BIOSIMILARS IN HEMATOLOGY: INCREASING CHOICE, EXPANDING ACCESS

Summary of Presentations from the Sandoz Biopharmaceuticals-Sponsored Educational Session, which was part of the 'Updates-in-Hematology' Programme, held at the 19th EHA Congress, Milan, Italy, on 11th June 2014

Chairperson

Pier Luigi Zinzani[1]

Speakers

Joerg Windisch,[2] Steffen Thirstrup,[3] Wojciech Jurczak,[4] Paul Cornes[5]

1. Institute of Hematology and Medical Oncology 'L. e A. Seràgnoli', University of Bologna, Bologna, Italy
2. Chief Science Officer, Sandoz Biopharmaceuticals, Kundl, Austria
3. Director, NDA Regulatory Advisory Board
4. Department of Hematology, Jagiellonian University, Krakow, Poland
5. Bristol Haematology and Oncology Centre and Bristol Royal Hospital for Children, Bristol, UK

Disclosure: Pier Luigi Zinzani has a financial interest/relationship or affiliation in the form of consultancy for Bayer AG and Sandoz and has participated in speaker bureaus for Celgene International Sàrl, MundiPharma International Ltd, Pfizer Inc., and Takeda Pharmaceutical Company Limited. Pier Luigi Zinzani has received honoraria from and served on scientific advisory boards (SABs) for Celgene International, Sàrl, F. Hoffmann-La Roche Ltd., GlaxoSmithKline, MundiPharma International Ltd, and Takeda Pharmaceutical Company Ltd., and honoraria from Pfizer Inc. and SAB for Bayer AG and Gilead. Joerg Windisch is an employee of Sandoz Biopharmaceuticals. Steffen Thirstrup is a full-time employee at NDA Regulatory Services Ltd., which has a contractual agreement for his participation in this educational session. Wojciech Jurczak has received research funding from Celgene, Eisai, Gilead, Janssen, Pharmacyclics, Pfizer, Roche, Sandoz–Novartis, Spectrum, Takeda, and Teva, and has served on SABs for MundiPharma, Sandoz–Novartis, Spectrum, Takeda, and Teva. Paul Cornes has received salary from the UK NHS and honoraria from Roche, Janssen, Sandoz, Lilly, European Generics Association, Teva, and Hospira.

Acknowledgements: Writing assistance provided by Dr Tom Priddle, ApotheCom ScopeMedical.

Support: The publication of this article was funded by Sandoz Biopharmaceuticals. The views and opinions expressed are those of the authors and not necessarily of Sandoz Biopharmaceuticals.

Citation: EMJ Hema. 2014;1:30-39.

MEETING SUMMARY

Professor Pier Luigi Zinzani

Biologicals have revolutionised modern medicine by offering vital therapeutic options to treat or prevent complex, disabling, and life-threatening diseases. Between 2013 and 2018, seven of the top ten pharmaceuticals worldwide will be biologicals; however, growing demand, combined with historically-limited competition, will continue to strain healthcare budgets and limit patient access to these treatments. Since 2006, when the first biosimilar Omnitrope® was approved in Europe, 18 other biosimilars, including the first biosimilar monoclonal antibody (mAb), infliximab (approved in 2013), have received marketing authorisation with many others currently in development. There is now extensive clinical experience with biosimilar epoetin (EPO) and filgrastim in patients with cancer, and many studies have reported comparable efficacy with the originator products, no unexpected safety concerns, and significant economic savings. Nevertheless, misconceptions concerning biosimilars remain. This educational session discussed these issues and gave an overview of biosimilar use in hematology.

Dr Joerg Windisch highlighted the particular challenges and considerations associated with

the development of biosimilars while Prof Steffen Thirstrup covered the approval of biosimilars from the regulatory perspective. Dr Wojciech Jurczak gave a presentation on the development of biosimilars in hematology, with a particular focus on rituximab from a clinical perspective. Dr Paul Cornes concluded with the opportunities that the introduction of biosimilars offer in terms of health economics and improved patient access to care.

Target-Directed Development for Biosimilars

Doctor Joerg Windisch

Biologicals are useful in a wide variety of difficult-to-treat diseases and provide the opportunity to target disease pathways in a highly specific and systematic manner. The average marketed biological is around 20-times more expensive than a small molecule drug, and for this reason almost one-quarter of 46 European countries do not provide access to biologicals for the treatment of rheumatoid arthritis.[1] Cancer patients in the USA are twice as likely as the general population to go bankrupt a year after their diagnosis[2] and costs are considered an important barrier for biological use in psoriasis by 19–24% of European and Canadian dermatologists.[3]

