PHARMA NEWS

Top developments in biosimilars during 2015

Once again the biosimilars industry has had a busy year [1]. Perhaps the most important milestone achieved during 2015 was the landmark decision made by the US Food and Drug Administration (FDA) on 6 March 2015 to approve Sandoz's filgrastim biosimilar, Zarxio (filgrastim-sndz), for all five indications of the originator product (Neupogen).

FDA is also reviewing applications for Hospira's epoetin alfa biosimilar (Retacrit), Celltrion's infliximab biosimilar candidate (CT-P13), Sandoz's etanercept biosimilar (GP2015), and Apotex's filgrastim (Grastofil) and pegfilgrastim biosimilars.

The Centers for Medicare & Medicaid Services (CMS), which provides health insurance for the elderly and children in the US, issued three biosimilar reimbursement documents in April 2015. The documents cover Medicare Part B, Part D and Medicaid and aim to remove incentives from physicians to prescribe more costly brand-name originator biologicals rather than biosimilars.

In Europe, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended approval of Benepali (SB4) in November 2015. The drug is an etanercept biosimilar produced by Samsung Bioepis, which is a joint venture between South Korean electronics giant Samsung and biotechnology company Biogen. The agency is also currently reviewing biosimilar applications for enoxaparin sodium, etanercept, infliximab, pegfilgrastim and rituximab.

In February 2015, injectable generics specialist and biosimilars maker Hospira launched its infliximab biosimilar, Inflectra, in several major European markets. This increased the number of European countries Inflectra is marketed in to 24 and nearly doubled its presence across Europe. This was followed by the launch of Accofil (filgrastim), which is generics company Accord Healthcare's first biosimilar approved in Europe. In March 2015, Mundipharma launched Remsima (infliximab biosimilar) in several major markets, including Germany and The Netherlands.

In May 2015, Australia's Pharmaceutical Benefits Advisory Committee (PBAC) recommended the listing of Eli Lilly's biosimilar insulin glargine, Basaglar, in the country's Pharmaceutical Benefits Scheme (PBS). Basaglar is the first biosimilar insulin to be approved in Australia. Australia's PBAC has also recommended that biosimilars are suitable for substitution at the pharmacy level. Meanwhile, Australia's drug regulator, the Therapeutic Goods Administration (TGA), approved Hospira's infliximab biosimilar Inflectra in August 2015.

In March 2015, Hospira launched its infliximab subsequent entry biological (SEB) Inflectra in Canada, the country's first SEB monoclonal antibody therapy.

Elsewhere, the Korean Ministry of Food and Drug Safety (MFDS, formerly the Korea Food and Drug Administration) approved the infliximab biosimilar Renflexis on 4 December 2015 and the etanercept biosimilar Brenzys in September 2015, both from Samsung Bioepsis.

Partners Eli Lilly and Boehringer Ingelheim received Japanese regulatory approval for their biosimilar insulin glargine product (LY2963016) in January 2015.

In May 2015, Iran's National Regulatory Authority, the Food and Drug Organization (FDO), approved its first rituximab biogeneric (Zytux). The medicine received its marketing authorization based on the previously published national guideline for marketing of biogenerics in Iran.

Russia's Ministry of Health (*Министерство здравоохранения Российской Федерации; Rosminzdrav*) approved Celltrion's non-originator biological infliximab, Remsima, in July 2015.

Brazil's medicines agency, the Brazilian Health Surveillance Agency (*Agência Nacional de Vigilância Sanitária,* ANVISA), announced in April 2015 that it had approved its first follow-on biological medicine Remsima (infliximab) through its 'development by comparability' pathway. The Venezuelan medicines agency, the *Instituto Nacional de Higiene 'Rafael Rangel'* (INHRR National 'Rafael Rangel' Institute of Hygiene) also approved Celltrion's infliximab *bioterapéuticos similares* in April 2015.

Meanwhile, India's drug regulator, the Drugs Controller General of India (DCGI), granted marketing approval for a rituximab 'similar biologic' from Reliance Life Sciences in February 2015. Indian drugmaker Intas Pharmaceuticals (Intas) launched its 'similar biologic' of etanercept (Intacept) in India in March 2015. Intas then launched its ranibizumab similar biologic, Razumab, in June 2015. India-based generics maker Hetero Group launched a similar biologic of rituximab, Maball, in August 2015.

