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Top developments in biosimilars during 2014

The past year has once again been a busy one for the biosimilars industry. One of the most important milestones during 2014 was the news that the US Food and Drug Administration (FDA) had accepted several biosimilars applications, and even recommended the approval of one product, moving the country one step closer to getting biosimilars on to the US market.

Sandoz, the generics division of Novartis, announced on 24 July 2014 that FDA had accepted its application for the company's filgrastim biosimilar. Sandoz was the first company to announce it had filed for approval of a biological under the biosimilars pathway created in the Biologics Price Competition and Innovation Act of 2009 (BPCI Act) [1].

South Korean biotechnology company Celltrion submitted its application for approval of its infliximab biosimilar to FDA on 8 August 2014 [2]. While US-based injectables specialist Hospira submitted a biosimilar application for its epoetin alfa biosimilar Retacrit to FDA on 16 December 2014 [3]. The submission marks Hospira's first biosimilar application in the US and is the first US submission for an epoetin alfa biosimilar. Canada-based Apotex announced on 17 December 2014 that FDA had accepted the company's application for a biosimilar version of Amgen's Neulasta (pegfilgrastim) [4].

In a landmark decision, on 7 January 2015, advisers from FDA's Oncologic Drugs Advisory Committee voted 14–0 in favour of the recommendation to approve Sandoz's filgrastim biosimilar for all five indications of the originator product (Neupogen) [5].

FDA also granted tentative approval for a new insulin glargine product (LY2963016) on August 2014. The insulin glargine, called Basaglar in the US, is produced by US pharma company Eli Lilly and its partner Boehringer Ingelheim. The drug is intended to be a competitor to, and has the same amino acid sequence as, French drugmaker Sanofi's diabetes drug Lantus (insulin glargine) [6]. The same product was approved in Europe as a biosimilar, Abasaglar (previously Abasria), in September 2014 [7].

In fact, the European Medicines Agency (EMA) has approved three biosimilars during 2014. As well as Abasaglar (insulin glargine), these included a filgrastim biosimilar (Accofil) from Accord Healthcare and a follitropin alfa biosimilar (Bemfola) from Finox Biotech [8]. The agency is also currently reviewing biosimilar applications for human insulin and etanercept [9].

Interestingly, a survey of diabetes sufferers concluded that if insulin biosimilars are significantly cheaper and equally effective, most patients will accept them [10]. Other companies working on insulin biosimilars include Mylan, Biocon, Sanofi [7], Merck and Samsung Bioepis (Samsung's specialized biologicals unit) [11].

US generics company Alvogen launched its infliximab biosimilar Inflectra in Central and Eastern Europe in February 2014 in collaboration with Hospira [12].

Two biosimilars were also approved in Japan during 2014. Japanese pharma firm Nippon Kayaku launched its infliximab biosimilar, Infliximab BS, in Japan in November 2014 [13].

Sandoz received marketing authorization approval for its biosimilar filgrastim (Filgrastim BS Sandoz) in March 2014 [14].

A trastuzumab biosimilar, Herzuma, from South Korean biotechnology company Celltrion, was approved in South Korea in January 2014 [15].

The Russian Ministry of Health approved Russian biotechnology company Biocad's non-originator biological rituximab, AcellBia (BCD-20), in April 2014 [16].

In a decision somewhat at odds with the rest of Europe, France introduced legislation allowing substitution of biosimilars, which came into effect on 1 January 2014 [17]. To date, no other EU country has explicitly authorized the substitution of biologicals from different manufacturers and a number of EU Member States have gone as far as banning this practice [18].

The contentious issue of how to name biosimilars was once again a hot topic for discussion during 2014. In July 2014, 32 organizations signed a letter calling on FDA to require biologicals and biosimilars to have the same International Nonproprietary Name (INN) [19]. However, to the contrary, in August 2014, more than 10 medical associations and 20 individual specialists sent a signed letter to FDA Commissioner Margaret Hamburg saying that biosimilars 'must have distinguishable non-proprietary names' [20]. In addition, the European Crohn's and Colitis Organisation (ECCO) and the European Association for Bioindustries (EuropaBio) both called for distinguishable names for biosimilars in their respective position papers on biosimilars [21, 22].

