Making Progress

With patents expiring on key drugs, new legislation coming into effect and payers pushing for wider adoption of cost controlling measures, the market for biosimilars looks set to expand globally as the demand for these lower-cost alternatives increases.

When the concept of biosimilars was introduced in the EU in 2004, it was eyed with suspicion by several stakeholders, including Big Pharma, clinicians and some policy-makers. This is because biosimilars were not expected to have equal efficacy, and were associated with serious safety issues such as immunogenicity. However, the EU regulatory system and regulators moved ahead with their discussions, leading to the subsequent approval of biosimilars as a concept.

Since then, there has been increasing global recognition of their value, and universal acceptance that biosimilars are not just biological generics, due to their complexity. The first monoclonal antibody was approved in 2013 in the EU, following positive opinion by the Committee for Medicinal Products for Human Use. This could mark the start of a new era of progress in complex biosimilars.

**Early Development**

The last decade saw active regulatory discussions on biosimilar products in the EU, leading to the adoption and publication of general and product-specific guidelines by the EMA. In addition, several early biosimilar applications received positive opinions for less complex recombinant proteins such as erythropoietin, somatropin and filgrastim (granulocyte colony stimulating factor).

However, the global development of biosimilars faced problems in the beginning as only the use of an EU-licensed comparator had approval in the EU. This meant that statistics using non-EU comparators for the purpose of global development were not permissible as part of the primary evidence collection of biosimilarity. Reciprocally, the use of only an EU comparator was insufficient in non-EU countries. This led to unnecessary duplication of studies, especially in situations where the EU and non-EU comparators used would have been identical – potentially manufactured and supplied by the same facility.

Recognising these difficulties, the EMA guideline on biosimilars was revised to allow for the use of non-EU-licensed reference comparators in development programmes, provided that any approval given was based on comparators reaching the same standards as those used in the EU. The quality comparison for similarity would still be expected to be held against an EU reference product.

**Current Recommendations**

In a workshop on biosimilars organised by the EMA in 2013, several points were reiterated by representatives of the EMA/Biosimilar Medicinal Products Working Party (1):

- Necessity of a step-wise approach
- Avoidance of novel expression systems which could introduce additional risks such as atypical glycosylation pattern
- Avoidance of in vivo animal studies – these should only be considered if needed, on the basis of in vitro data being insufficient to exclude differences
- Avoidance of non-relevant animal species
- Application of primary clinical end-points to novel products might not be suitable
- Equivalence is the preferred approach, although non-inferiority might be acceptable in certain situations

Experts representing the biosimilar and innovator industries agree that global development is the way forward. This might not come as a surprise, as many innovator companies are embarking on biosimilar development – a well-established and well-understood expression system is no longer considered to be a risk.

Furthermore, it is the expectation of biosimilar developers that quality comparison is likely to become more important in the future, especially with increasing improvements in analytical technology. Whether or not this becomes a reality will be of immense interest, as it will likely make drug development less expensive. Whether regulators will ever have the confidence to rely mainly on quality comparison data and accept lesser clinical data remains to be seen.

**Global Attitudes**

Another aspect to be considered is a comparison between EU- and non-EU-licensed comparators, and whether they can introduce multiplicity issues from a statistical perspective. The recently published draft FDA Guidance for Industry, Clinical pharmacology data to support a demonstration of biosimilarity to a reference product, reiterates the step-wise approach and the value of fingerprint similarity (2). It also refers to residual uncertainty following initial comparison between results, and how this should drive the need for further studies. Four categories are referred to based on analytical characterisation: not similar, similar, highly similar, and highly similar with fingerprint similarity.

The conclusions reached from this approach should be enough to determine whether to continue to develop a product as a biosimilar,
and the extent to which further investigations are necessary, depending on which category the product belongs to. Furthermore, significant importance is given to pharmacokinetic/dynamic (PK/PD) comparison as a sensitive measure of similarity.

The FDA also acknowledges that some trials may be with a non-US-licensed reference; in which case, a three-way comparison between the biosimilar, US-licensed (legal reference product) and non-US-licensed reference in a PK/PD study is recommended.

In addition, the Australian regulatory agency, Therapeutic Goods Administration (TGA), has produced a guideline which broadly seems to accept the EU approach, while insisting on the reference being licensed in Australia (3). The TGA also appears to accept that vaccines and polysaccharides can follow the biosimilar pathway. Additionally, it emphasises that batch release testing or tests specified in monographs are insufficient, and the importance of complying with WHO International Non-Propriety Names (WHO-INN).

**WHO Guideline**

The WHO is responsible for designating the INN, which is considered important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among healthcare professionals and scientists worldwide (4). In the context of biosimilars, this is important as ‘brand name prescribing’ is an effective tool and it is better to keep the INN the same as the originator. This brand name prescribing approach has been taken up by many national competent authorities in the EU, including the UK Medicines and Healthcare Products Regulatory Agency (MHRA), which published a safety update to that effect in 2008 (5).

Furthermore, the WHO guideline on the evaluation of similar biotherapeutic products excludes vaccines and plasma-derived products under the biosimilar approach (6). The reason for the exclusion is not clear. It states that comprehensive characterisation and comparison at the quality level are the basis for possible data reduction in non-clinical and clinical development, therefore giving significant importance to the quality (Module 3) comparison.

The importance of quality characterisation and PK/PD comparison cannot be overemphasised. Clinical efficacy and safety comparison are not sufficiently sensitive to compensate for shortcomings in quality and PK/PD comparative data. If in doubt, the biosimilar approach might not be appropriate for all companies, and early engagement with regulators is advisable before deciding on whether to go down the biosimilar pathway or follow a stand-alone route. Even with this latter direction, it might be possible to use an abridged approach – if the primary molecular structure is identical to the originator, then the primary mode of action is likely to be the same.

**Next Steps**

Biosimilars have come a long way in the last few years. They are no longer an EU regional issue, although the EU continues to take the lead in biosimilar development and has reiterated its commitment to providing a scientific basis to enhance their global development. The WHO and other agencies such as the TGA have followed this up with the publication of their own guidelines.

It is encouraging that the concept of biosimilarity is finding increasing global acceptance and, with the recent FDA draft guidelines taking a pragmatic approach, this could help biosimilar manufacturers by potentially reducing the number of trials and patients. This should also lead to a significant drop in development costs.

If this reduction in costs is reflected in the pricing, it should help reimbursement authorities in their decision-making by lowering the cost to them. In turn, patients will benefit from increased availability of affordable drugs. For the EU regulators – and possibly non-EU regulators as well – there will no longer be a dilemma regarding data, which was considered to be acceptable scientifically, but not legally. For ethics committees, there will no longer be the challenge to approve duplicate trials with possible ethical implications.

The end result ought to be a win/win for most stakeholders. Biosimilar developers should be careful in choosing the most representative reference product and follow the step-wise approach to achieve regulatory approval.

If the reference product has multiple manufacturing sites, any comparability issues should be addressed early, and if in doubt, advice should be sought from regulators.

**References**

2. FDA Guidance for Industry: Clinical pharmacology data to support a demonstration of biosimilarity to a reference product, May 2014
3. Evaluation of biosimilars, TGA Health Safety Regulation, July 2013
5. MHRA Drug Safety Update, 1(7): 2008

**About the author**

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