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James Wright is a Consultant at Valid Insight. He has twenty years' experience in the healthcare industry, and has been involved in many pricing and access research projects. Most recently James led projects involving the development of EU patient access solutions in rare diseases and assessment of payer acceptance of limited clinical data submissions to EU agencies. He has also headed up research projects ranging from competitor landscaping and stakeholder mapping, through treatment pathway analysis and value message development, to payer and KOL engagement. James also has considerable experience in managing and running advisory boards with payers and clinical KOLs, as well as running commercial programs to develop B2B strategies.

ARE BIOBETTERS BETTER?

Both biosimilars and biobetters are derivative variants of an original biologic molecule. While biosimilars are close copies of the marketed originator, the term biobetter refers to a drug that is in the same class as an existing product but is not identical; it has been improved, for example in efficacy, safety, tolerability or dosing regimen. Biobetters have been described as *“antibodies that target the same validated epitope as a marketed antibody, but have been engineered to have improved properties”*.¹

From a regulatory standpoint biobetters are considered new products and afforded the same patent protection as any other originator. Biobetters are therefore required to provide the same clinical and non-clinical data packages as all other originator products, whilst an attractive element for biosimilar developers must be the reduced clinical data package required (Table 1).

While biobetters are considered new chemical entities, they do rely on a starting point in development, the true originator, on which the modifications/improvements have been based. This creates a time pressure for the manufacturer if the biobetter is to make it to market before a biosimilar, and avoid the downward price pressure a biosimilar creates. Together the price pressure and cost of development brings the question to mind: **are biobetters worth the investment?**

Table 1 Summary of regulatory data requirements

Regulatory data package	Biosimilar	Biobetter
Quality package	✓	✓
Non-Clinical	✓	✓
Clinical Phase I	✓	✓
Phase II	X	✓
Phase III	✓ covers all originator indications	✓ per indication
Phase IV	✓	✓

Source: ²

Biologic modification through PEGylation

One way of improving or modifying the originator is through PEGylation. PEGylation is the modification of biological molecules by covalent conjugation with polyethylene glycol (PEG), a non-toxic, non-immunogenic polymer. This process can be used to change the properties of the molecule to, for example, increase drug stability and reduce drug administration frequency.³

PEGylation has been used to adapt several molecules including the development of Methoxy polyethylene glycol-epoetin beta (Mircera®) and Pegfilgrastim (Neulasta®). Both products were developed using PEGylation technology to achieve reduced dosing frequency, without diminishing efficacy over the originator products.

Mircera, used in the treatment of symptomatic anaemia in Chronic Kidney Disease (CKD)⁴, was created as a PEGylated version of epoetin alfa. In 2007, the EMA approved Mircera⁵ for once-monthly dosing to anaemic patients as opposed to weekly dosing for the biosimilar version of epoetin alfa (Epogen®).

In guidance⁶ the National Institute for Health and Care Excellence (NICE) found **“no evidence to distinguish between ESAs (erythropoietic stimulating agents) in terms of efficacy”** and attention instead was given to the route of administration in different environments.

In 2007, the Haute Autorité de Santé (HAS) found **“In view of the data available (in particular, insufficient quality of life data), Mircera is not expected to have any additional impact on morbidity or patients' quality of life despite the fact that it is more convenient”**⁷ and provided an ASMR rating of V – no added benefit.

The shift from once daily or three times per week, to once fortnightly or monthly dosing frequencies makes a more convenient product for patients and may reduce healthcare burden, however convenience does not always translate into value for payers.

Biobetter or 2nd generation product?

Using PEGylation is one way in which an originator can be modified to develop a new product, another is using biotechnical engineering bringing together two chemical entities into one.

In 2000 Herceptin® (trastuzumab) received its first EU approval⁸ for use in HER2+ metastatic breast cancer. Herceptin is a humanised monoclonal antibody (MAb) targeting the HER2 receptor, a member of the human epidermal growth factor receptor family. In 2013 Kadcyla® (trastuzumab emtansine) received its first EU approval⁹ based on for HER2+, unresectable, locally advanced or metastatic breast cancer who had previously received Herceptin and a taxane, separately or in combination. Kadcyla is the combination by biotechnical engineering of Herceptin and DMI (a cytotoxic chemotherapy agent, derived from maytansine, a microtubule inhibitor).¹⁰

At the time of introduction Herceptin was a stepped change in the treatment of breast cancer and remains the dominant standard of care for HER2+ metastatic breast cancer. In its first pivotal trial (EMILIA, NCT00829166¹¹) Kadcyla demonstrated superior efficacy over Tykerb® (Lapatinib) in 2nd line treatment, however, subsequently, in its 2nd pivotal trial, Kadcyla failed to demonstrate superiority over Herceptin¹² in 1st line treatment (MARIANNE, NCT01120184¹³).

