By Orestis Mavroudis-Chocholis

The first biosimilar, Sandoz’s Omnitrope (somatropin) launched in Europe in 2006, shortly after the European Medicines Agency (EMA) published guidelines for the development of biosimilars in 2005. Since then, the European Commission (EC) has approved more than 30 biosimilars for use in the European Economic Area (EEA), 26 of which were on the market as of July 2017, making the EEA the most advanced biosimilars market, globally. Japan’s biosimilar regulatory pathway came into effect in 2009, and by mid-2017, 11 biosimilars had entered the market. In contrast, the United States established a biosimilar approval pathway in 2010, through the Biologics Price Competition and Innovation Act (BPCIA); of the five biosimilars approved in the United States by June 2017, only two have launched.¹

In addition to Europe, Japan and the United States, multiple other countries, and the World Health Organization, have created clinical and non-clinical biosimilars guidance, typically based on EMA guidelines. The worldwide proliferation of biosimilar regulatory pathways has paved the way to the global expansion of biosimilar research and development. As of July 2017, over 370 biosimilars were in development globally, with clinical development focused in the India, Russia and the EEA.²
Of the biosimilars in development, just over half are currently being evaluated in preclinical studies, while one third is currently in clinical development. Biosimilar developers are focusing their R&D on high-sales and high-profit therapy areas, such as oncology and immunology, however approximately one third of projects are in more niche areas, such as ophthalmology and infertility.\(^2\)
Figure 1-3: Biosimilars Development Pipeline by Drug Class

- **Oncology monoclonal antibody**: 40%
- **TNF-α inhibitor**: 21%
- **Granulocyte colony-stimulating factor**: 5%
- **Insulin**: 5%
- **Erythropoiesis-stimulating agent**: 4%
- **Ophthalmology monoclonal antibody**: 4%
- **Parathyroid hormone**: 14%
- **Enzyme-replacement therapy**: 12%
- **Others**: 3%

Roche/Chugai’s Herceptin (trastuzumab), Avastin (bevacizumab), and Rituxan/MabThera (rituximab), and AbbVie’s Humira (adalimumab) are the top targets for biosimilar development, collectively accounting for over 40% of biosimilar projects, globally. However, the intensity of biosimilar R&D activity does not appear to correlate with revenue. Thirty-seven adalimumab biosimilar candidates are currently in development, aiming for a share of the $16.5 billion Humira 2016 market, but that number is smaller than the total number of trastuzumab, bevacizumab and rituximab biosimilar candidates in development (43, 39 and 38, respectively), targeting significantly smaller opportunities (Herceptin, Avastin and Rituximab/MabThera together generated approximately $21 billion in 2016).

Figure 1-4: Top 10 Biosimilar Development Projects by Number of Biosimilars vs. Reference Molecule 2016 Sales

Based on company reported sales and Decision Resources Group’s Global Emerging Biosimilars Pipeline (last updated July 2017)
**Physician Insights**

As a result of approvals of novel biosimilars, continued uptake, ongoing physician-directed education by various stakeholders, and increasing biosimilar R&D efforts, physician familiarity with biosimilars is increasing year-on-year, according to Decision Resources Group research. Historically, familiarity with biosimilars has been higher in Germany, compared with France and the United States, however, research conducted in 2017 suggests that physician familiarity with biosimilars is similar in these markets.

By definition, biosimilars offer no efficacy or safety advantages to the reference brand, because they are “highly similar to the reference product, notwithstanding minor differences in clinically inactive components” and “there are no clinically meaningful differences between the biological product and the reference product, in terms of the efficacy, purity and potency of the product”, according to the U.S. definition. As such, uptake depends on other drivers, primarily their lower net cost. According to surveyed physicians, lower cost to payers, institutions or clinics and patients are among the top drivers for prescribing a biosimilar. Despite the increasing familiarity, experience, and comfort with biosimilars, physicians remain cautious about prescribing them to their patients. Key barriers to prescribe remain concerns about the efficacy, safety and immunogenicity of biosimilars.
Case Study: Uptake of Zarxio in the United States

Amgen’s Neupogen (filgrastim), is a granulocyte colony-stimulating factor, indicated for the use in cancer patients receiving myelosuppressive chemotherapy, bone marrow transplant patients and patients undergoing leukapheresis. In the EU5, filgrastim biosimilars have been available since 2008, significantly eroding Neupogen sales; in 2016, filgrastim biosimilars held approximately 75% of filgrastim’s market share.\(^5\)

Zarxio, Sandoz’s filgrastim biosimilar (filgrastim-sndz), was approved in the United States in March 2015, for all indications Neupogen had secured in the United States at the time of filing; since Zarxio’s approval, Neupogen was approved for use in patients acutely exposed to myelosuppressive doses of radiation (March 2015). Zarxio launched after a regulation-mandated 180-day delay, in September 2015, to become the first biosimilar to be marketed in the United States.