The costliness of biologicals stems partly from their complexity, since biologicals have a 20-800-times higher molecular weight than small molecules they cannot be readily synthesised and are therefore expressed in bacteria or in the case of complex glycoproteins, such as mAbs, in mammalian cell lines. Once the relevant gene is inserted into the cell line, cells are grown in large bioreactors. The biological is isolated, purified to a typical level of at least 99.99%, before being formulated with stabilisers and filled into the final dosage form. Currently there are >40 methods, based around chromatography and mass spectrometry that can provide a quality profile on a mAb with >100 attributes, such as glycosylation, glycation, and higher order structure.[4] Some therapeutic mAbs function by simply blocking their target, but most also act via 'effector functions' to activate the immune system or trigger programmed cell death. These functions can be tested, alone or in combination, using a number of sensitive biological assays.[5-7]

Variability in glycosylation is a normal feature of naturally occurring glycoproteins, and recombinant glycoproteins are no different. Individual batches of proteins contain a mixture of differentially glycosylated sites that have slightly different levels of biological activity,[8] which can occur due to variability in the manufacturing process. These differences in attributes are often greater than batch-to-batch variability; they are stringently controlled by regulators and are approved only if they do not lead to clinically meaningful differences.[9,10] Biosimilars are approved biologicals with comparable safety, quality, and efficacy to a reference product with no clinically meaningful differences. A non-comparable or alternative biological is not a biosimilar and will not be approved for use in highly regulated markets.[11,12]

Once an effective biological enters the market the development of a biosimilar starts by assessing the quality of this 'reference product' and defining the target for technical development, which will stem from variability of the reference product. The structure, function, biological activity, and final dosage form must match that of the originator. The biosimilar must have comparable pharmacokinetics (PK) and pharmacodynamics (PD), and efficacy and safety must be confirmed via tailored Phase III studies. Examples of comparable glycosylation, higher order structure, and biological activity of biosimilar rituximab have been reported.[13]

Ultimately, a biosimilar must match its originator in terms of primary structure (amino acid sequence), post-translational modifications (particularly glycosylation pattern), higher order structure, biological activity, and purity level, although here a biosimilar can surpass the original biological (Figure 1).[4] Following preclinical toxicology studies, biosimilarity is then confirmed in the clinic in studies designed to detect subtle differences between the biosimilar and the original product, which is the essence of biosimilar development. PK and PD studies are crucial and can require recruitment of up to 300 individuals or patients to provide the power and sensitivity to detect these subtle differences. Tailored Phase III studies demonstrate biosimilarity using an equivalence-based design.[14] It is not a requirement to use the same primary efficacy endpoints as the reference product, but rather to choose those endpoints which are most sensitive in detecting potential differences.[15] Immunogenicity should be investigated in a comparable manner to the original product

and, as with product purity, this can potentially be improved upon without invalidating the claim of biosimilarity.

Extrapolation of indications can arise due to the biological having different uses and indications in different patient populations. However, if a biosimilar has been tested for one indication, regulatory authorities do not automatically grant approval for the use of others without separate justification. Justification for extrapolation includes mechanism of action, patient related factors, the relationship between the structure and the target, and PK and PD in different populations.[14,16,17] Crucially, the justification is not based on comparisons between one indication and another; it is always between the reference product, for which safety and efficacy has been established in each indication, and the biosimilar. When extrapolating, one must select a sensitive indication in a patient population that is fully immunocompetent and also exhibits a sufficient effect size to ensure potential differences are detected.[15,18,19] When developing a novel biological, the majority of key data come from clinical studies and the information from analytical studies is relatively unimportant. Conversely, biosimilar development relies heavily on analytical studies, which provide the necessary high sensitivity, with clinical studies providing confirmation.

In conclusion, current analytical methods allow a deep understanding of biologicals that facilitate the development of safe and effective biosimilars of highly complex molecules. Biosimilars must meet the same quality standards as the original products and must be approved by the EMA/FDA with extrapolation of indication building upon the entire similarity paradigm.