Biosimilars naming

The contentious issue of how to name biosimilars was once again a hot topic for discussion during 2015 [2]. According to the World Health Organization, almost half of the comments on its proposed biological qualifier (BQ) for naming biologicals were positive. WHO published a draft policy 'Biological Qualifier – an INN proposal' proposing a possible four-letter alphabetic code for all biologicals in July 2014. The Generic Pharmaceutical Association (GPhA), however, argued that 'INN [International Nonproprietary Name] naming has been simple and intuitive and this should not be changed', stating that the brand name is the distinguishing factor. Hospira also argued that 'it is essential for biosimilar drugs to be given the same non-proprietary names as original biologic[al]s to ensure that patients receive the full benefit of greater access and lower costs that these medicines can bring.'

On the other hand, the American College of Rheumatology (ACR) has stated that 'biosimilars must have distinct names allowing them to be distinguished from each other and their reference products'. This, the ACR states, 'is essential for ongoing pharmacovigilance'. The ACR also believes that 'the decision to substitute a biosimilar should only be made by the prescriber' and 'objects to compulsory switching of stable patients to a different medication (including a biosimilar)'.

FDA has also proposed that all biologicals and biosimilars have non-proprietary names and that a four-letter suffix be added

Submitted: 14 January 2016; Revised: 26 January 2016; Accepted: 27 January 2016; Published online first: 9 February 2016

to the names to distinguish them from each other. Biosimilars makers, however, would prefer to use the same non-proprietary names as the brand-name biologicals without any suffix, while originator manufacturers would prefer completely different names. Others, however, are concerned that using a 'suffix deliberately designed to be "devoid of meaning" creates an unnecessary barrier to the use of distinguishable suffixes'.

Results of a survey carried out by the Alliance for Safe Biologic Medicines (ASBM) showed that 90% of physicians thought that it was important that a product label for a biosimilar clearly indicates that it is a biosimilar.

Australia's drug regulatory agency, TGA is also reviewing its plans for naming biosimilars, 'following recent international developments in the area of biosimilar naming'. The agency had previously proposed that all biosimilars in Australia have distinguishable names.

Substitution of biosimilars for originator biologicals can also be a contentious issue. However, according to a survey carried out in US pharmacists, most (75%) would be confident in substituting an interchangeable biosimilar with the reference product if both shared the same active ingredient or non-proprietary name of the reference biological.

The *Sociedade Portuguesa de Reumatologia* (Portuguese Society of Rheumatology) advised in its position statement that biosimilars should have a different INN or be prescribed by brand name. The society also recommended that automatic substitution of originators by biosimilars should not be allowed.

State legislation in the US

In January 2015, biologicals companies including Amgen, Actavis, Sandoz, Hospira and Genentech; and the GPhA agreed to support compromise automatic substitution legislation that would allow interchangeable biologicals to be automatically substituted at the pharmacy. Critical points are that the wording does not specify the notification period, and that the communication is to be done via the use of an electronic system where possible – thus reducing any delays for patients and reducing the burden on pharmacists.

During 2015 additional state legislation has been considered that would allow the substitution of biosimilars [3]. Many of these proposed bills use the compromise wording proposed by the GPhA. The latest states to consider or pass legislation allowing substitution of a biosimilar for an originator biological include California, Colorado, Georgia, Idaho, Illinois, Maryland, Massachusetts, New Jersey, North Carolina, Tennessee, Texas, Utah and Washington.

On 18 June 2015, US lawmakers Steve Stivers and Peter Welch reintroduced the Fair Access for Safe and Timely (FAST) Generics Act to increase consumer access to generics, boost market competition and ultimately save consumers money.

Guidance and recommendations

FDA issued four final biosimilars guidance documents in 2015. These included one on questions and answers about the biosimilars pathway, one on formal meetings between FDA and biosimilars sponsors, one on quality considerations in demonstrating biosimilarity, and one on scientific considerations in demonstrating biosimilarity. The agency also published a draft guidance document addressing additional questions and answers, which includes a question on the issue of interchangeability with reference biologicals.

