mAbs 5:5, 621–623; September/October 2013; © 2013 Landes Bioscience

Approval of the first biosimilar antibodies in Europe

A major landmark for the biopharmaceutical industry

Alain Beck[1] and Janice M. Reichert[2]

[1]Centre d'Immunologie Pierre Fabre; Saint-Julien-en-Genevois, France; [2]Reichert Biotechnology Consulting LLC; Framingham, MA USA

Keywords: adalimumab, antibody, biobetters, biosimilars, bevacizumab, cetuximab, etanercept, Fc-fusion protein, follow-on biologicals, infliximab, mass spectrometry, rituximab, trastuzumab

Drs. Beck and Reichert are Associate Editor and Editor-in-Chief, respectively, of mAbs

In a defining moment for the European Medicines Agency (EMA) and the biopharmaceutical industry, on June 27, 2013 EMA's Committee for Medicinal Products for Human Use adopted a positive opinion for two biosimilar infliximab products (Celltrion's Remsima® and Hospira's Inflectra®), and recommended that they be approved for marketing in the European Union (EU). The European Commission's decision on an application is typically issued 67 d after an opinion is provided; thus, decisions are expected in early September 2013. If approved, the products will comprise the first biosimilar antibody made available to patients in a highly regulated market, although launch may be delayed due to an extension of the reference product's (Remicade®) patent in the EU.

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 (infliximab) 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 drugs[5] 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 antibodies[7] 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 proteins[11] 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

Correspondence to: Alain Beck and Janice M. Reichert; Email: alain.beck@pierre-fabre.com and reichert.biotechconsulting@gmail.com
Submitted: 07/23/13; Accepted: 07/23/13
http://dx.doi.org/10.4161/mabs.25864

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 (Asp^{359} and Leu^{361} instead of Glu^{359} and Met^{361}) 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 publically-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, $Val^{119}Ala$)[22] and cetuximab (+58 Da in the light chain, Ala^{213} instead of $Glu^{213}Cys$)[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 regions[24] 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.[17] 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,[28,29] bevacizumab[30] 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.[31-33] 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.

References

1. Beck A, Carter PJ, Gerber HP, Lugovskoy AA, Wurch T, Junutula JR, et al. 8th Annual European Antibody Congress 2012: November 27-28, 2012, Geneva, Switzerland. MAbs 2013; 5:339-57; http://dx.doi.org/10.4161/mabs.24105
2. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars-why terminology matters. Nat Biotechnol 2011; 29:690-3; PMID:21822237; http://dx.doi.org/10.1038/nbt.1936
3. Visser J, Feuerstein I, Stangler T, Schmiederer T, Fritsch C, Schiestl M. Physicochemical and functional comparability between the proposed biosimilar rituximab GP2013 and originator rituximab. BioDrugs 2013; PMID:23649935; http://dx.doi.org/10.1007/s40259-013-0036-3
4. Beck A, Wurch T, Bailly C, Corvaia N. Strategies and challenges for the next generation of therapeutic antibodies. Nat Rev Immunol 2010; 10:345-52; PMID:20414207; http://dx.doi.org/10.1038/nri2747
5. Beck A. Biosimilar, biobetter and next generation therapeutic antibodies. MAbs 2011; 3:107-10; PMID:21285536; http://dx.doi.org/10.4161/mabs.3.2.14785
6. Beck A. Glycosylation Engineering of Biopharmaceuticals. Methods in Molecular Biology, Vol. 988. Beck, Alain (Ed.) Springer, 2013.
7. Beck A, Sanglier-Cianférani S, Van Dorsselaer A. Biosimilar, biobetter, and next generation antibody characterization by mass spectrometry. Anal Chem 2012; 84:4637-46; PMID:22510259; http://dx.doi.org/10.1021/ac3002885