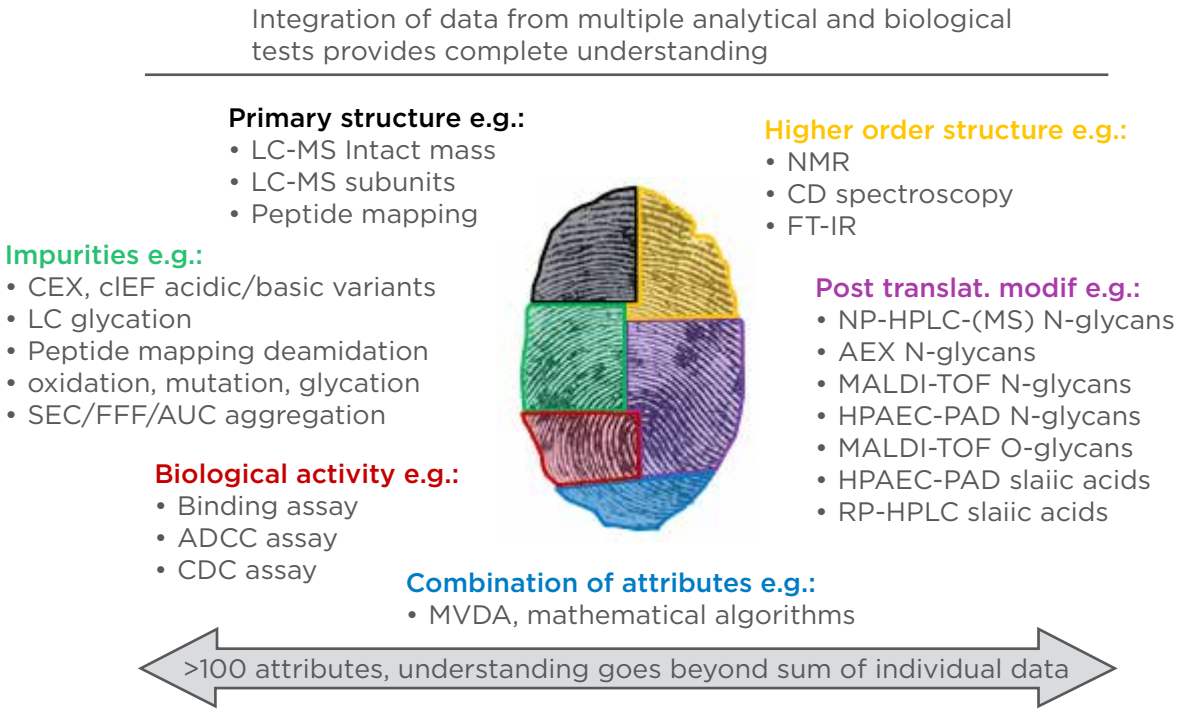

Figure 1: Analytical and biological tools used to characterise biopharmaceuticals and assess biosimilarity. ADCC: antibody-dependent cell-mediated cytotoxicity; AEX: anion exchange; AUC: analytical ultracentrifugation; CD: circular dichroism; CDC: complement dependent cytotoxicity; CEX: cation exchange; cIEF: capillary isoelectric focusing; FFF: field flow fractionation; FT-IR: fourier transform-infrared; HPAEC-PAD: high performance anion exchange chromatography-pulsed amperometric detection; LC: liquid chromatography; LC-MS: liquid chromatography-mass spectrometry; MALDI-TOF: matrix-assisted laser desorption ionisation-time of flight; MVDA: multivariate data analysis; NMR: nuclear magnetic resonance; NP-HPLC-(MS): normal phase-high performance liquid chromatography-(mass spectrometry); RP-HPLC: reverse phase-high performance liquid chromatography; SEC: size-exclusion chromatography.
Modified from Berkowitz et al.[4]

Table 1: Proposal for a more precise terminology.

Terms	Definition	Implications
Biosimilar*	Copy version of an already authorised biological medicinal product with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based on a comprehensive comparability exercise.	Only very small differences between biosimilar and reference with reassurance that these are of no clinical relevance. Extrapolation of clinical indications acceptable if scientifically justified.
Me-too biological/biologic Noninnovator biological/biologic	Biological medicinal product developed on its own and not directly compared and analysed against a licensed reference biological. May or may not have been compared clinically.	Unknown whether and which physiochemical differences exist compared to other biologicals of the same product class. Clinical comparison alone usually not sensitive enough to pick up difference of potential relevance. Therefore, extrapolation of clinical indications problematic.
Second-generation (next-generation) biological/ biologic Biobetter	Biological that has been structurally and/or functionally altered to achieve an improved or different clinical preformance.	Usually stand-alone developments with a full development program. Clear (and intended) differences in the structure of the active substance, and most probably different clinical behaviour due to, for example, different potency or immunogenicity. From a regulatory perspective, a claim for "better" would have to be substantiated by data showing a clinically relevant advantage over a first- or previous-generation product.
*Comparable terms defined by the same/similar scientific principles include the WHO's "similar biotherapeutic products" and Health Canada's (Toronto) "subsequent entry biologicals."		

Modified from Weise M et al.[21]

Regulatory Perspectives on the Approval of Biosimilars

Professor Steffen Thirstrup

An application to market the first biosimilar, a 'generic' version of a growth hormone in Europe, was made in 2001. The application was, however, rejected by the European Commission despite positive opinion from EMA's Committee for Medicinal Products for Human Use (CHMP), since there was no biosimilar legislation at this time. In the aftermath, the European legislators modified the definition of generic drugs to account for biosimilars, leading to the adoption of new directives in 2005. In 2006 the first biosimilar was finally approved. As each new class of biosimilar has emerged the regulators have developed product or therapeutic-specific guidelines, most recently the mAb guidelines in 2012; many of these early guidelines are currently under revision.[20] Similar biosimilar guidelines are now in place globally.[20] The FDA regulations recognise two distinct types:

1) Biosimilars: considered to be a new active ingredient, are not interchangeable, and have no market exclusivity.

