FDA Makes First Move on Biosimilars in the US

PEER REVIEWED

The US Food and Drug Administration (FDA) approved Zarxio (filgrastim-sndz), the first biosimilar product (or biosimilar), on March 6, 2015, making for a quick approval decision following a meeting of the Oncologic Drugs Advisory Committee (ODAC) just two months prior. ODAC members unanimously favoured the granting of licensure to EP2006, at the time a proposed biosimilar to Amgen Inc's Neupogen (filgrastim), for all five indications in the Neupogen labelling. Panellists commended the sponsor, Sandoz Inc, on the extensive data in support of the application, including robust results from outside the US (*AdComm Bulletin*, 2015). This application is the first to have been brought for review before an FDA advisory committee.

Having been classified as a biosimilar means that Zarxio was concluded to be *highly similar* to the reference product, Neupogen, notwithstanding minor differences in clinically inactive components; and that there are *no clinically meaningful differences* between the two products in terms of safety, purity, and potency. A biosimilar product can be prescribed by a healthcare provider in place of the FDA-approved reference product. The provider has to write the specific name of the product on the prescription in order to prescribe the biosimilar.

Neupogen, a human granulocyte colony-stimulating factor (G-CSF), was originally licensed in 1991. As a result of the FDA's decision, Zarxio is now approved for the same indications as Neupogen. Since there is no precedent for naming a biosimilar in the US, the assigned name "filgrastim-sndz" will act as a non-proprietary name; the FDA has noted its intention to release guidance in the future on the standards to be applied to naming biosimilar products.

Regarding pediatric use of Zarxio, the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) requires all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The FDA deferred the assessment of Zarxio for pediatric patients who weigh less than 36 kg because this product is ready for approval for use in adults and assessment in the pediatric population has not yet been completed.

Table 1: EP2006 Clinical Program

EP2006 Clinical Program			
Trial	**Design**	**Regimen**	**Primary Endpoint**
EP06-301	Open-label, single-arm, multicenter study	EP2006 (pre-filled syringes), SC, daily dose of 5 mcg/kg, from day 2 of each chemotherapy cycle until the ANC recovered to 10×10^9/L after the nadir or up to a maximum of 14 days	Mean DSN in cycles 1 to 4; incidence of febrile neutropenia; and time to neutrophil recovery
EP06-302	Randomized, double-blind, parallel-group, multicenter study	EP2006 and US-licensed Neupogen (supplied in vials, 480 mcg in 1.6 mL), SC, daily dose of 5 mcg/kg, from day 2 of each chemotherapy cycle until the ANC recovered to 10×10^9/L after the nadir or up to a maximum of 14 days (whichever occurred first)	Mean DSN, defined as the number of consecutive days with ANC < 0.5 Gi/L during cycle 1
ANC = absolute neutrophil count; DSN = duration of severe neutropenia; SC = subcutaneous			

Reviewing a 351(k) Application

The quest for the FDA's approval of a biosimilar product in the US was formally launched with the signing of the March 2010 Biologics Price Competition and Innovation Act of 2009 (BPCI Act), part of the Patient Protection and Affordable Care Act. Section 7002 of *Title VII—Improving Access to Innovative Therapies, Subtitle A* amended section 351 of the Public Health Service Act (PHS Act) to provide an approval pathway for biosimilar or interchangeable biological products in the new "subsection (k)" of the PHS Act. The application for a biosimilar under this section is known as the 351(k) application.

In reviewing available data to support biosimilarity, the FDA takes into account the "totality of the evidence" and recommends a stepwise approach to developing the data and information needed. Sponsors are required to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. In the cases where a development programme includes data generated using a non-US-licensed comparator to support biosimilarity to the US-licensed reference product, the sponsor must provide adequate data to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product. The FDA's recommendations on data needed to support approval of biosimilars are further outlined in various FDA guidance documents.

According to the ODAC briefing materials on EP2006 (filgrastim-sndz), the FDA concluded in its review that the data submitted demonstrate that EP2006 is highly similar to US-licensed Neupogen, and that there are no clinically meaningful differences between the two products. The review further noted that the totality of the evidence supports licensure as a biosimilar for EP2006 for all five of the indications for which US-licensed Neupogen is licensed.

Clinical Programme

Support for licensure of this product was submitted in the form of results from two clinical studies (EP06-301 and EP06-302) that evaluated efficacy and safety endpoints. EP06-301 (n = 170) was a non-comparative study in which patients with breast cancer were treated with chemotherapy and then one day later were given daily EP2006 until neutrophil recovery. EP06-302 (n = 218), a comparative study that enrolled women with breast cancer undergoing chemotherapy, was the pivotal trial for the evaluation of the biosimilarity of EP2006 to US-licensed Neupogen. An overview of the trial designs are provided in Table 1.

