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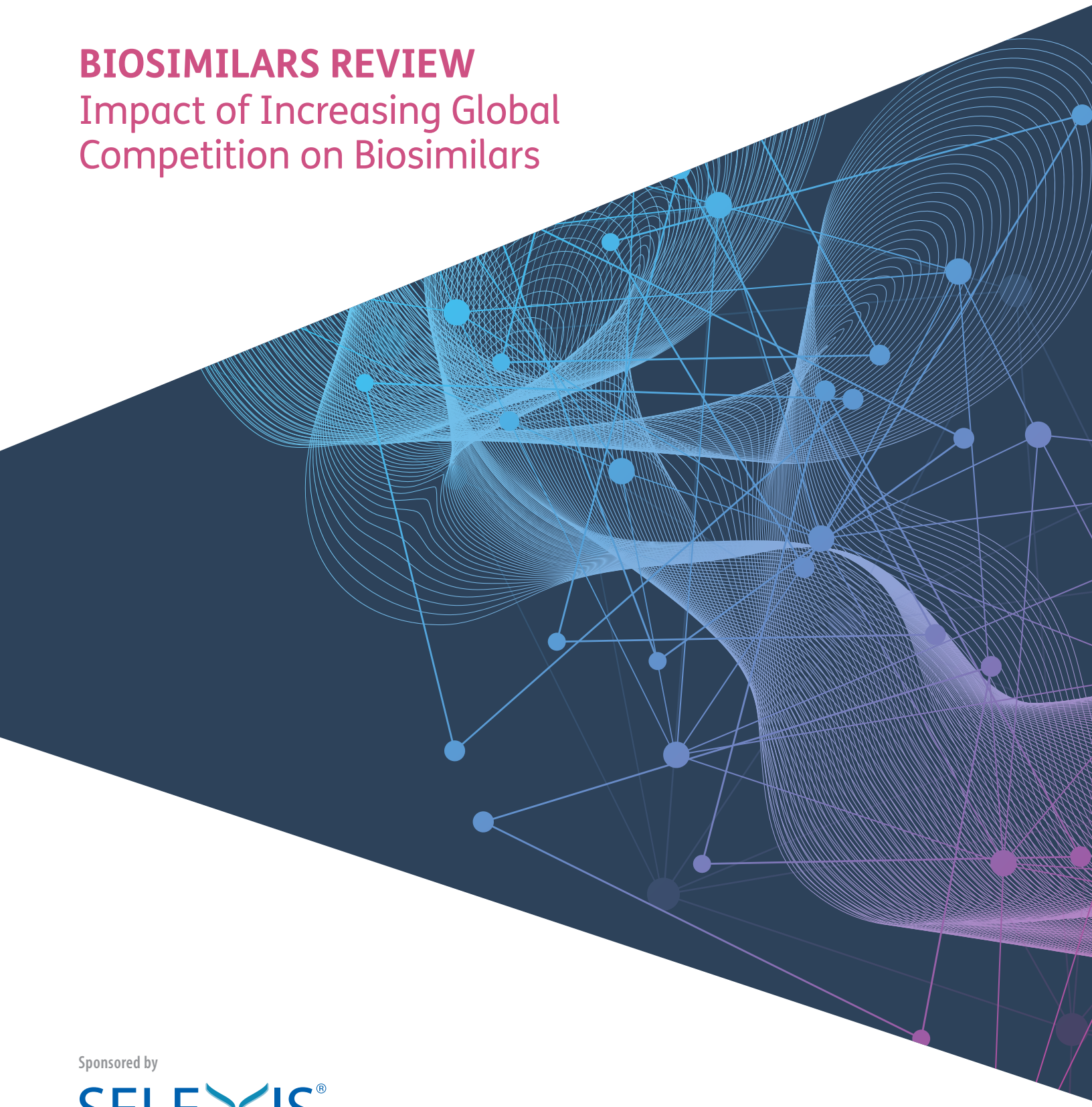
BIOSIMILARS REVIEW

Impact of Increasing Global Competition on Biosimilars



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The biosimilars market has been gaining momentum over the past few years, as a result not just of the growing number of products available, but of gradual changes in attitudes. They key question now is not whether biosimilars should be used, but how best to approach pricing and reimbursement issues to increase patient access while preserving a sustainable and competitive market.