The World Health Organization (WHO) drafted a proposal in 2014 for a biological qualifier (BQ), which would assign a four-letter alphabetic code to all biologicals [23]. However, Sandoz claimed that 'no additional component is needed in most jurisdictions including the European Union, where existing naming systems, which require biologicals to be identified through the recording of brand name and batch number, have worked very well'. Also, according to the European Generic Medicines Association (EGA), who represent the generics industry, 'biosimilars have been used safely since 2006, and pharmacovigilance data shows that current tracking and adverse event reporting systems work well' [24].

A survey conducted by the patient advocacy group RetireSafe was reported to have found that elderly patients in the US lack knowledge on biosimilars, but that they overwhelmingly support strong patient safeguards and notification of patients and physicians when biosimilar substitution takes place [25]. In addition, results of a survey carried out by ECCO highlighted a 'lack of confidence in biosimilars and the need for continued education' [26]. Results of a survey carried out by the Alliance for Safe Biologic Medicines (ASBM) was also reported to have highlighted a lack of knowledge, this time of physicians [27]. In response to this need for education, EGA has called upon national authorities and medical societies to actively engage in reducing the knowledge gap about biosimilars [28].

During 2014 additional state legislation has been considered that would allow the substitution of biosimilars, but with, in many cases, restrictions requiring physician and/or patient notification,

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as well as record keeping. The latest states to consider or pass legislation include Delaware, Idaho, Indiana, Massachusetts, and Pennsylvania [29-32]. In a turnaround from its previous stance, the Generic Pharmaceutical Association (GPhA) announced on 9 December 2014 that it was supporting compromise legislation that would allow biosimilars designated as 'interchangeable' by FDA to be automatically substituted at the pharmacy [33]. The GPhA had previously stated that laws concerning biosimilar substitution were 'premature and unnecessary at this time' [34].

Guidelines have been a hot topic during 2014. EMA updated its overarching guidelines in 2014. The agency issued its revised guidelines on biosimilars quality in June 2014, on similar biological medicinal products in November 2014 and on non-clinical and clinical issues for biosimilars in December 2014. The guidelines come into effect on 1 December 2014, 30 April 2015 and 1 July 2015, respectively [35-37]. The agency also issued a concept paper in March 2014 for revision of the immunogenicity guideline for biologicals. The guideline was open to comment from stakeholders until the end of June 2014 [38].

China's Center for Drug Evaluation (CDE), which is part of CFDA (simplified Chinese: 国家食品药品监督管理局), issued draft guidance on 29 October 2014 outlining the principles for developing biosimilars of biologicals already approved in China. The draft guidance was released for a one-month consultation period, which ended on 29 November 2014 [39].

Despite FDA issuing three draft guidance documents on biosimilars in February 2012 [40], the agency is still yet to issue final guidance. The agency did, however, release draft guidance on reference product exclusivity for biologicals [41] and guidance on how to use clinical pharmacology data to show biosimilarity to a reference product [42]. The agency also published its first-ever edition of the 'Purple Book' in September 2014, a new set of lists of licensed biological products and interchangeable biosimilars [43]. The sooner biosimilars hit the US market the sooner savings from these products can begin to be realized. According to an analysis carried out by the RAND Corporation, introducing biosimilars of complex biologicals used to treat illnesses, such as cancer and rheumatoid arthritis, could cut spending on biologicals in the US by US\$44 billion over the next decade [44].

Sandoz has once again been leading the way in biosimilars' development, with its landmark filgrastim biosimilar decision in the US [5]. The company claimed in December 2014 that results from a pivotal phase III clinical study of its filgrastim biosimilar (EP2006) had 'demonstrated similarity' with respect to safety and efficacy compared to Amgen's Neupogen (filgrastim) [45]. These results were used in its US filing. The company also completed patient enrolment in its phase III trial with biosimilar etanercept (EGALITY). The trial aims to demonstrate the equivalent efficacy of Sandoz's biosimilar etanercept (GP2015) and Amgen's Enbrel in patients with moderate to severe chronic plaque-type psoriasis [46].

