Approval of the first biosimilar antibodies in Europe
A major landmark for the biopharmaceutical industry

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The positive opinion represents validation of the process established in the EU for approval of biosimilar antibodies, and paves the way for approval of other products with patents that have expired or are expiring soon, including rituximab (Rituxan®, MabThera®), bevacizumab (Avastin®), trastuzumab (Herceptin®), adalimumab (Humira®), as well as the Fc fusion protein etanercept (Enbrel®). Global sales for these products were between $6.1 billion (inflixi®mab) and $9.3 billion (adalimumab) in 2012.¹ Companies working in the biosimilar antibody space include established generics/biosimilars manufacturers, e.g., Celltrion, Hospira, Sandoz, as well as innovator companies that may either have in-house capacity to develop biosimilars or may acquire a biosimilars company. For example, Amgen and Pfizer are reportedly considering acquisition of Biocad, a biosimilar company based in Russia that is currently evaluating biosimilars of trastuzumab, bevacizumab and rituximab in Phase 3 studies. Final data collection for the primary outcome measures of these studies is estimated to be complete by the end of 2013; thus, marketing applications for more biosimilar antibodies may be submitted in 2014.

Defining a Biosimilar Product

In the EU, a biosimilar is defined as a copy of an already authorized biological drug, which is referred to as the reference product.² Demonstration of similarity between the biosimilar and reference products in their physicochemical characteristics, efficacy and safety must be based on a comprehensive comparability exercise.³ Biosimilars are known as follow-on biologics in the United States (US) and subsequent entry biologics in Canada.⁴ Biobetter, biosuperior and next-generation biologics are categories of drugs⁵ that contain differences in primary structure or major differences in glycosylation patterns compared with marketed products.⁶ Because it is not possible to produce exact copies of large proteins, especially glycoproteins such as antibodies⁷ due to their structural complexity and the inherent variability of bioproduction, the term biogeneric is avoided.

The EMA has pioneered the regulatory framework for approval of biosimilar products since 2005,⁸ resulting to date in marketing authorizations for 14 recombinant drugs.⁹ In 2010, the EMA released a draft guideline on similar medicinal products containing monoclonal antibodies (mAbs), following a workshop organized by the EMA.¹⁰ The guideline discusses relevant animal-model, nonclinical and clinical studies that are recommended to establish the similarity and the safety of a biosimilar compared with a reference mAb product approved in the EU. The final version was released by the end of 2012. IgG1 Fc-fusion proteins¹¹ were included in the scope of the final CHMP guidelines on biosimilar mAbs.¹²

The EMA and the US Food and Drug Administration (FDA) engage in scientific discussion intended to facilitate global biosimilar development.⁹ For its part, FDA has issued draft guidances on demonstrating biosimilarity to a reference product.¹³,¹⁴ As in the EU, biosimilar...
products intended for the US market must undergo strictly regulated comparability exercises, including physicochemical, analytical, functional, non-clinical and clinical evaluations. FDA recommends use of a step-wise approach that starts with basic evidence, e.g., identical protein sequence, and the totality of the evidence from all studies will be used to make a final determination of the similarity between the biosimilar and reference products. Comparability of the specific manufacturing processes for the biosimilar and reference products is not required in either EU or US.

**Primary Sequence Assessment of mAbs and Fc-fusion Proteins**

Extensive structural and functional comparisons of the biosimilar and the reference product comprise the foundation of biosimilar development.15,16 The primary amino acid sequence should be the same for the biosimilar and the reference product. Small differences in the micro-heterogeneity pattern of the molecule may be acceptable if appropriately justified with regard to its potential effect on safety, and pharmacokinetic (PK) and pharmacodynamic (PD) properties.7 As a consequence of the strict requirements for data, the analytical package for a biosimilar mAb submission is considerably larger than that of a ‘stand-alone’ mAb.17

It is important to note that amino acid variations for several antibody biosimilar candidates have been recently reported. For example, liquid chromatography-mass spectrometry intact mass measurement revealed that a candidate biosimilar trastuzumab had a total mass difference of −64 Da compared with the originator molecule.18 The mass difference was located on heavy chains (Asp359 and Leu211 instead of Glu359 and Met211) and produced a 32 Da lower mass per heavy chain for the biosimilar compared with the originator trastuzumab.19 The identified sequence variants demonstrated that the biosimilar candidate was derived from a different allotype compared with the originator mAb. Similar small differences between originator mAbs on the market and the corresponding amino acid sequences found in publicly-available databases and in the literature have been recently noted in reports for another biosimilar trastuzumab candidate,20 as well as etanercept,21 rituximab (+54 Da in the heavy chain, Val19′Ala)22 and cetuximab (+58 Da in the light chain, Ala211 instead of Glu211/Cys)23 candidates.

Taken together, these cases indicate that extensive mass spectrometry of both the reference product and the biosimilar should be done at the beginning of new biosimilar programs. The cases also suggest that distinctions should be made between locally-produced copies of protein products intended for markets within potentially resource-limited countries or regions24 and biosimilar products intended for the EU and US markets, which by definition must have the same amino acid sequence as the reference product and undergo strictly regulated comparability exercises.

**Micro-Variation in Originator Antibody Batches**

Numerous studies examining the structure-function relationships of the antibody therapeutics have been published in the past decade, with the aim of identifying micro-variants (glyco-variants, charge and size variants) and investigating their influence on antigen binding, stability, PK and PD.7 There is virtually no biological product for which the manufacturing process has remained unchanged since initial approval.12 It is in fact common for biopharmaceuticals to undergo process improvements and changes during the life cycle of the drug that trigger comparability exercises that must be reviewed and accepted by regulatory authorities.25 As a result, the profiles of micro-variants that are present in the drug substance have been shown to vary without affecting quality, safety and PK/PD. Only a limited number of papers on this topic have been published recently for marketed antibodies and Fc-fusion proteins,22 such as trastuzumab,26 rituximab,27 cetuximab,28 bevacizumab29 and etanercept.27 These papers and others indicate that quality profiles of batches of several marketed biologicals vary over time, including important quality attributes such as glycoform patterns and charge variants.30-32 These cases indicate the level of changes that may be acceptable by the health authorities following an extensive comparability exercise.

**Expectations for the Future**

The regulatory pathways to register biosimilar antibodies in the EU and US represent a way to decrease healthcare costs and to extend the use of mAb and Fc-fusion protein therapeutics. By the end of 2012, 35 biosimilar antibodies and Fc-fusion proteins were being evaluated in clinical trials in the EU.12 The approval of the first biosimilar antibody products in the EU represents a landmark, and it will undoubtedly pave the way for the approval of other biosimilar antibodies and Fc-fusion proteins. As with many other drugs, pharmacovigilance plans will need to be implemented for biosimilar products as they enter the market to enable accumulation of evidence of issues, including those associated with switching or alternating between biosimilars and reference products.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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