8. Schneider CK, Kalinke U. Toward biosimilar monoclonal antibodies. Nat Biotechnol 2008; 26:985-90; PMID:18779806; http://dx.doi.org/10.1038/nbt0908-985
9. Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. Blood 2012; 120:5111-7; PMID:23093622; http://dx.doi.org/10.1182/blood-2012-04-425744
10. Reichert JM, Beck A, Iyer H. European Medicines Agency workshop on biosimilar monoclonal antibodies: July 2, 2009, London, UK. MAbs 2009; 1:394-416; PMID:20065643; http://dx.doi.org/10.4161/mabs.1.5.9630
11. Beck A, Reichert JM. Therapeutic Fc-fusion proteins and peptides as successful alternatives to antibodies. MAbs 2011; 3:415-6; PMID:21785279; http://dx.doi.org/10.4161/mabs.3.5.17334
12. Schneider CK, Vleminckx C, Gravanis I, Ehmann F, Trouvin JH, Weise M, et al. Setting the stage for biosimilar monoclonal antibodies. Nat Biotechnol 2012; 30:1179-85; PMID:23222783; http://dx.doi.org/10.1038/nbt.2447
13. Scientific considerations in demonstrating biosimilarity to a reference product [Internet]. Washington (DC); US Food and Drug Administration: c2012 [cited 23 July 2013]. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf
14. Quality considerations in demonstrating biosimilarity to a reference protein product [Internet]. Washington (DC); US Food and Drug Administration: c2012. [cited 23 July 2013]. Available from: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf
15. Kálmán-Szekeres Z, Olajos M, Ganzler K. Analytical aspects of biosimilarity issues of protein drugs. J Pharm Biomed Anal 2012; 69:185-95; PMID:22633839; http://dx.doi.org/10.1016/j.jpba.2012.04.037
16. Berkowitz SA, Engen JR, Mazzeo JR, Jones GB. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov 2012; 11:527-40; PMID:22743980; http://dx.doi.org/10.1038/nrd3746
17. Beck A, Wagner-Rousset E, Ayoub D, Van Dorsselaer A, Sanglier-Cianférani S. Characterization of therapeutic antibodies and related products. Anal Chem 2013; 85:715-36; PMID:23134362; http://dx.doi.org/10.1021/ac3032355
18. Xie H, Chakraborty A, Ahn J, Yu YQ, Dakshinamoorthy DP, Gilar M, et al. Rapid comparison of a candidate biosimilar to an innovator monoclonal antibody with advanced liquid chromatography and mass spectrometry technologies. MAbs 2010; 2:379-94; PMID:20458189
19. Gahoual R, Burr A, Busnel JM, Kuhn L, Hammann P, Beck A, et al. Rapid and multi-level characterization of trastuzumab using sheathless capillary electrophoresis-tandem mass spectrometry. MAbs 2013; 5:479-90; PMID:23563524; http://dx.doi.org/10.4161/mabs.23995
20. Chen SL, Wu SL, Huang LJ, Huang JB, Chen SH. A global comparability approach for biosimilar monoclonal antibodies using LC-tandem MS based proteomics. J Pharm Biomed Anal 2013; 80:126-35; PMID:23563225; http://dx.doi.org/10.1016/j.jpba.2013.02.040
21. Tan Q, Guo Q, Fang C, Wang C, Li B, Wang H, et al. Characterization and comparison of commercially available TNF receptor 2-Fc fusion protein products. MAbs 2012; 4:761-74; PMID:23032066; http://dx.doi.org/10.4161/mabs.22276
22. Beck A, Diemer H, Ayoub D, Debaene F, Wagner-Rousset E, Carapito C, et al. Analytical characterization of biosimilar antibodies and Fc-fusion proteins. Trends Analyt Chem 2013; 48:81-95; http://dx.doi.org/10.1016/j.trac.2013.02.014
23. Ayoub D, Jabs W, Resemann A, Evers W, Evans C, Main L, et al. Correct primary structure assessment and extensive glyco-profiling of cetuximab by a combination of intact, middle-up, middle-down and bottom-up ESI and MALDI mass spectrometry techniques. MAbs 2013; 5:699-710; http://dx.doi.org/10.4161/mabs.25423
24. Cheraghali AM. Current status of biopharmaceuticals in Iran's pharmaceutical market. GaBI J 2013; 2:26-9; http://dx.doi.org/10.5639/gabij.2013.0201.008
25. McCamish M, Woollett G. The continuum of comparability extends to biosimilarity: how much is enough and what clinical data are necessary? Clin Pharmacol Ther 2013; 93:315-7; PMID:23443756; http://dx.doi.org/10.1038/clpt.2013.17
26. Damen CW, Chen W, Chakraborty AB, van Oosterhout M, Mazzeo JR, Gebler JC, et al. Electrospray ionization quadrupole ion-mobility time-of-flight mass spectrometry as a tool to distinguish the lot-to-lot heterogeneity in N-glycosylation profile of the therapeutic monoclonal antibody trastuzumab. J Am Soc Mass Spectrom 2009; 20:2021-33; PMID:19744865; http://dx.doi.org/10.1016/j.jasms.2009.07.017
27. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol 2011; 29:310-2; PMID:21478841; http://dx.doi.org/10.1038/nbt.1839
28. Sundaram S, Matathia A, Qian J, Zhang J, Hsieh MC, Liu T, et al. An innovative approach for the characterization of the isoforms of a monoclonal antibody product. MAbs 2011; 3:505-12; PMID:22123057; http://dx.doi.org/10.4161/mabs.3.6.18090
29. Janin-Bussat MC, Tonini L, Huillet C, Colas O, Klinguer-Hamour C, Corvaïa N, et al. Cetuximab Fab and Fc N-glycan fast characterization using IdeS digestion and liquid chromatography coupled to electrospray ionization mass spectrometry. Methods Mol Biol 2013; 988:93-113; PMID:23475716; http://dx.doi.org/10.1007/978-1-62703-327-5_7
30. Toyama A, Nakagawa H, Matsuda K, Sato TA, Nakamura Y, Ueda K. Quantitative structural characterization of local N-glycan microheterogeneity in therapeutic antibodies by energy-resolved oxonium ion monitoring. Anal Chem 2012; 84:9655-62; PMID:23004563; http://dx.doi.org/10.1021/ac3023372
31. McCamish M, Woollett G. The rise of the biosimilar. Expert Rev Clin Pharmacol 2012; 5:597-9; PMID:23234317; http://dx.doi.org/10.1586/ecp.12.60
32. McCamish M, Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther 2012; 91:405-17; PMID:22318617; http://dx.doi.org/10.1038/clpt.2011.343
33. McCamish M, Woollett G. Worldwide experience with biosimilar development. MAbs 2011; 3:209-17; PMID:21441787; http://dx.doi.org/10.4161/mabs.3.2.15005