Progress hasn't been uniform, and Europe is still way ahead in this field. As of October 2018, 50 biosimilar products containing a total of 15 substances had been authorized for marketing in the EU. In 2018, we've seen the first European versions of Roche's Avastin (bevacizumab) and Amgen's Neulasta (pegfilgrastim). Then in October, AbbVie's blockbuster drug Humira (adalimumab) lost its exclusivity, opening the way to biosimilar competition in an estimated $4.4bn market. In a surprise move, though, AbbVie pre-empted the competition by offering aggressive discounts in the first European tender.

Europe has consolidated its strong lead in this area as payers, physicians and patients grow more comfortable with the biosimilar concept, particularly the hitherto thorny issue of switching. Moreover, tenders are increasingly being used in the Nordic markets, effectively taking prescribing decisions out of the hands of doctors, while one or two countries are toying with the idea of biosimilar substitution.

By comparison the US is trailing in the biosimilars area, with just 12 products approved to date. The rate of approvals has been picking up of late, but competition is being constrained by issues such as patent disputes, interchangeability rules, and confusion over naming conventions. Concern has also been expressed that originator companies are trying to stymie the development of the biosimilars market using rebates and contracting provisions to discourage market entry.

The Food and Drug Administration can be expected to take different stance from the European Medicines Agency in some circumstances. Prior approval in the EU and elsewhere is no guarantee of approval in the US. A case in point is Sandoz's recent decision to give up on US approval of a biosimilar version of Rituxan (rituximab) after the FDA asked for additional information.

This e-book showcases Informa Pharma Intelligence's coverage of the expanding biosimilars market, touching on issues such as the risks that excessive price discounting might pose for the sustainability of the biosimilars market, how US payers are approaching the question of biosimilars, and the likely uptake of adalimumab biosimilars in Europe.

Estimates of the size of the global biosimilars market by 2022 vary widely, with sources valuing it at anything between $21bn and $36bn. Whatever the exact figure turns out to be, the prospects for the market over the next few years seem bright.

Ian Schofield
Executive Editor
Pink Sheet & Scrip, Pharma Intelligence

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The promise of biosimilars starts with extensive experience in cell line development, superior manufacturing capabilities, and a commitment to the highest-quality science and analytics.

Over the past 30 years, biological therapeutics have significantly transformed treatment options and improved outcomes for millions of individuals who face a range of life-threatening diseases. Not only have biologics improved outcomes, but in many cases, they have resulted in fewer side effects and have fostered a better quality of life compared with earlier therapies.

As brand name, innovator biological drugs go off patent, biosimilars represent an opportunity to develop lower-cost options. US Food and Drug Administration (FDA) commissioner Scott Gottlieb, MD, says, "Effective biosimilar products are key for patients and our nation's health care system."[1] In fact, the FDA has approved 12 biosimilars since 2016.[2] However, the successful generation of a biosimilar product is challenging; in the past 2 years, the FDA has rejected four biosimilar applications for approval, including:

- Pfizer's epoetin alfa (warning letter issued February 2017, now approved in 2018)
- Pfizer's trastuzumab
- Sandoz's rituximab
- Amgen's trastuzumab

Although the news coverage has not always disclosed the reasons for these rejections, the FDA rejections highlight that making a biosimilar or interchangeable product for a biological therapeutic is neither easy nor straightforward.

Selexis SA (Geneva, Switzerland) and Turgut Pharmaceuticals (Istanbul, Turkey) have a long-standing collaboration that has resulted in the successful generation of three separate, high-quality biosimilar candidates for inflammatory diseases, certain cancers and the treatment of paroxysmal nocturnal hemoglobinuria (PNH) and atypical hemolytic uremic syndrome (aHUS).[3] These successes are the combined result of the strength of the Selexis SURE*technology* Platform for the development of biosimilar cell lines and Turgut Pharmaceutical's high-quality expertise in the process development, scale-up and analytics supported by Merck Millipore.

The US and European regulatory agencies require that biosimilars (interchangeable products) meet stringent similarity requirements when compared with innovator (original) drugs. Biologics are complex, high-molecular-weight molecules generated from living cells that change in behavior in response to environmental pressures. As a result, generating biosimilars with demonstrable structural equivalence to innovator drugs is challenging. Due to the increased scrutiny of innovator drugs during the development of biosimilars, it has become clear that the range of post-translational variability between lots is substantial, even for an innovator molecule. In the US, biosimilarity must be demonstrated between the proposed product and a single reference product that has previously been approved by the FDA. However, because there is lot-to-lot variability within reference products, most biosimilar developers also compare their product with a panel of innovator lots.