2) Interchangeable biosimilars: deemed to have the same active ingredient but are interchangeable and have 1-year market exclusivity.

As discussed above, biosimilar development is not about efficacy and safety per se of the active substance, but to demonstrate biosimilarity.

All biologicals will regularly undergo manufacturing changes that are subject to certain guidelines, which do not differ substantially from those that govern biosimilar development. For instance, Remicade®'s manufacturing process has changed 37 times since the product was first approved in the European Union (EU).[8] A biosimilar product will have to meet all the requirements of the manufacturing process in addition to the regulations governing biosimilarity.

The first wave of biosimilars consisted of EPO-alfa, growth hormone, and filgrastim, small biologicals that can be regarded as having tested the maturity of the emerging regulations. More biosimilars are now on the market but some have since been withdrawn and others have failed to meet the regulatory requirements.

There are currently contentious issues surrounding the terminology of biosimilars and the nature of the regulatory review process in Europe. There are a number of definitions and a number of related terms such as 'me-too biological', 'follow-on biological', and 'biobetter' (Table 1), which all describe products that may not be regarded as biosimilars according to European standards.[21] Inappropriate use of the term 'biosimilar' has contributed to misconceptions about the regulatory requirements and the efficacy and safety of such products. Use of the term 'biosimilar' should only be done in relation to products approved in accordance with EU or equivalent regulatory standards. Studies have shown that the review time for a biosimilar is neither abridged or accelerated,[8] nor is the process more lenient.[22] Another unresolved issue in Europe, unlike in the USA, is that of interchangeability. In Europe, there are currently no requests for 'switching' studies, and practices governing interchangeability are decided on a national basis and, where applicable, left to the discretion of the prescribing doctor. In addition, a biosimilar will not automatically be granted a licence for all indications of the reference product, whereas it may be possible for biosimilars to be developed for new indications beyond those approved for the originator.

For >10 years Europe has led the way in quality, science-driven regulation, and manufacturing of biosimilars. Similar regulatory principles govern manufacturing changes and biosimilars. Biosimilars can drive innovation by competing with the established biological industry.

Developing Biosimilars in Hematology: a Clinical Perspective

Doctor Wojciech Jurczak

The development of biosimilars will reduce the mounting costs of developing new treatments and pass savings on to healthcare providers and ultimately to patients. As discussed above, the 'art' of biosimilar development is to demonstrate, within current technical and scientific limitations and taking into account the inherent variability of biologicals, that all relevant functional and structural aspects are as close to the reference product as possible.[8,18] Biosimilars, unlike 'copy biologicals,' have similar biological activities, enabling physicians to treat patients confidently,[12] and the focus below will be on growth factors,[23,24] rituximab, and EPO.[11]

Phase I studies demonstrated the biosimilarity of Zarzio® and Neupogen® in terms of PD and PK profiles, over doses ranging from 1-10 µg/kg, following both subcutaneous and intravenous administration. A Phase III clinical trial further confirms the efficacy and safety of filgrastim biosimilar Zarzio® in neutropaenic breast cancer patients.[23-25] Furthermore, safety data for Zarzio® were consistent with the well-known safety profile of the granulocyte colony stimulating factor (G-CSF) class and the 21% incidence of musculoskeletal pain (8.8% bone pain) is comparable to incidences reported with Neupogen®.[24] Local tolerability was good and none of the patients developed anti-G-CSF antibodies.[24] As a result, the latest European Organisation for Research and Treatment of Cancer (EORTC) G-CSF guidelines recognise the use of biosimilar G-CSFs in Europe.[26]

Following the introduction of filgrastim biosimilars in 2008, the use of growth factors as primary prophylaxis has increased by 25%, despite the introduction of newer, more sophisticated drugs.[27] As biosimilars are made available and their usage increases, costs fall, thereby increasing access to therapy for more patients.[7] Manufacturers currently produce 13 EPO and G-CSF biosimilars, registered in Europe. They have achieved a market share of >50% in some countries such as the UK, but other countries, for example Italy and Spain, have been slower in adopting biosimilars.[28]

The patents for EPO and filgrastim have already expired in the USA, and those for pegfilgrastim

will expire soon in both the EU and USA.[29] Rituximab's EU patent has expired and its US patent will expire soon,[29] making it a prime target for biosimilar development, especially when one considers its efficacy.[30-32]

Rituximab was first approved for relapsed or refractory, low grade, CD20-positive B cell, non-Hodgkin's lymphoma (NHL) in 1997 before being approved as a frontline treatment for these patients in 2004 in the EU and in 2006 in the USA. In 2010 in the EU and 2011 in the USA, rituximab was approved as a frontline maintenance therapy for follicular lymphoma (FL). Sandoz began clinical trials for its biosimilar rituximab, GP2013, in 2011. GP2013 is intended for treatment in all indications currently approved for rituximab and, as of 2014, three clinical trials are in progress. Other companies are developing rituximab biosimilars, as shown in Table 2.