Meanwhile, Amgen has expanded its biosimilars portfolio to include nine different molecules. Biosimilars in its sights include Avastin (bevacizumab), Herceptin (trastuzumab) and Rituxan/MabThera (rituximab) from Roche, Erbitux (cetuximab) from Eli Lilly, Humira (adalimumab) from AbbVie, and Remicade (infliximab) from Johnson & Johnson [47]. The company started

a global phase III trial of its biosimilar rituximab in 2014 and is also currently conducting two phase III clinical trials for its biosimilar adalimumab [48]. In November 2014 Amgen launched an app which aims to provide a source of information about biosimilars [49].

Preclinical assessments claimed that Amgen's biosimilar bevacizumab candidate (ABP 215) is 'highly similar' to Avastin [50] and a primary efficacy analysis from a phase III trial of Amgen's adalimumab biosimilar (ABP 501) compared with Humira (adalimumab) claimed that the products 'demonstrated clinical equivalence' [51]. Amgen is carrying out a global phase III clinical trial for a biosimilar version of Roche's blockbuster arthritis/non-Hodgkin's lymphoma drug MabThera/Rituxan (rituximab) [52]. The company has also started recruiting patients for a clinical trial to study the effect of switching patients from the originator biological Aranesp (darbepoetin alfa) to biosimilar epoetin alfa, in other words, from a long-acting to a short-acting epoetin [53].

However, despite Amgen's recently increasing interest in biosimilars, it is still suing Sandoz to stop the biosimilars maker from marketing a biosimilar of its top-selling product Neupogen (filgrastim) in the US [54].

Polish biologicals company Mabion announced in November 2014 that it had received the consent of the appropriate regulatory authorities in Bosnia and Herzegovina, Croatia, Poland and Serbia to start a phase III clinical trial for its rituximab biosimilar (MabionCD20) in patients with diffuse large B-cell lymphoma [55]. US-based Momenta Pharmaceuticals also announced in December 2014 the acceptance by the UK Medicines and Healthcare Products Regulatory Agency of a clinical trial application to initiate a clinical trial for its adalimumab biosimilar, M923 [56].

The Polish Society of Gastroenterology started an observational trial to study the long-term safety of anti-tumour necrosis factor (TNF) antibodies, including biosimilars, in the treatment of inflammatory bowel disease (IBD) [57].

Analysis of results from a phase I trial of CKD Pharma's darbepoetin alfa biosimilar (CKD-11101) compared with Nesp (darbepoetin alfa), were reported by CKD Pharma to show 'a comparable pharmacokinetic, pharmacodynamic and tolerability profile to that of Nesp' [58].

Phase I trials of pharma giant Pfizer's biosimilar infliximab and rituximab candidates were reported to have found 'similar pharmacokinetic properties compared to the originator products' [59]. Pfizer also started recruiting patients in 2014 for its phase III biosimilar trastuzumab trial [60].

A retrospective analysis of cancer patients who received either originator rituximab (MabThera) or 'similar biologic' rituximab (Reditux) chemotherapy concluded that the two drugs had 'comparable efficacy and safety' [61].

Results from phase I and phase III clinical trials completed during 2014 reported the 'bioequivalence' and 'clinical comparability' of an infliximab biosimilar (BOW015) when compared to the originator product Remicade (infliximab) [62-64] in non-inferiority trials, as well as the 'safety of switching to biosimilar infliximab' [65].

PHARMA NEWS

A phase III trial comparing Hanwha Chemical Corporation's biosimilar etanercept, HD203, with Enbrel (etanercept) also reported equivalent efficacy [66].

A study of the treatment of patients with chronic kidney disease undergoing haemodialysis with 'biocomparable' and originator erythropoietin in Mexico reported 'comparable' efficacy (in terms of changes in haemoglobin levels) and safety [67]. Additionally, a post-authorization observational safety study of Hospira's biosimilar epoetin product Retacrit/Silapo (epoetin zeta) reported that the safety profile in patients with renal anaemia was 'comparable to data reported for other epoetin alfa products' [68].

Studies of the biosimilar granulocyte colony-stimulating factor (G-CSF), Nivestim, with the originator G-CSF, Neupogen (filgrastim), reported that 'there were no statistical differences when used for the mobilization of peripheral blood stem cells in patients treated for haematological malignancies' [69, 70].

