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Going Global

As commercial factors drive firms to implement biosimilar programmes that meet the technical specifications and regulatory requirements of all major markets, it looks as though greater collaboration and international development strategies will be the way forward

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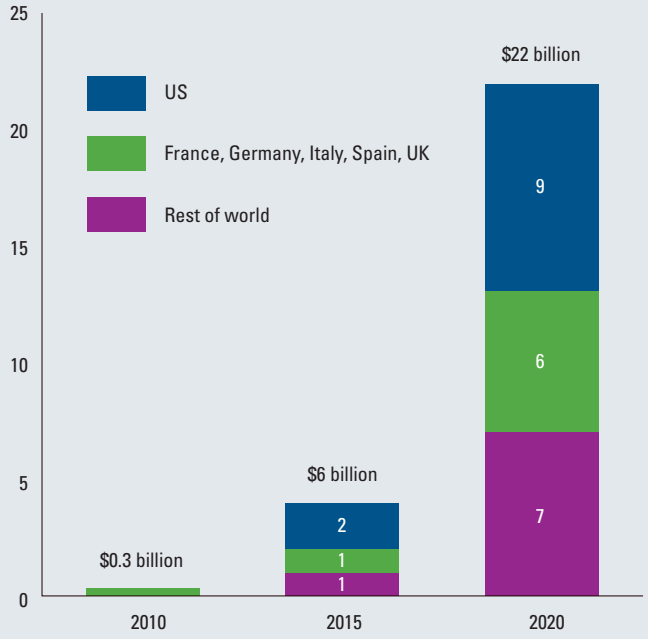
The huge sales and profits envisaged by many in the biosimilar market is being challenged by the rapidly increasing competition in this area (1). Large pharmaceutical and major biotechnology companies, in addition to new entrants, are competing for a limited number of opportunities and having to invest vast sums of money in development programmes – especially in clinical trials.

Asian companies have adopted a leading role in the global development and commercialisation of biosimilars, as seen by the 2013 EU approval of Celltrion's infliximab (Remsima) – the world's first biosimilar monoclonal antibody (2). Up until then, the market comprised recombinant growth factors and hormones in the EU – the leading region in terms of biosimilar regulation (3,4) – various originator copies in certain emerging markets, and no approved

Figure 1: Global biosimilars market potential



Source: Presented at Biosimilars Conference, Spain, April 2014 by S Opdyke, Pfizer

products in the US (with the arguable exception of Omnitrope, which was approved under different legislation). The latter has changed with the introduction of US biosimilars draft guidance (5) and the anticipated approval of the first product under US legislation: Sandoz's filgrastim (6).

The first US monoclonal antibody will certainly be a milestone. Undoubtedly, we are about to see a succession of approvals in the EU and US, but we should also remember that Celltrion has also gained approval for its infliximab in South Korea, and other Asian companies are likely to be within the leading group of biosimilars marketers. Celltrion has shown that it is possible for an Asian company to succeed in the West, but will the opposite be true? Although China and other Asian markets represent a major market opportunity for Western companies, Asia also poses significant development, regulatory and cultural challenges.

Market Competition

With the changes in legislation and attractive market opportunities in China and other Asian countries, it is increasingly important for biosimilar companies in the West to adopt a global approach to their product development programmes. Similarly, Asian firms are using biosimilars as a test ground to register and market complex – in this case, biological – products in the EU and US, as opposed to the much simpler, generic, chemical-based products more traditionally the domain of businesses from India and other Asian countries.

For Asian companies expanding operations into Europe and the US, it is therefore essential that their products comply with the highest level of technical and clinical standards, as well as meeting the regulatory requirements of the EMA and FDA. The EMA – the clear leader in the generation of legislation and guidance for biosimilars – together with the WHO, is usually the regulatory agency to which biosimilar manufacturers from the East look for their initial guidance (7).

The ferocity of competition in the biosimilars markets will be matched only by the race to recruit patients into the confirmatory trials required to secure marketing approval. These two features are inherently linked. It is accepted that to be successful with a biosimilar, one needs to be in the first three to five companies entering the market. However, the ability to recruit patients into the confirmatory trials is probably the single most important obstacle to achieving this – even when assuming that the funds are available to conduct these increasingly costly trials.

This competition is not only with other biosimilar studies, but also at study centres focused on the clinical trials of novel development products. The latter is a particular problem in areas of continued high unmet medical need such as lung cancer, or where there is a major market opportunity like arthritis – both of which have many novel products in development, as well as multiple competing biosimilars. For example, it was estimated in 2009 that there were around 122 novel lung cancer compounds, and about 20 biosimilars of both Avastin and Humira in development (8,9).