The aim of biosimilar development is not to establish patient benefit per se but to demonstrate high similarity to the reference product convincingly. This has been achieved in the case of GP2013, which is pharmacologically similar to the originator rituximab,[33] and shows high similarity in physicochemical and functional characteristics.[13] GP2013 is currently in Phase II trials in rheumatoid arthritis (ASSIST-RA)[34] and Phase III trials in FL (ASSIST-FL).[35] ASSIST-FL is running in >120 sites across 22 countries, comparing GP213-CVP against R-CVP in 618 previously untreated adult patients with advanced stage (Grade 1, 2, or 3a) CD20-postitive FL.

In the 6 years since their introduction in the EU, biosimilar use is increasing and establishing confidence with respect to safety and efficacy. Rituximab has changed the treatment of NHL but access remains an issue for many patients. Biosimilar rituximab candidates are now being developed to meet stringent regulatory requirements for quality and safety. GP2013 is currently being tested against originator rituximab in a sensitive population of FL patients receiving CVP (cyclophosphamide, vincristine, prednisone) chemotherapy. Biosimilars can be considered the 'generics' of the 21st century, allowing the reallocation of resources for 'biobetter' drugs. Nevertheless, the introduction of biosimilars is highly dependent on their acceptance by physicians, patients, and especially key opinion leaders.

Introducing Biosimilars to Expand Patient Access to Care

Doctor Paul Cornes

Cancer is now the world's biggest killer and has the most devastating economic impact of any cause of death in the world. It is responsible for 16.7% of all 'healthy' years lost in the EU, and ~83 million years lost worldwide.[36] The total economic impact of premature death and disability from cancer worldwide was $895 billion in 2008.[36]

The good news is that basic cancer science is delivering one medical paper a minute to the PubMed US National Library of Medicine,[37] and from this come innovations and advances in cancer care.

Table 2: Selected rituximab biosimilars in clinical development.

Company	Drug	Immunology	Oncology	Status
Amgen	ABP-		X	Announced
Boehringer Ingelheim	BI1695500	X	X	Ph III active
Celltrion & Hospira	CT-P10	X	X	Ph I/III active
Merck	MK-8808	X	X	ACTIVE; NOT RECRUITING
Pfizer	PF-05280586	X	X	Ph I/II active
Samsung	SAIT101			PROGRAM HALTED
Sandoz	GP2013	X	X	Ph I/II/III active
Teva	TL011			PROGRAM ABANDONED

Modified from 'Biosimilars: 11 Drugs to Watch.'[72]

Moreover, deaths from cancer in the G7 countries are falling.[38] Impressively, in the last three decades the median survival of cancer patients has increased from 1 to 10 years[39] due to innovations in drug development that will see almost 70 new drugs on the market by 2020.[40] Targeted therapies have already delivered on their promise, showing striking advances in otherwise hard-to-treat cancers. They have tripled survival rates in acute promyelocytic and chronic myeloid leukaemia, as well as medullary thyroid cancer.[41]

However, the costs of cancer treatments are increasing[42-44] and there are two main drivers behind this. Firstly, the rates of cancer are predicted to increase as the population ages,[45-47] and secondly, the innovations in cancer treatment come at an increasing cost, with cancer drug prices rising five-times faster than other classes of medicine.[42] Of the 12 cancer drugs approved by the FDA in 2012, 11 were priced above $100,000 per year.[48] This inflation puts enormous strain on health services worldwide,[49] which provides the incentive for the adoption of 'Value-Based Medicine' in oncology. While the budget to treat increasing numbers of patients rises annually, there is no evidence that more spending will consistently improve health;[50] instead, this investment needs to be directed to where it can be most beneficial.

One example of lost resource is from doctors prescribing branded drugs when a generic equivalent is just as good.[51] Generic drug promotion in the USA is estimated to have saved $1 trillion between 2002 and 2011,[52] but the uptake of generic drugs within Europe varies considerably, with some countries missing out on this benefit.[53]

The use of generic drugs may bring treatments into reimbursement that would otherwise be unaffordable, increasing access.[54] Biosimilars offer the same possibilities; for instance, many oncologists in the USA, Brazil, Mexico, and Russia would offer more trastuzumab to breast cancer patients if a lower cost biosimilar was available.[55] Skane University Hospital in Sweden made an annual saving of €650,000 by switching to biosimilar human growth hormone (rhGH) with no loss of efficacy or increase in adverse drug reactions, providing evidence that cost savings from biosimilars are real and increase access to treatment.[56] University College London Hospital's NHS Trust, UK, made annual savings in excess of €240,000 by switching patients from originator rhGH to biosimilar rhGH.[57] G-CSF access has improved in the UK since the introduction of biosimilar G-CSF; use has now surpassed that of the originator[58,59] and standards of care have improved.[49] Net savings of €2 million (representing 4–5% of the total drug budget) followed the switch to biosimilar G-CSF in southern Sweden, despite a 5-fold increase in daily G-CSF usage.[58]

