PHARMA NEWS

Top developments in biosimilars during 2013

The past year has been a busy one for the biosimilars industry. Perhaps one of the most important milestones during 2013 was the European approval of the first monoclonal antibody biosimilar [Remsima/Inflectra (infliximab)] made as a collaboration by South Korean biotechnology company Celltrion and US-based generics major Hospira [1]. Celltrion has also gained approval for Remsima in South Korea [2] and Colombia [3], and has applied for approval in Japan [4].

In fact in Europe, the European Medicines Agency (EMA) has been busy during 2013 approving five biosimilars during the year. As well as Remsima and Inflectra, these included a filgrastim biosimilar (Grastofil) from Apotex, a follitropin alfa biosimilar (Ovaleap) from Teva Pharmaceutical Industries and a somatropin biosimilar (Somatropin Biopartners) from Switzerland-based biotech company Biopartners [5]. The agency is also currently reviewing biosimilar applications for follitropin alfa and insulin glargine [6].

Perhaps the hottest debated topic during 2013 has been the issue of how to name biosimilars at both the international and national level. Healthcare giant Johnson & Johnson is just the latest stakeholder to add its opinion to the ongoing debate by sending a Citizen Petition to the US Food and Drug Agency (FDA) asking the agency to require biosimilars to bear non-proprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars [7]. Whereas in October 2013, a letter was sent to FDA by a bipartisan group of US senators calling for biosimilars to have the same active ingredient name as the brand-name originator product. Swiss drug giant Novartis also submitted a petition to FDA in October 2013 calling for biosimilars to 'share the same International Non-proprietary Name (INN) as the reference product'. Originator biologicals developer Amgen, on the other hand, supports the use of distinguishable names [8]. During the October 2013 World Health Organization's meeting on INNs for pharmaceuticals stakeholders, including the European Generic medicines Association (EGA), called for biosimilars to be assigned the same INN as their reference biologicals. While others, including the Alliance for Safe Biologic Medicines (ASBM), called for the use of distinct non-propriety names for biological medicines [9].

Another significant development in the US during 2013 was the passing or rejection of state legislation allowing the substitution of biosimilars, but with, in many cases, restrictions requiring physician and/or patient notification, as well as record-keeping [10,11].

EMA has also drafted new guidelines during the last year. The agency issued a draft concept paper on comparing quality in biologicals and biosimilars in June 2013. The guideline was open to comment from stakeholders until the end of September 2013 [12]. EMA also held a workshop in October 2013 as part of the agency's public consultation exercise on its three draft revised overarching guidelines on biosimilars [13].

Canada's regulatory agency, Health Canada, clarified in August 2013 that drugmakers seeking approval of similar drugs containing low molecular weight heparins (LMWHs) should use the approval pathway for subsequent entry biologicals [14]. There has been much debate over whether LMWHs should be considered as biosimilars or not.

One disappointing aspect of 2013 was the lack of progress made in the US. In February 2012, FDA issued three draft guidance documents on biosimilars to assist industry in developing such products [15]. However, despite almost a year having passed since then, the agency has yet to issue final guidance and there have still been no biosimilars approved using the biosimilars pathway in the US. FDA did manage to introduce its user fee programme during 2013 [16] and issued draft guidance for biosimilar meetings [17].

Sandoz, the generic drug division of Swiss drug giant Novartis, has once again been leading the way in biosimilars development. The company announced in December 2013 the start of a phase III clinical trial for a biosimilar version of the tumour necrosis factor inhibitor monoclonal antibody adalimumab in patients suffering from psoriasis [18]. Sandoz also demonstrated the innovative nature of biosimilars manufacturers with the launch in September 2013 of a new device for its somatropin biosimilar. The device aims to simplify the administration of the human growth hormone by using cartridges that require no reconstitution or priming, and a sliding injection button that requires minimum force to operate [19].