As with all biologics, the development of biosimilars is fundamentally a two-step process. First, a high-producing, stable cell line must be established. Following second is a scale-up process that supports generation of properly folded and glycosylated products. Like small-molecule generics, the value proposition of biosimilars is a reduction in the cost of goods. Therefore, a cell line that generates high quantities of product, stably over time and under high-cell-density conditions in large bioreactors, is critical to a biosimilar's success. Achieving these parameters is not straightforward. Biologics are complex, can be challenging to express and are quite sensitive to changes in the manufacturing process. Once a cell line is established,

[1]https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm613881.htm

[2]https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm

[3]http://selexis.com/selexis-sa-turgut-pharmaceuticals-advance-partnership-third-commercial-license-agreement/

optimizing the manufacturing scale-up for the biosimilar requires tight control and detailed analytics to ensure the composition profile fits within the originator's specifications. There are far fewer degrees of freedom in this type of development. For example, if an innovator drug was manufactured in a Chinese hamster ovary (CHO) cell line, the biosimilar must be as well.

Selexis has a long history of success in efficiently generating such a cell line. The company's global partners utilize the modular SURE*technology* Platform to advance more than 100 products in clinical development and to manufacture three commercial products that include biosimilars. Furthermore, Selexis has extensively characterized the genome and transcriptome of its CHO cell line (CHO-M) and can modify its activity and productivity using its SURE CHO-*Mplus* Libraries, resulting in a very versatile CHO cell line development platform. In one of the three projects between Selexis and Turgut, Selexis generated the commercial-ready cell line for the production of TUR01, which was transferred to Turgut and Merck Millipore (Martillac, Bordeux, France) for process development and successful scale-up.

To determine biosimilarity, Turgut conducted a full comparability analysis on TUR01 using state-of-the-art analytical methods (*see Table 1*) to evaluate protein structure and folding, relative subunits, N-glycan composition, binding kinetics and protein activity.