Throughout the EU, G-CSF biosimilar use compared with the originator averages 71%, but the use in many countries remains much lower.[49] Value Based Medicine is not directed simply at cutting costs, but at improving care. Poorly targeted budget cuts may cost more than they save. There is evidence from Germany to suggest that originator filgrastim is frequently under-dosed in an effort to cut costs;[60] however, the drug is extremely dose-sensitive and ineffectual at suboptimal dosage.[61] Clearly a cheaper alternative would be of great benefit both therapeutically and financially. Adoption of biosimilars to a significant extent throughout Europe has the potential to make >€30 billion available for healthcare reinvestment.[62,63] In the USA, replacement of the top 12 biologicals with biosimilars was predicted to yield savings of up to $380 billion over 20 years.[62] These enormous savings make the widespread introduction of biosimilars a high priority in health economic terms.[64]

Safety is paramount when switching to biosimilars and concerns have been raised about the potential to miss rare events due to the small numbers of patients in trials performed to date; however, one meta-analysis encompassing 12,039 patients did not reveal any safety concerns.[65] In patients taking the original EPO-alfa, rates of pure red cell aplasia (PRCA) rose from the natural incidence of 1/100,000 to 50/100,000 due to the failure of the molecule to remain in suspension.[66] A study of biosimilar EPO-alfa is currently underway[67] and initial results suggest a similar association of biosimilar EPO-alfa and PRCA is unlikely.

Despite the financial and therapeutic benefits that biosimilars provide, many physicians remain poorly informed. A survey of 470 European prescribers from France, Germany, Italy, Spain, and the UK revealed that 25% cannot define, or have not heard of biosimilars, and only 22% consider themselves as very familiar with them.[68] Similar findings were reported from a survey in the USA.[69] The methods for promoting the use of generic drugs and biosimilars differ throughout Europe and remain inconsistent even between countries that have a high uptake, such as in Germany and

the UK (Figure 2). This suggests that much of the drive to promote better value comes from individual physicians and guideline groups.[53] Currently in the USA the majority of medical societies explicitly take cost-effectiveness into consideration when making their recommendations, which was not the case in 2002.[70,71]

'Biosimilar' is a specific regulatory term used by the EMA. Biosimilar drugs offer another chance for cost-savings and increased access of Europe's patients to innovative treatments, without compromising safety or efficacy.

	Rules and Incentives														
Market Rules	Mandatory price reduction	✓	✓					✓		✓	✓				✓	
	Patient co-pay		✓	✓			✓			✓	✓				✓	
	Price referencing			✓	✓	✓	✓		✓		✓	✓	✓			
	Pharmacy-level substitution				✓	✓				✓	✓	✓	✓	✓		✓
Market Incentives	At the pharmacy				✓	✓			✓	✓	✓		✓	✓		✓
	With the health insurers						✓			✓			✓	✓		
	With wholesalers										✓					
	With payers	✓	✓			✓										
	Favouring brands							✓				✓				
	Favouring generics	✓		✓			✓		✓		✓			✓	✓	✓

Figure 2: Differing rules and incentives for use of generic medicines across EU markets.
Modified from Sheppard A.[53]

REFERENCES

1. Putrik P et al. Inequities in access to biologic and synthetic DMARDs across 46 European countries. Ann Rheum Dis. 2014;73:198–206.

2. Ramsey SD et al. Addressing the American health-care cost crisis: role of the oncology community. J Natl Cancer Inst. 2013;105:1777–81.

3. Nast A et al. Barriers to the prescription of systemic therapies for moderate-to-severe psoriasis--a multinational cross-sectional study. Arch Dermatol Res. 2013;305:899–907.

4. Berkowitz SA et al. Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars. Nat Rev Drug Discov. 2012;11:527–40.

5. Hulse J, Cox C. In vitro functional testing methods for monoclonal antibody biosimilars. BioProcess International. 2013;11(S6):24–7.

6. Weiner GJ. Rituximab: mechanism of action. Semin Hematol. 2010;47:115–23.

7. Taylor RP, Lindorfer MA. Drug insight: the mechanism of action of rituximab in autoimmune disease: the immune complex decoy hypothesis. Nat Clin Pract Rheumatol. 2007;3:86–95.

8. Schneider CK. Biosimilars in rheumatology: the wind of change. Ann Rheum Dis. 2013;72:315–8.

9. Schiestl M et al. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. Nat Biotechnol. 2011;29:310–2.

10. Schneider CK. Biosimilarity: a better definition of terms and concepts. Session 0304. Presented at: the 25th Annual DIA EuroMeeting, Amsterdam, the Netherlands, 4th-6th March 2013.