It is noted that Kadcyla has performed well in the 2nd line treatment setting and is still under investigation for further indications including the treatment of patients with HER2+ breast cancer who have residual tumour present in the breast or axillary lymph nodes following preoperative therapy and, in combination with Perjeta® (pertuzumab), for the adjuvant treatment of patients with operable HER2+ primary breast cancer.

In the example of HER2+ breast cancer it could appear that the ‘biobetter’ is not in fact ‘better’ than the originator, having failed to demonstrate superiority, however it is important to remember that as a 2nd line treatment for those patients who have not responded to treatment, Kadcyla represents an improvement in standard of care and therefore remains an important treatment option.



Future of biobetters

If we apply the definition of a biobetter from Beck¹, then we can consider margetuximab to be the next biobetter from the same ilk as Herceptin. Later this year phase III trial results of margetuximab plus chemotherapy vs trastuzumab plus chemotherapy in the treatment of HER2+ Metastatic Breast Cancer (SOPHIA)¹⁴ are expected. Margetuximab is an Fc-modified monoclonal antibody (MAb) engineered for optimal antibody-dependent cellular cytotoxicity (ADCC) against HER2+ tumours¹⁵. It is expected that the binding properties enhance margetuximab's ADCC activity in HER2+ tumours, including those with lower levels of HER2 expression¹⁶. It remains to be seen whether this 'biobetter' will demonstrate superiority or whether it can find the niche of non-responders to which it will provide much benefit.

While it is yet to be seen if biobetters can demonstrate improved value over the originator, new and innovative products, based on the originator or not, do provide stepped up value to patients providing improvements in convenience and further treatment options should disease progression occur.

For manufacturers having a target in mind and optimising the clinical trial program can support earlier market entry. The biobetter currently appears to be one way of maintaining market share and defending against biosimilar entry if superiority can be achieved.

For payers, the issue becomes one of magnitude of improvement – how much better, or efficacious, is the biobetter than the originator in a directly comparative way? The willingness to pay for biobetters will be directly proportionate to this; if the originator takes patients 80% of the way to cure; what can the biobetter offer, 90%? **What is 90% cure worth?**

Attaching a high price tag on a biobetter, will hinder commercial success in a price competitive market unless you can justify

the price on many levels, not just primary efficacy outcomes. Innovation typically affords new products leverage to command higher prices, but in the biologics market, differentiation will be key, not just innovation, and pricing expectations will need to be realistic in a world where your comparators are fast going generic and biosimilar products are entering with around 30% lower prices.

Ensuring market access for biobetters

Biobetters do have a chance for commercial success, because existing treatments are not perfect, but understanding the market and developing products that can offer parity in some clinical domains, and improvements in others, will be of value. To achieve this, manufacturers will need to heed certain considerations to help ensure market access. These considerations are:

1. Addressing an unmet need

Identify and address unmet needs by engaging with clinicians and payers, understand the elements your product can address and those it cannot, but also be clear that while your product will not address every unmet need, some are more important to payers and clinicians than others, and your product should certainly not add to any unmet needs. The example used above, Mircera, is one example where the reduction in frequency of administration highlighted and met a previously unmet need of patients.

2. Addressing non-responders to current treatment

The second way is through focusing on patient sub-populations that may not be responding well, or well enough, to current standards of care. Defining and identifying the market segments with high unmet needs may require population and position scanning, as well as the in-depth evaluation of various disease indications and patient types. As we can see from the example of Kadcyla, payers, patients and clinicians benefit from the options in treatment available despite lack of superiority.



3. Timing entrance to market and negotiating from the start

Securing biobetter market access also requires scanning the market landscape for competitor products. To establish market share over price-driven biosimilars, biobetters need to enter the market before the exclusivity period of the patented reference biologic expires, which is the only time that biosimilars can start commercialisation¹⁷.

At the same time, be mindful that payers are likely tracking originator patent expiry, and when biosimilars are likely to launch, so they will have these price tags in their minds. In countries such as Scotland, the HTA process picks the comparator based on market share, so getting in before

biosimilars have had long on the market, can mean the branded originator is still the comparator, which will help with gaining higher prices. However, once the biosimilar is on the market, its market share will grow, and be difficult to compete against without pricing incentives. Biobetters may also need to compete with other innovative products, and so with all of this in mind, a solid economic-focused negotiation strategy will be necessary.

Biobetters are enhanced versions of originator biologics, which potentially offer added value to patients and payers. Premium pricing will be a barrier to patients gaining access to these innovative treatments, and so manufacturers need to put together the right evidence and strategy to secure market access.

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