The Value of Biobetters

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EXECUTIVE SUMMARY: The Value of Biobetters

The market of biologics is growing at a nearly twice the rate of pharma as a whole. Biologics are expected to account for approximately 17% of total global spending on medicines by 2016, and reach an overall market value of $200 billion to $210 billion in 2016, up from $157 billion in 2011.\(^1\) Seven of the top 10 global medicines by spending will be a biologic within the next 5 years.

Biotherapeutic development is costly and can take up to 15 years from discovery to market. For companies that have launched more than 3 drugs, the median cost per new drug is $4.2 billion; for those that have launched more than 4, it is $5.3 billion. Even if a company only develops 1 drug, the median spending is still estimated at a staggering $351 million.\(^2\) Cost coupled with the risk of a drug failing during experimental development, 19 in 20 drugs fail to go to market, means that companies are turning their attention to the development of biobetters and biosimilars which are perceived to have a lower business risk than developing an originator biologic product.

\(^1\) The Global Use of Medicines: Outlook Through 2016 July 2012 analysis by the IMS Institute for Healthcare Informatics.
TERMINOLOGY

Follow-on biologics, which include biobetters and biosimilars, are approved subsequent versions of an originator biologic molecule.

A biobetter, sometimes used interchangeably with the term biosuperior, is a biological that has been structurally and/or functionally altered to achieve an improved or different clinical performance, compared to an approved reference product. The term currently has no legal/regulatory recognition.

The requirement for “better than” the reference product/originator product is an important differential from biosimilar products, which are structural imitations of the originator, promising the same effect as the originator biological, but at a reduced cost.

Modification of the originator product is accomplished through chemical (eg, polyethylene glycol [PEG]) or molecular (eg, recombinant gene technology site-directed mutagenesis or amino acid additions) modifications with functional changes that include, but are not limited to, increased half-life, reduced toxicity, reduced immunogenicity, and enhanced pharmacodynamic effects.

Biobetters are not actually a new concept, for example, pegylation of existing molecules is a well-known method for extending the half-life of a biologic molecule, which in turn means a reduced dosing schedule for the patient. For example, the first pegylated version of the interferon alfa (Pegasys®) was approved by the European Medicines Agency in 2002, but it wasn’t until 2007 that the term “biobetter” was first coined by the CEO (G.V. Prasad) of Dr. Reddys Laboratories at bioinvestor’s conference.

With the rapid growth in the biologics market, the term biobetter appears to have recently gained more media attention, as pharma companies choose how they will pursue this lucrative market.

DEVELOPING BIOBETTERS COMPARED TO BIOSIMILARS

Regulatory Considerations

Biosimilar development follows a stringent legal and regulatory pathway across the globe. From a regulatory stance, a biobetter is a new chemical entity, and therefore applications follow the established regulatory pathways for a new chemical entity in both the US via the BLA (Biologics License Application), and the EU ie, a stand-alone application.

There are a number of significant differences between a biobetter and a biosimilar biologic development program (see Table 1), as by definition a biosimilar is claiming similarity to originator product rather than “better than”.

<table>
<thead>
<tr>
<th>*CTD Module</th>
<th>Biobetter</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality Package</td>
<td>√</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ additional comparative data</td>
</tr>
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<tr>
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</tr>
<tr>
<td>Phase IV/Safety</td>
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</table>

*CTD - Common Technical Document

Table 1 - Summary of Differences Between a Biobetter and Biosimilar Development

Whilst the additional quality comparability requirement for biosimilar development can be of significant cost, the abbreviated non-clinical and clinical package, combined with the possibility of extrapolation of therapeutic similarity from one indication to another is a major advantage for biosimilars compared to that of biobetters, as this represents a significant cost and time saving.

### Scientific Considerations

The biosimilar guidelines provide guidance regarding the criteria for assessing biosimilarity, and make it clear that the aim is not to establish patient benefit (this has been established by the reference product), but rather biosimilarity. The focus of biosimilar development is to convincingly demonstrate high similarity to the reference product. The type and extent of clinical data requirements for biosimilars vary, and depend on the complexity of the active substance and how well it can be characterized on the availability of an accepted surrogate endpoint to compare efficacy, and on the type and seriousness of safety concerns that have been seen with the reference product or the substance class. In addition, an acceptable non-inferiority/equivalence margin should be defined, taking into account the
historical data and relevant clinical and statistical considerations in accordance with ICH Topic E 10 and FDA non-inferiority draft guideline. When considering assay sensitivity, important details of the trial design, eg, study population, concomitant therapy, endpoints, and run-in periods should adhere closely to the design of the trials used to determine that historical evidence of sensitivity to drug effects exists. For biobetter development, the most important element is being able to define the “better than”, which in itself determines the study endpoints and design. Given that the claim is “better” comparative studies are required against the originator.