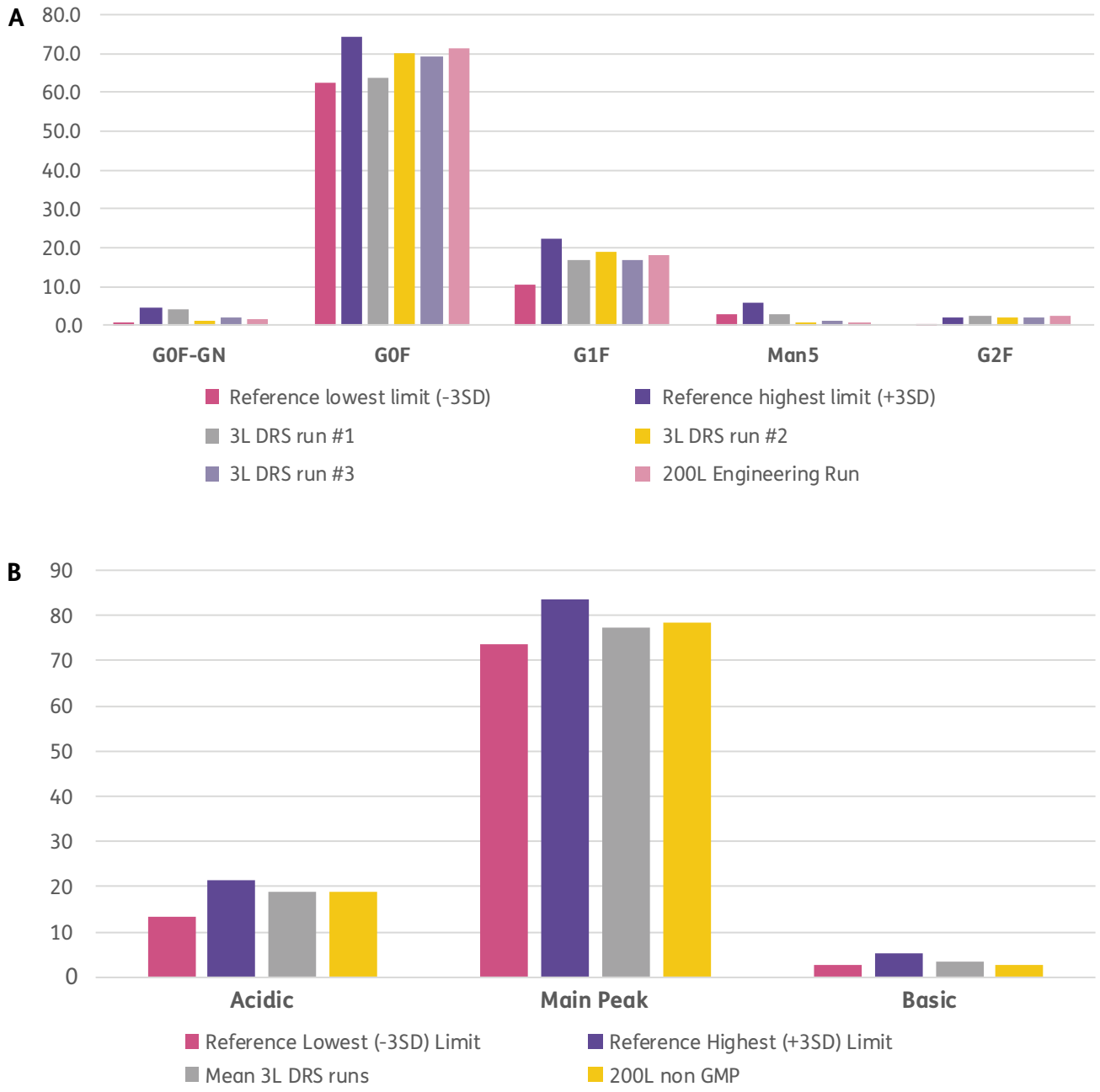
Feeding strategies, cultivation temperature, culture pH and galactose addition all can impact the cell growth, titer, glycosylation pattern and cell behavior in bioreactors. Feedstreams, feed duration, temperature shifts and pH for TUR01 manufacturing were optimized in shake flasks and 3L bioreactors prior to scale-up. Glycosylation is the major post-translational modification having impact on efficacy, immunogenicity and safety. Based on Turgut's experience, temperature effects on the glycan structures, G0F-GN and G0F, may vary depending on the biosimilar molecule, and pH has significant effects on fucosylated glycan complexes. For TUR01, both temperature and pH decreases in the manufacturing process were shown to affect G0F-GN and G0F. G0F-GN decreased by 83% (from 12% to 2%) and G0F increased by 8% (from 72% to 78%). To provide high biosimilarity, G0F levels were moderated by converting G0F to G1F with Gal+ supplement addition. By

Table 1. List of Comparability Analyses Conducted Between TUR01 and the Innovator

Biosimilarity Characterization	Physicochemical and Functional Analysis
Protein structure	Intact mass analysis Peptide mapping analysis Capillary electrophoresis-sodium dodecyl sulfate analysis (CE-SDS) Capillary electrophoresis-isoelectric focusing (cIEF) Size exclusion chromatography (SEC) Subunit mass analysi
Post-translational modifications	N-glycan analysis Oxidation Deamidation N-terminal pyroglutamic acid formation C-terminal lysine truncation
Protein folding	Circular dichroism (CD) analysis Fourier transform infrared spectroscopy (FITR) analysis
Protein activity	Antibody/Antigen binding kinetics Cell-based assays ADCC and CDC assays