In January 2015, FDA also asked drugmakers to comment on the information requirements for biosimilars interchangeability.

EMA released its finalized guideline on the non-clinical and clinical development of insulin biosimilars in March 2015. The new guideline lays down the non-clinical and clinical requirements for recombinant insulin-containing biosimilars, including human insulin and insulin analogues (both referred to as insulin). The final guideline, however, rejected requests to accept batches of reference (approved) biological products sourced from outside the European Economic Area (EEA), as is now possible for other biosimilars.

The TGA announced on 10 April 2015 that it was carrying out public consultations on the adoption of two European Union (EU) guidelines (the overarching biosimilars guideline and the guideline on non-clinical and clinical issues) in Australia. The TGA has already adopted many of EMA's guidelines for biosimilars, as well as publishing its own guidance on the evaluation of biosimilars.

The Dutch Medicines Evaluation Board (MEB) updated its position on biosimilars, stating that 'biosimilars have been proven to have no relevant differences compared to an innovator biological medicinal product as far as quality, safety and efficacy are concerned'.

In May 2015, the Finnish Medicines Agency, Fimea, announced that it was recommending the interchangeability of biosimilars for their reference biologicals. The Fimea recommendation does not, however, recommend automatic substitution at the pharmacy level. The agency specifically recommends that biosimilars are interchangeable with their reference products only under the supervision of a healthcare professional.

Following increasing interest in biosimilars in Canada, the Canadian Generic Pharmaceutical Association (CGPA), which represents Canada's generics industry, set up a new CGPA Biosimilars Board in April 2015. Canada's federal department responsible for health, Health Canada, has thus far approved three SEBs for use in Canada. Similarly, in the US, the US Generic Pharmaceutical Association (GPhA) launched its Biosimilars Council, which aims to be an educational resource for the general public and patient groups seeking information about the safety and effectiveness of biosimilars.

In March 2015, the Mexican regulatory body for approval of medicines, the Federal Commission for the Protection against Sanitary Risks (*Comisión Federal para la Protección contra Riesgos Sanitarios,* COFEPRIS), issued rules for older non-originator biologicals registered prior to 19 October 2011, when the country's guidelines for 'biocomparables' were first published, mandating that companies conduct clinical trials to prove biosimilarity.

Clinical trials for biosimilars

In October 2015, Baxalta – a spinoff company from Baxter International – and US-based biotechnology firm Momenta Pharmaceuticals (Momenta) started a phase III clinical trial for their adalimumab biosimilar (M923) in patients with chronic

plaque psoriasis. Meanwhile, in The Netherlands another study into the effects of switching patients from originator infliximab to biosimilar infliximab was initiated.

In February 2015, US biopharmaceutical giant Amgen announced positive results from its phase III clinical trial for its adalimumab biosimilar (ABP 501) in patients suffering from rheumatoid arthritis. The company is also carrying out a phase III clinical trial of its biosimilar adalimumab in patients suffering from plaque psoriasis.

Phase III trials of etanercept biosimilar SB4 and infliximab biosimilar SB2 from Merck and Samsung Bioepis reportedly 'met their primary endpoints, demonstrating equivalence' to the originator biological in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy.

A study of adverse drug reactions reported in Italy showed no relevant difference between the number and type of side effects reported for biosimilars and their corresponding originators, according to researchers from the Clinical Pharmacology Unit at the University of Messina, Italy.

Results of clinical experience with Celltrion's infliximab biosimilar Remsima (CT-P13) reportedly show comparable safety and efficacy in inflammatory bowel disease patients.

Results of a post-marketing clinical study of infliximab biosimilar Inflectra claim that the biosimilar has equivalent effectiveness compared to the originator biological (Remicade) in patients with rheumatoid arthritis and ankylosing spondylitis when switched from Remicade.

A study of the treatment of patients with chronic kidney disease undergoing haemodialysis with 'biocomparable' and originator erythropoietin in Mexico reportedly showed comparable efficacy and safety in terms of changes in haemoglobin levels.