An adalimumab biosimilar (CHS-1420) from fledgling biotech company Coherus Biosciences was reported to have met the criteria for comparable pharmacokinetics in a clinical study in healthy subjects [71]. The company also started a phase III trial in June 2014 for its etanercept biosimilar [72].

A study of the use of epoetin biosimilars in the therapeutic management of anaemia secondary to chemotherapy in haematology and oncology concluded that the biosimilars 'were effective and well tolerated in the management of chemotherapy-induced anaemia in patients with solid tumours, lymphoma and myeloma' [73].

Extrapolation of indications was also a topic of interest during 2014. EMA has stated that 'if clinical similarity can be shown in a key indication, extrapolation of efficacy and safety data to other indication(s) of the reference product may be possible' under certain conditions [74]. However, results of a survey carried out by ECCO found that most respondents (63.7%) claimed they would not switch a patient onto a biosimilar monoclonal antibody, until there was sufficient disease-specific evidence about their interchangeability [75].

However, EMA justified its decision on extrapolation of indications in approval of biosimilar epoetins and filgrastim, stating that 'to date, no specific efficacy or safety issues have been identified in clinical practice for biosimilar epoetins licensed in Europe' and that 'post-marketing studies have confirmed the efficacy and safety of filgrastim biosimilars in the approved indications' [76, 77]. Despite this assurance by the European regulator, many medical societies, including the American College of Rheumatology, the European CanCer Organisation, the Mexican College of Rheumatology, the Portuguese Society of Rheumatology, and the Spanish Society of Gastroenterology [78-80] have all specifically recommended against the use of biosimilars in extrapolated indications.

Biosimilar deals were also popular during 2014. Some notable deals made during 2014 include those of Epirus Switzerland, a subsidiary of US-based Epirus Biopharmaceuticals (Epirus) and India-based Ranbaxy Laboratories for BOW015, an infliximab 'similar biologic' [81]. Meanwhile, Epirus and Livzon agreed to collaborate on copy biologicals for China [82]. Swedish biotech

company Xbrane Bioscience signed an agreement with a global Indian pharmaceutical company to assist them in developing an optimized production system for a specific biosimilar that will be marketed worldwide [83]. South Korea-based LG Life Sciences and Japan-based Mochida Pharmaceutical made a deal in October 2014 to co-develop and commercialize an adalimumab biosimilar for the Japanese market [84].

Other deals made during 2014 include those of PlantForm Corporation and PharmaPraxis, Oncobiologics and Laboratorios Liomont [85], Cipla and Mabpharm, Strides Arcolab and Oncobiologics, NeuClone and the Serum Institute [86], Oncobiologics and IPCA Labs [87], Kissei and Alteogen [88], Catalent and Zhejiang Hisun Pharma [89], and Lupin Pharmaceuticals and Yoshindo [90].

Meanwhile, India's drug regulator, the Drugs Controller General of India (DCGI), granted marketing approval for the infliximab 'similar biologic' BOW015 in September 2014 [91]. India-based Biocon introduced its trastuzumab 'similar biologic' CANMAB to the Indian market in January 2014 [92]. This was followed by Mylan's Indian subsidiary launching its trastuzumab 'similar biologic' Hertraz in February 2014 [93]. India-based active pharmaceutical ingredient (API) supplier Hetero launched its darbepoetin alfa 'similar biologic' in India in June 2014 [94].

Previously, in February 2014, India-based biologicals specialist Biocon and US generics maker Mylan challenged India's Delhi High Court interim order barring them from using Roche's data to sell their 'similar biologic' versions of Roche's breast cancer blockbuster Herceptin (trastuzumab) [95].

Finally, biopharmaceutical giant Amgen and US generics maker Actavis spoke to GaBI about their views on biosimilars and their biosimilar plans [96].

The increasing number of clinical trials being carried out for biosimilars, the number of global biosimilar approvals, the first FDA recommendation, and the growing number of biosimilar applications in the US, all suggest the future looks bright for the biosimilars' market in 2015.

According to a report published by IMS Health in October 2014, the use of biosimilars in Europe; however, still varies widely between countries and therapeutic areas [97]. This report highlighted the need for continuing education of patients, prescribers and healthcare payers.

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- References 81 to 97 can be found on page 32.

Top developments in biosimilars during 2014

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