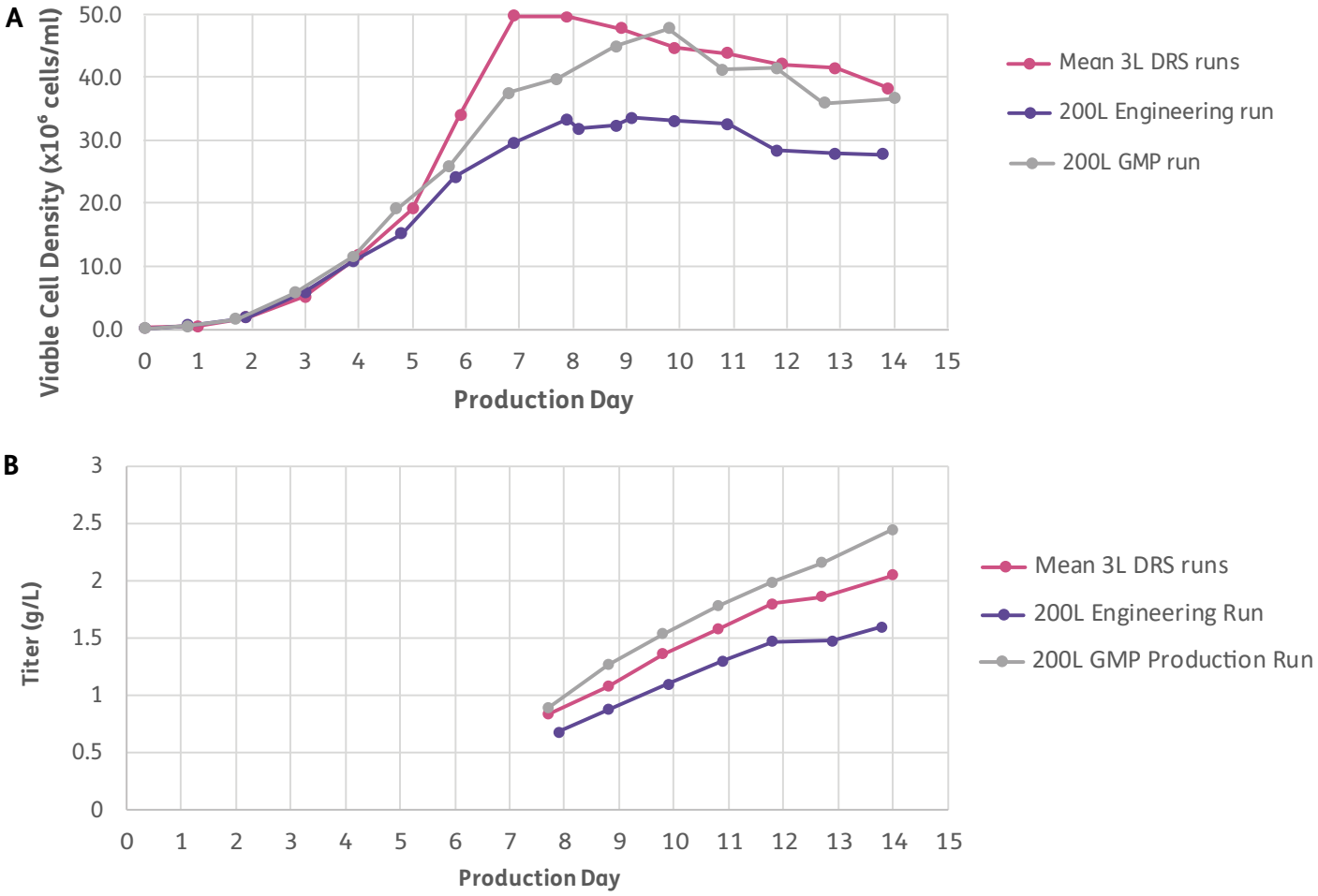
using Gal+ addition, optimum process parameters providing high biosimilarity were found. Figures 1A and 1B compare the glycosylation and charge variant profiles of TUR01 from both 3L and 200L against a reference standard and demonstrate high biosimilarity. Viable cell density and titer were also tested and results from both 3L and 200L bioreactor runs (Figures 2A and 2B) demonstrated high productivity and cell viability during early scale-up. The other assays, such as intact mass analysis, circular dichroism analysis, antibody/antigen binding kinetics and cell-based potency assays also demonstrated biosimilarity, proving the successful scale-up strategy and high biosimilarity during upstream production. The first GMP production of TUR01 has been completed for Phase I study, which will start in November 2018.

Figure 1. Establishing Glycosylation (A) And Charge Variant (B) Similarity Between 3L and 200L Bioreactors



Individually and collectively, Selexis and Turgut are key players delivering on the potential of biosimilars, and together, they hope to play a role in ensuring emerging countries will eventually have access to such therapies. Novel biologics have been used to treat many life-threatening diseases. The promise of biosimilars to expand patient access to these treatment options is enormous. That promise starts with extensive experience in cell line development, superior manufacturing capabilities, and a commitment to only the highest-quality science and analytics.