Sandoz reported the 'similarity', in a non-clinical study, with respect to *in vitro* and *in vivo* characteristics, of biosimilar etanercept (GP2015) and its reference product, Amgen's blockbuster autoimmune disease treatment Enbrel (etanercept) [20]. Fledgling biotech company Coherus Biosciences reported 'similar pharmacokinetics' for its biosimilar etanercept (CHS-0214) in a pivotal clinical study [21]. Sandoz started a phase III clinical trial for biosimilar etanercept in patients suffering from psoriasis in May 2013 [22]. Samsung Bioepsis initiated a phase III clinical trial for its biosimilar etanercept (SB4) during 2013, comparing SB4 to Enbrel, in terms of American College of Rheumatology 20% response criteria (ACR20) response rate in subjects with moderate to severe rheumatoid arthritis despite methotrexate therapy [23].

Celltrion reported results of its phase I trial for its rituximab biosimilar (CT-P10) in patients with rheumatoid arthritis. The trial showed no significant statistical differences in pharmacokinetics, efficacy and safety of CT-P10 and its reference product, Roche's rheumatoid arthritis blockbuster MabThera/Rituxan (rituximab) [24]. Pfizer also reported the 'similarity', with respect to *in vivo*, functional characteristics and pharmacokinetic and pharmacodynamic properties, of their rituximab biosimilar (PF-05280586) compared to MabThera/Rituxan in a phase I trial [25].

In August 2013, US-based Epirus Biopharmaceuticals announced that its biosimilar infliximab candidate (BOW-015) had met study endpoints, supporting the 'clinical comparability' of BOW-015 to Remicade (infliximab) in a phase III trial, as measured by the ACR20 response in severe rheumatoid arthritis patients [26]. Pfizer, on the other hand, started a phase I trial for its infliximab biosimilar (PF-06438179) in 2013, which was expected to be completed by September 2013 [23].

Biotechnology giant Amgen has also advanced its biosimilars programme during 2013, starting a phase III clinical trial in July 2013 for a biosimilar version of adalimumab in patients suffering from severe rheumatoid arthritis [27]. Pharma giant Pfizer also started a phase I study for its biosimilar adalimumab candidate (PF-06410293) in June 2013 [28].

Celltrion and Pfizer both presented robust data from their respective biosimilar trastuzumab programmes in June 2013. Celltrion's phase III data for its biosimilar trastuzumab (CT-P6) showed 'equivalent efficacy' of CT-P6 to trastuzumab in terms of overall response rate in patients with HER2+ metastatic breast cancer. Pfizer's phase I data for its biosimilar trastuzumab (PF-05280014) showed 'demonstrated similarity' in terms of pharmacokinetic properties for PF-05280014 compared to Roche's breast cancer blockbuster Herceptin (trastuzumab) [29]. While injectable generics specialist Hospira presented positive post-marketing data for biosimilar epoetin [30].

Biosimilar deals have also been on the agenda again during 2013. Some notable deals made during 2013 include those of Baxter International (Baxter) with fledgling biotech company Coherus Biosciences, US-based Oncobiologics and Zhejiang Huahai Pharmaceutical, Hospira and NovaQuest Co-Investment Fund I, mAbxience and Brazil-based Libbs Farmacêutica, and Agila Biotech, a subsidiary of India-based Strides Arcolab, and US-based biotech firm Pfenex [31–34]. However, others, such as Teva Pharmaceutical Industries and Swiss active pharmaceutical ingredient producer Lonza, have ended their biosimilar collaborations [35].

Guidelines have also been a hot topic for 2013, with Colombia issuing a draft decree for the registration of biologicals, which includes similar biotherapeutic products in January 2013 [36]. Australia's drug regulatory agency, the Therapeutic Goods Administration (TGA), also published specific guidance for biosimilars on its website in July 2013, which included a section on naming conventions for biosimilars [37].

Meanwhile, India's drug regulator, the Drugs Controller General of India (DCGI) granted marketing approval for the world first trastuzumab 'similar biologic' in November 2013 [38]. While India-based generics company Intas Pharmaceuticals launched its rituximab similar biologic in India in May 2013 [39].

With the number of clinical trials being carried out for biosimilars in 2013, the future looks bright for 2014 in the biosimilars market.

Notes from Editor-in-Chief

It should be noted that for non-inferiority studies failing to find differences larger than a given amount does not necessarily 'demonstrate equivalence'.

Competing interests: None.

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

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DOI: 10.5639/gabij.2014.0301.014