11. Brockmeyer C et al. Binocrit: Assessment of quality, safety and efficacy of biopharmaceuticals. Eur J Hosp Pharm Pract. 2009;15:34–40.

12. Schellekens H. Biosimilar therapeutics-what do we need to consider? NDT Plus. 2009;2:i27–i36.

13. Visser J et al. Physicochemical and functional comparability between the proposed biosimilar rituximab GP2013 and originator rituximab. BioDrugs. 2013;27:495–507.

14. EU guidelines for biosimilars. GaBI Journal. 2010. http://gabi-journal.net/news/eu-guidelines-for-biosimilars.

15. Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies – non clinical and clinical issues. 2012;EMA/CHMP/BMWP/403543/2010. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf.

16. Kozlowski S. Biosimilars – an update focused on quality considerations. 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf.

17. Lucio SD et al. Biosimilars: implications for health-system pharmacists. Am J Health Syst Pharm. 2013;70:2004–17.

18. Weise M et al. Biosimilars: what clinicians should know. Blood. 2012;120:5111–7.

19. Kurki P et al. ECCO position challenged by European drug regulators. J Crohns Colitis. 2014;8:258.

20. Weise M. European Regulation of Biosimilars – past, present and future. Presented at: 26th Annual EuroMeeting, DIA, Vienna, Austria, 25th-27th March 2014.

21. Weise M et al. Biosimilars-why terminology matters. Nat Biotechnol. 2011;29:690–3.

22. Schneider CK et al. Setting the stage for biosimilar monoclonal antibodies. Nat Biotechnol. 2012;30:1179–85.

23. Sörgel F et al. Physicochemical and biologic comparability of a biosimilar granulocyte colony-stimulating factor with its reference product. BioDrugs. 2010;24:347–57.

24. Gascón P et al. Development of a new G-CSF product based on biosimilarity assessment. Ann Oncol. 2010;21:1419-29.

25. European Medicines Agency; Evaluation of Medicines for Human Use. CHMP Assessment Report for Zarzio. Procedure No. EMEA/H/C/000917. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000917/WC500046528.pdf.

26. Aapro MS et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011;47:8–32.

27. IMS Quarterly Database.

28. IMS MIDAS/MTA Global Database: March 2011, Monthly Sales, Units IMS MIDAS/MTA Global database. 2011.

29. Top 8 blockbuster biologicals 2013. GaBI Journal. 2013. http://gabionline.net/Biosimilars/General/Top-8-blockbuster-biologicals-2013.

30. Schultz N et al. Does combined immunochemotherapy with the monoclonal antibody rituximab improve overall survival in the treatment of patients with indolent non-Hodgkin lymphoma? Preliminary results of a comprehensive meta-analysis. Blood (ASH Annual Meeting Abstracts). 2005;106:Abstract 351.

31. Marcus R et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26:4579–86.

32. Marcus R. MabThera (Rituximab) plus cyclophosphamide, vincristine and prednisone (CVP) chemotherapy improves survival in previously untreated patients with advanced follicular non-Hodgkin's lymphoma (NHL). Blood. 2006;108:Abstract 481.

33. da Silva A et al. Leuk Lymphoma. 2014;55:1609-17.

34. Sandoz. GP2013 in the treatment of RA patients refractory to or intolerant of standard therapy. Clinical trial: NCT01274182.

35. Sandoz. GP2013 in the treatment of patients with previously untreated, advanced stage follicular lymphoma (ASSIST_FL). Clinical trial: NCT01419665.

36. Livestrong/American Cancer Society. The Global Economic Cost of Cancer. 2010. http://www.cancer.org/acs/groups/content/@internationalaffairs/documents/document/acspc-026203.pdf.

37. MEDLINE® Citation Counts by Year of Publication. http://www.nlm.nih.gov/bsd/medline_cit_counts_yr_pub.html. Accessed: 11th September 2012.

38. Carroll A. How do we rate the quality of the US health care system - disease care. The Incidental Economist. 21st October 2010. http://theincidentaleconomist.com/wordpress/how-do-we-rate-the-quality-of-the-us-health-care-system-disease-care/. Accessed: 29th April 2014.

39. Triggle N. Half of cancer sufferers 'live a decade or more'. BBC News. 29th April 2014. http://www.bbc.co.uk/news/health-27194823.

40. Savage P. Development and economic trends in cancer therapeutic drugs: analysis of modern and historical treatment costs compared to the contemporary GDP per capita. J Clin Oncol. 2014;32 (Suppl):e17535.

41. Munoz J, Kurzrock R. Targeted therapy in rare cancers--adopting the orphans. Nat Rev Clin Oncol. 2012;9:631–42.

42. Elkin EB, Bach PB. Cancer's next frontier: addressing high and increasing costs. JAMA. 2010;303:1086–7.

43. Meropol NJ et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. J Clin Oncol. 2009;27:3868–74.

44. Adams CP, Brantner VV. Estimating the cost of new drug development: is it really 802 million dollars? Health Aff (Millwood). 2006;25:420–8.