Figure 2. Viable Cell Density (A) And Titer (B) In 14-Day Fed-Batch Culture



Imraldi Sets Pace On German Price Cuts

By Aidan Fry

Biogen's Imraldi (adalimumab) biosimilar has entered the German market with a list price just over 40% lower than the cost of the reference brand, AbbVie's Humira, according to the association of statutory health insurance doctors for the North Rhine region, the KVNO. And while Amgen's Amgevita and Sandoz/Hexal's Hyrimoz currently offer more modest list-price discounts to Humira, the KVNO says both suppliers of adalimumab biosimilars have announced price cuts that will come into effect from 15 November.

Citing data from Germany's *Lauer-Taxe* price list, as well as company information, the KVNO says a pack of two Imraldi pre-filled syringes currently has a list price of €1,144.64 (US$1,305.80), which is 40.1% below Humira's €1,911.47 price.

Amgen's €1,577.54 launch list price for Amgevita offers a 17.5% reduction compared to Humira, while Sandoz and Hexal have set an initial price of €1,510.06, representing a 21.0% discount to the reference brand (see Figure 1).

Pointing out that with sales of €106 million last year, Humira was the drug on which most was spent in the North Rhine region, the KVNO said the entry of biosimilar competition could reduce the cost of anti-tumour necrosis factor (anti-TNF) alpha inhibitors "by up to 40%". Initial pricing levels suggest that adalimumab discounts may exceed that forecast.

With the exception of uveitis in children and adolescents for Amgevita and Imraldi, the biosimilars are authorised for the same indications as Humira, the KNVO noted, adding that approval processes and switching studies have proven biosimilars to be equal to their reference drugs.

Imraldi Boosts Biogen's Total

Biogen's Imraldi, launched on 17 October, joins the firm's two existing biosimilars in Europe, which saw their combined sales rise by a third to US$135 million in the third quarter of this year. This was due in large part to Benepali (etanercept) sales rising by nearly a quarter to just over US$123 million, while Flixabi (infliximab) sales were more than five times higher at US$11.4 million. "Benepali continues to be the market leader in countries such as the UK, Denmark and Norway, and exceeds 40% volume share in Germany, Italy and Sweden," chief financial officer Jeff Capello commented.

"Biogen is now able to offer biosimilars of all three major anti-TNFs in Europe," the firm pointed out, noting that it was also developing trastuzumab and bevacizumab through its Samsung Bioepis joint venture in which it plans raise its stake to 49.9% by the end of this year. "We believe that there are now more than 100,000 patients treated with our biosimilars in Europe," Biogen's chief executive officer Michel Vountasos claimed, pointing out that Imraldi would compete in a US$4 billion European adalimumab market.

Published November 2, 2018 in Generics Bulletin

Figure 1: List prices in Germany for packs of two adalimumab pre-filled syringes as of 26 October (Source – KVNO)

Brand	October list price (€)	Difference to Humira (€)	Discount to Humira (%)
Humira	1,911.47	–	–
Amgevita	1,577.54	-333.93	-17.5
Hyrimoz	1,510.06	-401.41	-21.0
Imraldi	1,144.64	-766.83	-40.1

Amgen Enlists Orion For Finnish Amgevita

Amgen and Orion have struck a sales and marketing collaboration for the US firm's Amgevita (adalimumab) biosimilar in Finland. The deal for "Finland's first adalimumab biosimilar" comes as Amgen competes with Biogen, Mylan and Sandoz to take market share in Europe away from AbbVie's Humira reference brand after the arthritis blockbuster lost its supplementary protection certificate (SPC) monopoly in mid-October (**Generics *bulletin***, 26 October 2018, page 1).

Estimating Finnish sales of Humira to be around €50 million (US$57 million) per year at present, Orion's president and chief executive officer, Timo Lappalainen, told investors that the firm would unveil its pricing strategy upon launch, "probably during the fourth quarter of this year". Questioned about the possibility of broadening the firm's relationship with Amgen, he simply confirmed that the deal was limited solely to adalimumab in Finland.

"Based on its sales value," Orion commented, "the original adalimumab product is the most-sold medicine globally and in Finland, and its impact on medicine reimbursement costs is substantial." The company intends to work with healthcare professionals to "make Amgevita accessible to patients with chronic inflammatory disease", supported by active encouragement to use biosimilars given by Finland's Fimea medicines agency, which is consulting on pharmacy-level substitution (**Generics *bulletin***, 11 May 2018, page 11).