As noted in the FDA briefing materials for the January advisory committee meeting, absolute neutrophil count (ANC) is a relevant pharmacodynamic (PD) marker for G-CSF as it reflects the mechanism of action (MOA) of G-CSF. US-licensed Neupogen is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive chemotherapy and for other indications. Neutropenia is generally defined by abnormally low neutrophils in the blood that increases the risks for infection and other complications. Duration of severe neutropenia (DSN) was considered a clinically relevant endpoint for the approval of US-licensed Neupogen. Moreover, incidence of infection is regarded as a clinically relevant outcome in the clinical trial used to support approval of US-licensed Neupogen.

When the advisory committee was asked directly by the FDA whether it agreed with the agency's conclusion that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen, there was discussion on the pharmacokinetic (PK) results from a sub-study of trial EP06-302. The panel noted that EP2006-treated patients experienced a longer delay to recover their neutrophil counts, and for this reason they had difficulty agreeing with the FDA's conclusion. Nonetheless, panellists acknowledged that the two agents achieved expected results that ultimately would be of benefit to patients.

Analytic Similarity in Biosimilars

A 351(k) application for a proposed biosimilar product must "include information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components." This statement and recommendations for achieving analytic similarity are explained in the FDA Draft Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product.

Biosimilar Guidance from the FDA

The FDA has developed several guidance documents, all currently in draft form, to assist sponsors in bringing new biosimilars to market:

Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, February-2012

Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, February-2012

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, February-2012

Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants, March-2013

Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, May-2014

Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act, August-2014

Analytical similarity of EP2006, US-licensed Neupogen, and European Union (EU)-approved Neupogen was assessed by evaluating lots of each of the three products. A total of 20 lots of EP2006 drug product, six lots of EP2006 drug substance, 10-15 lots of US-licensed Neupogen, and 34-52 lots of EU-approved Neupogen were evaluated. The sponsor tested several quality attributes to evaluate analytical similarity of the three products. Based on these results, the FDA concluded that EP2006 is analytically highly similar to the reference product, notwithstanding minor differences in clinically inactive components.

In addition, EP2006, US-licensed Neupogen, and EU-approved Neupogen met the pre-specified criteria for analytical similarity. Sandoz provided a sufficiently robust analysis for the purposes of establishing an analytical bridge between the three products to support the relevance of data generated from clinical and non-clinical studies using EU-approved Neupogen, to support a demonstration of biosimilarity of EP2006 to the US-licensed reference product.

In its review of the application, the FDA explained that the analytical data support the scientific bridge based on the relatively simple structure of the protein, the lack of post-translational modifications, and the robustness of the analytical characterisation, and do not raise residual uncertainty of the results of the analytical similarity studies, when taken together with the other data and information submitted, to support the demonstration of biosimilarity.

Immunogenicity Assessments

In the briefing materials for the January 2015 advisory committee meeting, the FDA explained that immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies [ADA]). Therefore, immunogenicity assessment for therapeutic biological products focuses on ADA.

Within the context of the development programme for EP2006, the agency advised that a multi-dose parallel-arm study design would allow for the clearest comparison of the immunogenicity of EP2006 to the US-licensed Neupogen and EU-approved Neupogen comparators. ADA to EP2006, US-licensed Neupogen, and EU-approved Neupogen were assessed in study EP06-302. Results from this study, as well as additional information on ADA incidence from study EP06-301, support a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen.

Approaches used in assessing animal and human immunogenicity are outlined in the draft guidance Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. In general, the clinical programme for a 351(k) application must include a clinical study or studies (including an assessment of immunogenicity and PK or PD) sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used, and for which licensure is sought for the biological product, as set forth in the PHS Act.

The Future of Biosimilars in the US

The FDA expects additional approvals of biosimilar products. Advisory committees will likely play a role in providing the FDA with expert opinions on the data presented to support the approval of biosimilar applications. One such meeting that was originally scheduled for March 17th was cancelled by the FDA, the agency referring to a request for additional information from the sponsor. The Arthritis Advisory Committee was to discuss biologics license application (BLA) 125544 for CT-P13, a proposed biosimilar to Janssen Biotech Inc's Remicade (infliximab), submitted by Celltrion, Inc. In August 2014, Celltrion had submitted a 351(k) application in the US for CT-P13; at that time, the sponsor had also submitted additional clinical trial data, along with the established global clinical trial data, as part of the application and approval was expected within one year.

Filgrastim-sndz has not been approved for interchangeability. Specifically, section 351(k) of the PHS Act sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. This requires some experience in humans prior to earning the approval. To meet the higher standard of "interchangeability," an applicant must:

- provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient; and
- if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

The question of the impact on the market and on the health of patients of products that are ultimately deemed interchangeable has yet to be answered. Until a product is deemed interchangeable, substitutions cannot be made automatically if an original prescription indicates Neupogen. Once that classification happens, the patient may receive the interchangeable instead of the reference product, even if the healthcare provider writes the prescription for the reference product.

The US medical reimbursement structure will also be impacted by this new approval and any future biosimilar products that are licensed in the US. The largest payer for medical care in the US is the Center for Medicare and Medicaid Services (CMS). CMS issued a question and answer guide through its Medicare Learning Network to address the many questions regarding how and when it will manage coverage it has received regarding reimbursement for filgrastim-sndz. Interestingly, the CMS policy may contradict the condition of interchangeability established by the FDA.

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