Managing Costs

The costs associated with clinical operations are looking increasingly prohibitive for many of the smaller biosimilars companies. In some cases, firms are having to initiate between 100 to 200 centres to conduct a confirmatory trial of 450 to 700 patients – a very small number of patients per centre (10). There are fixed set-up costs for each centre – independent of the number of patients that are ultimately recruited – all of which contributes to a high overall cost of developing a product that not only has to compete with other biosimilars, but also with novel treatments for the same condition. Furthermore, while the EMA and FDA will usually allow extrapolation of indications based on a single Phase 3 trial to all originator licensed indications, we are already seeing the larger manufacturers, such as Amgen, setting the bar high by conducting multiple trials for the same product (11,12).

When we consider the now fairly typical 'Phase 1 + Phase 3' approach for biosimilar products, it is, of course, essential to select the optimum Phase 1 and Phase 3 designs and study populations. The Phase 1 study is sometimes conducted in healthy volunteers and, in other cases, in patients, depending on the product and target indication. It is designed to show pharmacokinetic (PK) similarity to the originator, investigate the safety and immunogenicity profile, and support the previously demonstrated analytical and biological similarity exercise, comparing the test to originator product. Unlike for a novel product, the Phase 1 study is seen as the key clinical study by both the EMA and FDA.

Figure 2: Multiple approaches to biosimilar clinical development – adalimumab examples

	Phase 1	Phase 3
Amgen – adalimumab	PK study in normal healthy volunteers (NHV) France, Germany, Sweden, US N=100	• US and global – efficacy and safety of ABP 501 compared to Humira© in subjects with moderate to severe rheumatoid arthritis who have an inadequate response to methotrexate • US and EU – efficacy and safety of ABP 501 compared to Humira© in subjects with moderate to severe plaque psoriasis
Sandoz – adalimumab	PK/pharmacodynamic study in NHV India, Russia, Slovakia, Slovenia, Germany N=48	• US and global – efficacy, safety and immunogenicity of GP2017 compared to Humira© in patients with moderate to severe chronic plaque-type psoriasis
BI – adalimumab	PK, safety and tolerability study New Zealand N=193 Three-arm study: PK/safety Primary outcome measure: area under the curve N=324	• Not started

Varied development approaches make it difficult for stakeholders to evaluate results comparatively and enact standard policies

Source: Presented at Biosimilars Conference, Spain, April 2014 by S Opdyke, Pfizer

The Phase 3 trial is designed not to demonstrate efficacy per se, but to elucidate any 'residual uncertainties' in the biosimilarity comparison between the test product and the originator. The study results should provide an adequate body of evidence to support the registration dossier and, from a commercial perspective, this data package should be used in as many regions as possible. In order to accomplish this 'multi-regional' approach, key health authority discussions are necessary to assure that the study designs are acceptable.

Looking Abroad

On the positive side, the EMA and FDA have stated that it is the quality of clinical data that matters, not necessarily that trials must include US or EU patients. This provides an opportunity to conduct Phase 3 trials on a truly global basis, recruiting patients from Asia, Latin America and the Middle East.

However, while there may be a larger patient population in such regions, where the originator product may not be readily available (usually due to cost), the corollary is that the lack of the originator product may be a barrier in itself to the conduct of a comparative trial, and will require costly importation of drugs. In certain countries, such as China, drug importation can be difficult, if not impossible.

In addition, the varying length of time for regulatory review and approval of clinical trial applications must be balanced against potentially fast accrual rates when determining the country selection.

The availability of funds in Asia is opening up commercial opportunities to companies in the West with experience of developing biotech products. These important funds, alongside the greater patient populations for biosimilars trials in Asia – as well as in the Middle East/North Africa and certain other emerging market regions – together with EMA/FDA openness to clinical data from other regions, will probably drive a different approach to development of biosimilars compared to novel products. These features open up opportunities for truly international studies and global clinical, regulatory and commercial strategies.

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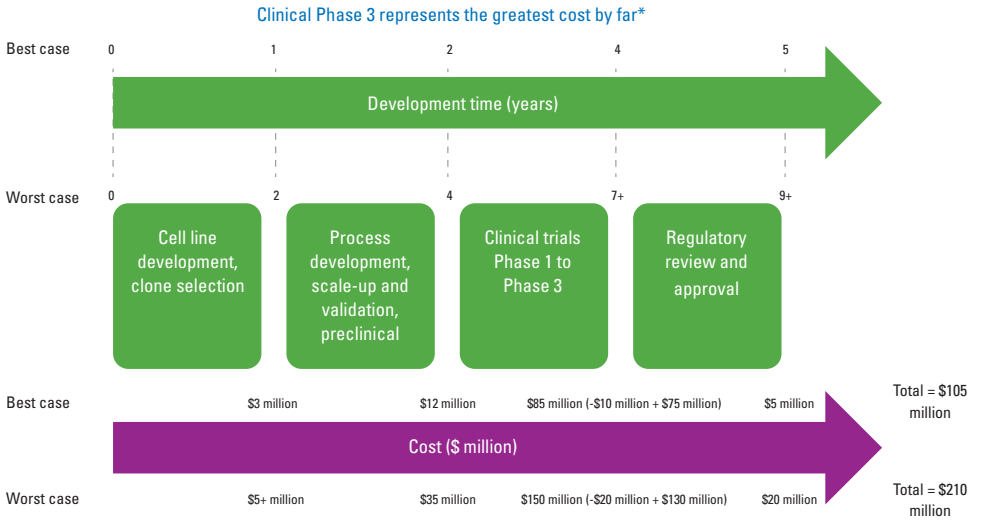
Convergence of Drivers