Amgevita will be Orion's first biosimilar for out-patient injection at home, adding to its existing Nordic deals for Celltrion's Remsima (infliximab) and Ritemvia (rituximab) biosimilars that are used predominantly in hospitals.

The Finnish firm also recently signed an agreement with South Korea's Celltrion for sales, marketing and distribution of biosimilar trastuzumab in the Nordic countries and Estonia (**Generics *bulletin***, 27 July 2018, page 5). However, it says, "the launch schedule for trastuzumab remains open and depends on the patent situation and on the timing of tendering competitions, among other things".

In the first nine months of 2018, Orion's biosimilars sales more than halved to €19.1 million as it failed in winner-takes-all infliximab tenders in both Denmark and Norway.

Published November 2, 2018 in Generics Bulletin

Four Adalimumabs Compete In EU

Four separate biosimilar versions of AbbVie's Humira (adalimumab) are competing for market share in the European Union (EU), after Amgen, Mylan, Samsung Bioepis and Sandoz all launched into European markets immediately after a key supplementary protection certificate (SPC) protecting the autoimmune treatment expired. Amgen, Mylan and Samsung Bioepis said their respective Amgevita, Hulio and Imraldi biosimilars had launched in markets across Europe, including in Italy for Amgen. A Sandoz spokesperson told **Generics *bulletin*** the company – which has received approval under the Hyrimoz, Halimatoz and Hefiya labels – had "launched and supplied" its adalimumab in Germany and the UK, while it had placed tender bids in the Netherlands and Ukraine.

The unprecedented multiple launch was preceded by a global patent-litigation settlement between AbbVie and Sandoz that provided guaranteed market entry dates (**Generics *bulletin***, 19 October 2018, page 19), following other deals struck by AbbVie with Amgen, Mylan and Samsung Bioepis. **Generics *bulletin*** understands that Boehringer Ingelheim – which has not publicly announced a settlement with AbbVie, but which has European Medicines Agency (EMA) approval for its Cyltezo version – does not have immediate plans to launch.

Meanwhile, Fresenius Kabi and AbbVie have just announced a global resolution of Humira patent disputes through a royalty-bearing deal that will grant Kabi a US licence starting on 30 September 2023 and that also allows the firm to launch in the EU upon EMA approval.

Published October 26, 2018 in Generics Bulletin

Three Blockbusters To Face 2019 Competition

Next year will see biosimilar entry in the US for Roche's three highest-selling blockbuster biologic originals, the originator anticipates, opening up a market that is tracking towards CHF10 billion (US$10.0 billion). "We expect the first entrants of biosimilars to the US in the first half of next year with MabThera/Rituxan (rituximab), the second half of next year with Herceptin (trastuzumab) and with Avastin (bevacizumab)," Roche's group chief executive officer, Severin Schwan, told investors during the company's third-quarter earnings call.

Mylan last year brokered a settlement deal on Herceptin that meant it anticipated "potentially being the first company to launch a biosimilar to Herceptin in the US", having since received approval for the firm's Ogivri (trastuzumab-dkst) biosimilar developed with partner Biocon. Amgen holds an approval for an Avastin biosimilar, Mvasi (bevacizumab-awwb), while Celltrion and Teva earlier this month saw a US Food and Drug Administration (FDA) committee recommend the firms' Rituxan biosimilar, CT-P10, for approval.

At-risk Launches Expected

Amgen and Celltrion and Teva together are currently embroiled in patent litigation over their respective bevacizumab and rituximab biosimilars in US district courts, while Pfizer, Celltrion and Teva, Amgen and Samsung Bioepis have all been sued for challenging patents protecting Herceptin. Schwan refused to comment on whether Roche anticipated biosimilar players launching at-risk in 2019.

In the first nine months of this year, the three brands brought in sales of CHF7.57 billion in the US: MabThera up by 4% to CHF3.19 billion; Avastin flat at CHF2.17 billion; and Herceptin ahead by 12% to CHF2.21 billion, all measured at constant-exchange rates.