Decision Resources Group tracked the launch of Zarxio in the United States through the first year of launch. Surveyed medical and hematology-oncologists reported limited initial uptake of Zarxio one month postlaunch (6% share of filgrastim-treated patients; 31% of surveyed oncologists had prescribed Zarxio to at least one patient). Uptake increased steadily through the first 12 months; according to surveyed oncologists, Zarxio held an 18% share of filgrastim-treated patients, with 67% of respondents having prescribed the drug to at least one patient.\(^6\) At the same time, Novartis was reporting that Zarxio had generated over $100 million in the United States over the first 12 months on the market.\(^5\)

Case Study: Uptake of Inflectra in the United States

Johnson & Johnson/Jansenn’s Remicade (infliximab) is a tumor-necrosis alpha inhibitor, indicated for use in various immunology indications, including rheumatoid arthritis, Crohn’s disease, ulcerative colitis, psoriatic arthritis and plaque psoriasis. In the EUS, where infliximab biosimilars launched in February 2015, Remicade’s sales and market share have been declining steadily; we estimate that infliximab biosimilars held up to 25% of the infliximab market share in 2016.\(^7\)
Celltrion/Pfizer’s Inflectra (infliximab-dyyb), became the second biosimilar to enter the United States (and the first monoclonal antibody biosimilar), in late November 2016. Inflectra was approved by the FDA in April 2015, for all the indications Remicade (infliximab) has been approved for (except pediatric ulcerative colitis).

Similar to our Zarxio launch tracker, we are studying the launch of Inflectra in the United States, based on surveys with rheumatologists, gastroenterologists and dermatologists. At one month postlaunch, approximately one quarter of surveyed specialists had prescribed Inflectra. Additionally, Inflectra’s uptake was limited; in the key indications examined, among the three cohorts of specialists, rheumatologists reported the highest patient share for Inflectra (5% in rheumatoid arthritis patients). Inflectra uptake in gastroenterology and dermatology is more limited. The slow uptake of Inflectra in the United States is also exemplified in Pfizer’s financial statements; by the end of March, 2017, Inflectra had generated approximately $25 million in the United States, which translate to approximately 1% of the infliximab market in the first quarter of 2017.

**Figure 1-7: Zarxio vs. Inflectra Patient Shares in the United States**

Zarxio’s patient share reflect the patient share of Zarxio among all filgrastim-treated cancer patients (Neupogen + Zarxio + Granix).
Inflectra’s patient share reflects the patient share of Inflectra among all infliximab-treated RA patients (Remicade + Inflectra).
Zarxio: Q. Of your cancer patients to whom you prescribe G-CSF products, what percentage currently receive the following agents? (n = 61, 62, 60)
Inflectra: Q. What percentage of all your RA patients currently receive the following agents? (n = 31)
Figure 1-8: Zarxio vs. Inflectra Prescribers\textsuperscript{6,8}

Decision Resources Group will continue to monitor Inflectra’s uptake in the United States through the first year of launch.\textsuperscript{8}
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Orestis Mavroudis-Chocholis directs a team of analysts who produce DRG's syndicated Biosimilars solution, providing insights and analysis on the rapidly evolving biosimilars field. DRG's biosimilar solution focuses four therapy areas, oncology, immunology, endocrinology and nephrology, with a focus in the major markets (United States, EU5 and Japan). He and the Biosimilars team conduct extensive primary market research with physicians and payers, to uncover the dynamics of the current and future biosimilars market landscape, secondary market research into the competitive and regulatory landscape, produce interactive forecasts assessing market opportunities of key biologics and their biosimilars, and strategically focused content that help shape biosimilars development and defense strategies.

Prior to his current role, Dr. Mavroudis-Chocholis was a director within Decision Resources Group's Oncology team, with expertise across several indications including non-small-cell lung cancer, malignant melanoma and the clinical application of biomarkers in oncology. Prior to joining DRG, he worked at Blueprint Partnership, an independent pharmaceutical market research agency, where he gained extensive expertise in quantitative market research methods. Dr. Mavroudis-Chocholis holds a Ph.D. in Medicine from the University of Manchester, U.K. and a B.Sc. in molecular genetics from the University of Dundee, U.K.

About Us:

Biosimilar Insights

DRG's Biosimilars Insights provide in-depth market analysis that's vital to successful business planning in the rapidly evolving biosimilars space. Put major events into context, understand what is emerging from the global biosimilars pipeline, and track the initial launch phase of key biosimilars through DRG's primary market research with physicians and payers. Interactive forecasts allow assessment of market opportunities and strategically focused reports help shape biosimilars development and defense strategies. Rely on Decision Resources Group to keep you up-to-date on the biosimilars landscape and poised to maximize opportunities for your business.

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