table 1). 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 plasma kinetic profile. In such cases, preferring a reformulation 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.

Summarizing the key drivers of success, competition will be much more severe for biosimilars compared to biobetters, because there are no product differentiation options for the earlier. Assuming similar marketing power, being among the first four products launched will be the most significant commercial success factor. For products falling behind in development, managers should therefore consider termination of development to avoid financial losses. The pipeline for biobetters is significantly less crowded compared to biosimilars, and there are opportunities for product improvement, differentiation, label expansion, and market exclusivity. For realizing such opportunities, there are specific success factors for biobetters that add to the ones mentioned for biosimilars:

- Outstanding scientific and/or reformulation know how
- Strong clinical development capabilities
- Specialized marketing capabilities

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These requirements limit the biobetters option to big pharma and dedicated biotech companies. Biobetters will usually not match the capability profile of traditional generics companies.

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