A retrospective analysis of cancer patients who received either originator or 'similar biologic' rituximab chemotherapy showed comparable efficacy and safety, according to a study by researchers from the Tata Memorial Centre, Mumbai, India.

Extrapolation

Extrapolation of indications was also a topic discussed during 2015 [4-6]. 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.

The Spanish Society of Rheumatology (*Sociedad Española de Reumatología*, SER) in its position statement on biosimilars agrees that 'extrapolation of indications must be justified by the standards of the EMA', but adds that 'if necessary' this should be 'individually proven via double-blind randomized clinical trials that directly compare the biosimilar with the reference drug'. Paediatricians from Europe are also concerned about extrapolation of the limited amount of available clinical data from adults with rheumatologic diseases to children with inflammatory bowel disease.

Biosimilars collaborations

Biosimilar deals were also popular during 2015. US-based injectables specialist Hospira and US biotechnology firm Pfenex announced in February 2015 that they had entered into an agreement to exclusively develop and commercialize PF582 (ranibizumab), Pfenex's leading biosimilar candidate. US-based Epirus Biopharmaceuticals (Epirus) announced in May 2015 that it had made a deal with biosimilars specialist mAbxience for distribution of BOW015 (infliximab) in Latin America.

Other biosimilar collaborations made during 2015 included deals between Cipla and Mabpharm, Strides Arcolab and Oncobiologics, and NeuClone and the Serum Institute.

The future

The increasing number of clinical trials being carried out for biosimilars in 2015, the number of global biosimilar approvals, the first FDA approval and the growing number of biosimilar applications in the US, all suggest that the future for biosimilars is a bright one.

An analysis carried out by the RAND Corporation highlights the cost-savings to be made and therefore the need for biosimilars. The report finds that 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. Furthermore, if countries can negotiate discounts, such as those seen in Norway (75%) [7] and France (45%), the savings could be even larger.

Biosimilars penetration in Europe still varies widely between different countries. Penetration of biosimilars varies from a low of 0% for human growth hormone (HGH) in countries such as Belgium and Ireland to an incredible high of 100% for granulocyte colony-stimulating factor (G-CSF) in Croatia. In fact, Eastern Europe is leading the way in biosimilars penetration, perhaps driven by economic factors.

Editor's comment

It should be noted that 'similar biologics' approved in India, 'follow-on biologicals' approved in Brazil, 'biocomparables', approved in Mexico and '*bioterapéuticos similares*' approved in Venezuela might not have been authorized following as strict a regulatory process as is required for approval of biosimilars in the European Union. The European Medicines Agency's regulatory requirements ensure the same high standards of quality, safety and efficacy for biosimilars as for originator biologicals, and also include a rigorous comparability exercise with the reference product.

Source: GaBI Online

Competing interests: None.

Provenance and peer review: Article prepared based on extensive research; internally peer reviewed.

Michelle Derbyshire, PhD, *GaBI Online* Editor

References

1. Derbyshire M. Top developments in biosimilars during 2014. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(1):42-7. doi:10.5639/gabij.2015.0401.010
2. Robertson JS. The challenges of nomenclature – INN, biosimilars and biological qualifiers. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(3):110-2. doi:10.5639/gabij.2015.0403.025

References 3 to 7 can be found on page 29.

Top developments in biosimilars during 2015

References (please see the full manuscript on page 42)

3. Derbyshire M. Update on US state legislation on biosimilars substitution. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(2):95-7. doi:10.5639/gabij.2015.0402.020
4. Perks B. Supporting biosimilarity and extrapolation. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(4):180-4. doi: 10.5639/gabij.2015.0404.041
5. Derbyshire M. European biosimilars conference highlights extrapolation as key issue. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(3):149-50. doi:10.5639/gabij.2015.0403.032
6. Gerrard TL, Johnston G, Gaugh DR. Biosimilars: extrapolation of clinical use to other indications. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(3):118-24. doi:10.5639/gabij.2015.0403.027
7. Mack A. Norway, biosimilars in different funding systems. What works?. Generics and Biosimilars Initiative Journal (GaBI Journal). 2015;4(2):90-2. doi:10.5639/gabij.2015.0403.027

DOI: 10.5639/gabij.2016.0501.010