45. Cancer Research UK. NHS faces huge cancer challenge as cases set to jump by 45 per cent. 2011. http://info.cancerresearchuk.org/news/archive/pressrelease/2011-10-28-NHS-burden-as-cancer-cases-to-jump-by-45-per-cent.

46. Potentially fatal cancer cases predicted to double by 2020. 2006. http://www.breakingnews.ie/archives/2006/0607/ireland/potentially-fatal-cancer-cases-predicted-to-double-by-2020-262312.html.

47. Ibrahim E et al. Current and future cancer burden in Saudi Arabia: meeting the challenge. Hematol Oncol Stem Cell Ther. 2008;1:210–5.

48. Kaitin KI. Deconstructing the drug development process: the new face of innovation. Clin Pharmacol Ther. 2010;87:356–61.

49. Walsh K. Biosimilars' utilization and the role payers do play in driving uptake in Europe: an industry perspective. Biosimilar Medicines 11th EGA International Symposium, April 2013. Accessed: 5th March 2014.

50. Hussey PS et al. The association between health care quality and cost: a systematic review. Ann Intern Med. 2013;158:27–34.

51. Wagstaff A. No-name heroes can save Europe billions. Cancer World. 2007:24–8.

52. Wyatt E. Justices to take up generic drug case. New York Times. 8th December 2012;B1.

53. Sheppard A. Generic medicines: essential contributors to the long-term health of society. IMS. Available at: http://www.imshealth.com/imshealth/Global/Content/Document/Market_Measurement_TL/Generic_Medicines_GA.pdf. Accessed: 21st January 2013.

54. Shrank WH et al. The use of generic drugs in prevention of chronic disease is far more cost-effective than thought, and may save money. Health Aff (Millwood). 2011;30:1351–7.

55. Lammer PE et al. Barriers to the use of trastuzumab for HER2+ breast cancer and the potential impact of biosimilars: a physician survey in the United States and emerging markets. J Clin Oncol. 2014;32:5s.

56. Flodmark CE et al. Switching from originator to biosimilar human growth hormone using dialogue teamwork: single-center experience from Sweden. Biol Ther. 2013;3:35–43.

57. Thakrar K et al. Assessing the efficacy and safety of Omnitrope. Br J Clin Pharm. 2010;2:298–301.

58. Gascón P et al. Clinical experience with Zarzio® in Europe: what have we learned? Support Care Cancer. 2013;21:2925–32.

59. McCamish M, Woollett G. The state of the art in the development of biosimilars. Clin Pharmacol Ther. 2012;91:405–17.

60. Hadji P et al. Cost comparison of outpatient treatment with granulocyte colony-stimulating factors (G-CSF) in Germany. Int J Clin Pharmacol Ther. 2012;50:281–9.

61. Scott SD. Days of prophylactic filgrastim

use to reduce febrile neutropenia in patients with non-Hodgkin's lymphoma treated with chemotherapy. J Manag Care Pharm. 2003;9:15-21.

62. Shapiro RJ et al. The potential American market for generic biological treatments and the associated cost savings. 2008. http://www.sonecon.com/docs/studies/0208_GenericBiologicsStudy.pdf.

63. Höer A. Saving money in the European healthcare systems with biosimilars. GaBI Journal. 2012;1(3-4):120–6.

64. Cornes P. The economic pressures for biosimilar drug use in cancer medicine. Target Oncol. 2012;7 Suppl 1:S57–67.

65. Ebbers HC et al. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12:1473–85.

66. Mikhail A, Farouk M. Epoetin biosimilars in Europe: five years on. Adv Ther. 2013;30:28–40.

67. Rodriguez Garzotto A et al. Erythropoiesis-stimulating agents for the treatment of chemotherapy-induced anemia: comparisons from real-world clinical experience. J Blood Med. 2014;5:43–8.

68. ASBM European physicians survey on biosimilars: key findings on knowledge, naming, traceability and physicians' choice. 2014. http://www.europabio.org/sites/default/files/report/asbm_european_physicians_survey

_on_biosimilars-_ex_summary.pdf. Accessed: 12th May 2014.

69. Li EC. Biosimilars: more education is needed. 2011. Available at: http://www.nccn.org/about/news/ebulletin/2011-04-18/biosimilars.asp.

70. Schwartz JA et al. Cost consideration in the clinical guidance documents of physician specialty societies in the United States. JAMA Intern Med. 2013;173:1091–7.

71. Wallace JF et al. The limited incorporation of economic analyses in clinical practice guidelines. J Gen Intern Med. 2002;17:210–20.

72. Biosimilars: 11 Drugs to Watch. GEN. 2014. http://www.genengnews.com/insight-and-intelligence/biosimilars-11-drugs-to-watch/77900135/.