The convergence of these three drivers can be summarised as follows:

- It is essential to be one of the first three to five companies to reach the market for any biosimilar product to maximise return on investment. Development costs of $100 million must have a reasonable chance of being recuperated in what is likely to be a crowded market
- One of the major hurdles to being among the first market entrants is rapid completion of the confirmatory (Phase 3) trial, especially for monoclonal antibody products. Some of these are among the largest global revenue earners – for example, Humira, Avastin and Herceptin – and therefore generate huge competition for patients
- It should be remembered that Phase 3 study costs are additional to those of earlier manufacturing and development. There is also the potential risk of failure to be considered, on top of earlier technical hazards. Although this risk is less than for a novel product, the impact of failure would be catastrophic for the product
- Recuperation of costs and generation of profits looks increasingly likely to be dependent on having access to major markets in both the East and West. This may be through business partnerships, but the objective should result in a single development programme and regulatory strategy should be cost-efficient
- It is essential to ensure that the overall development programme and individual studies comply with as many global regulatory requirements as possible
- Despite the EMA and FDA stating that extrapolation of indications with the same mechanism of action is allowed based on a single Phase 3 trial, some of the commercial benefit of this may be lost due to larger companies with deeper pockets conducting multiple trials for the same product, and thus having more clinical data for marketing purposes

Figure 3: Typical cost of a biosimilar product development



Source: Presented at International Drug Discovery Science and Technology, Therapy and Expo 2014, China, by G McGettigan, Kinesys Consulting

*Time and cost are product dependent

Potential Barriers

Many questions remain to be answered, but some appear to be recurring themes and demand serious consideration from all stakeholders. These include the following:

- Will all ICH regulatory agencies follow the EMA's lead in allowing, in principle, the use of reference products from other ICH regions, at least for some of the development work?
- How does the EMA and FDA flexibility towards the use of reference products from other regions extend to other countries?
- Will regulatory agencies follow the EMA's lead in not requiring animal toxicology studies, unless absolutely required, bearing in mind the cost and time implications and the damaging impact on higher species animals? Certain European regulators have already published their opposition to this (13)
- What is the required amount and detail of analysis necessary to support the clinical trial applications without animal data?
- Will we see some flexibility in terms of regional sourcing of drugs for multi-national trials?
- To what extent is it possible to expedite the clinical development of a biosimilar by using adaptive design studies – and is this approach cost-effective?
- Can we always find an indication that can be used for the confirmatory Phase 3 study that is globally accepted?
- Will we eventually see a reduction in the need for major Phase 3-type trials to demonstrate biosimilarity as the agencies gain more experience with different products? This is being discussed internally at both the EMA and FDA
- If Phase 3 studies are ultimately not required, and as our knowledge of manufacturing, purification and analytical development improves, to what extent will biosimilars resemble true generic versions of their originator medicines?

Increasingly, we will see companies striving to produce biosimilars that meet the technical standards and regulatory requirements for all of the major markets, from West to East, as a result

of the commercial drivers. It is almost certain that there will be pressure on regulators in all countries and regions to harmonise their technical requirements – otherwise the global market will remain fragmented.

New Pathway

Unlike with novel products, this pressure towards coordination should include non-ICH regions, especially as the current environment requires global trials that include significant patient numbers from each region. Without harmonisation of regulatory and clinical requirements, over powered studies to satisfy patient numbers from particular areas may be required, in order to avoid the need to, and risk of, running additional country-specific trials; statistically, a trial of a 'good' drug will occasionally fail, while poor trial logistics can also lead to failure.

For all but the largest multinationals, globalisation of development programmes and commercialisation strategies will probably require a different kind of partnership between Asian, US and EU companies. This includes smaller firms specialising in the development of certain types of products or those trying to gain a foothold in lesser, possibly emerging, markets. We have already seen one successful example of an East-West partnership, namely the Celltrion-Hospira (soon to be Pfizer) agreement.

With this in mind, we may be about to see an interesting change in how companies tackle their global commercialisation strategies, their clinical development challenges, and their interactions with regulatory agencies. This would benefit from the input and engagement of trade associations from all regions involved, and while the convergence of all drivers may signal the end the biosimilars, 'honeymoon' period for some, it may open up a pathway for those who embrace new types of partnerships and approaches to global clinical development.

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