If the claim is superiority for clinical efficacy or safety then the sponsor would likely want to consider superiority study. On the other hand, there is the possibility to choose a non-inferiority design, thereby reducing the sample size. However, this would not support a regulatory approval for superiority.

If a non-inferiority design is chosen, all design aspects should also adhere to the non-inferiority guidance, ICH Topic E 10, and FDA non-inferiority draft guideline. An acceptable non-inferiority margin should be defined, taking into account the historical data and study population. Endpoints should also adhere closely to the design of the trials used to determine historical evidence of sensitivity to drug effects exists.

Historically non-inferiority designs have been used for a biobetter medicine. An example is the clinical development for Amgen Neulasta® (peg-GCSF). Confirmatory efficacy studies consisted of 2 pivotal studies 990749 and 980226. Both were double blind studies that evaluated the comparability of a single administration of pegfilgrastim with multiple daily administrations of filgrastim. Both phase III studies used non-inferiority designs, and sample sizes were calculated accordingly with both studies adequately powered for efficacy.

MARKET POSITION

Both biobetter and biosimilar molecules target an established mechanism, safety and efficacy profile, thereby lowering the potential business risk when compared to the development of a new biologic molecule.

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However, there are several significant differences between biobetter and biosimilars development for a pharma company to consider before choosing which development strategy to follow.

In favor of biobetter development:

- A biobetter does not have to wait until a patent expires on the originator product before the product can be launched in the market.
- Greater potential to avoid infringing patents or at least lower litigation costs since it is not claiming similarity to the originator product.
- Biobetters have an advantage over biosimilars as they constitute an improvement over the originator and any biosimilar competitors, and should therefore be patentable.
- A biobetter can command a price premium, as it has a clinical advantage over the originator product. Biobetters should be less cost sensitive when compared to a biosimilar because they are in essence a new compound.
- As a new chemical entity a biobetter will be given data exclusivity for 12 years in the US and 8 years in the EU.

In favor of biosimilar development:

- Lower cost of development primarily due to biosimilars potentially having the significant advantage of extrapolation of the efficacy and safety data to all approved indications of the originator product.
- Biosimilars have the potential in the US for interchangeability and substitution.
- The potential for lower marketing sell costs compared to a biobetter since the product is an imitation of the originator product.

However, it turns out that getting biosimilars to market is harder than expected, especially in the US, where further guidance concerning the expectations of the US authorities for a biosimilars approval is still pending from the FDA. Looking towards Europe, there has been some success overall with several biosimilar molecules approved, but the market penetration with existing biosimilar products has proven to be more difficult than originally predicted.
Figure 1 below illustrates the investment/risk versus the potential marketing adsorption rate for biosimilars, biobetters, and innovative biologics showing the higher the business risk, the greater the potential returns.

Some originator companies are using the development of biobetters as a strategic move to protect their market share and prolong the mileage of an existing product. Companies can draw on previous knowledge to stream the development, thereby saving costs.

Companies are also trying to develop platform processes that can be applied to more than one existing product to develop panels of biobetter molecules. Although the modifications will need to be validated for each individual compound, a platform medication process allows for the rapid generation of multiple biobetters. Such a strategy has been seen recently, with large pharma companies partnering with smaller biotechnology companies that specialize in the modification of monoclonal antibodies to improve their effector functions.

CONCLUSION

Biosimilars have been approved in the EU including a monoclonal antibody (Infliximab). Getting a biosimilar in the market has been harder than expected, especially in the US, and the cost higher than originally predicted. The future of biobetters is difficult to predict, but many analysts believe that biobetters with their improved characteristics, are a more exciting and favorable proposition than biosimilars, and will offer a medical advantage along with a better price.
CONTACT INFORMATION

For further information or to discuss any aspect of PRA’s services offered in the field of biobetters, please contact your Business Development Manager or the employees listed below:

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