Following the entry of rituximab biosimilars across European markets early last year, MabThera sales halved to CHF731 million in Europe in the nine months to 30 September. Herceptin, which has faced biosimilar competition in Europe since the second quarter of this year, saw sales down by a tenth to CHF1.50 billion.

"We see a difference between the erosion rates between US and Europe," Schwan said, commenting on Roche's view of biosimilar penetration in the two markets. "We don't expect the erosion rate to be similar to Europe at this stage, even with some potential additional activities by the administration in the US government."

Published October 26, 2018 in Generics Bulletin

As Humira Biosimilars Arrive, Battle Lines Shift From Education To Sustainability

By Melanie Senior

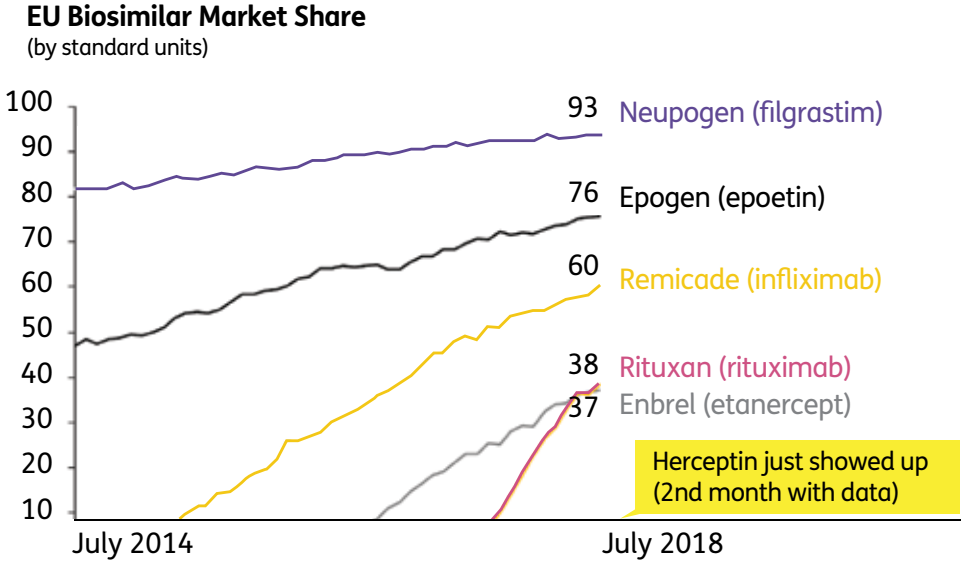
- Copies of the world's top-selling drug, Humira, will hit Europe in mid-October, launching the biggest biosimilar battle yet.
- Many of Europe's payers are poised to swiftly adopt these cheaper medicines.Their challenge has shifted from whether to use biosimilars, to how to use them – the practicalities of patient switching, information and monitoring.
- ***So what?*** Sponsors fear downward price-spirals may threaten the sector's sustainability. Yet, longer-term, biosimilars' impact may stretch beyond price and access, to change treatment pathways.

Over a decade since the first biosimilar was approved in Europe, these near-copies of large molecule drugs have taken hold. Physician confidence has grown as evidence accumulates to show biosimilars' equivalence to branded originals. Payers are saving money. Prices of medicines that can cost many tens of thousands of dollars per patient per year are falling by between 40-80% in some markets. And the savings are rolling in faster with each new biosimilar launch: Europe's first complex biosimilar, infliximab (a copy of **Merck & Co. Inc./Johnson & Johnson**'s TNF-blocker *Remicade*, used in a range of inflammatory conditions), took a couple of years after its 2015 launch to get off the ground. Biosimilar versions of Roche's cancer and rheumatoid arthritis treatment *MabThera* (rituximab), however, launched in 2017, captured almost 40% volume share in Europe within a year. In the UK, that share is now over 80%, according to IQVIA.

After a slow start, Europe is now adopting biosimilars "at the high end of expectations," says Ronny Gal, senior analyst at Bernstein. Biologics make up the largest, and fastest-growing share of drug spend in most systems. IQVIA estimates that Europe's top five markets (UK, Germany, France, Spain and Italy) could save €10 billion ($11.6 billion) from biosimilars between 2016 and 2020.

As well as being critical to health system sustainability, biosimilars are increasing patient access to biologics in certain countries and conditions. They have boosted European sales

Exhibit 1: Europe Market Overview: Biosimilars As Volume Share Of The Reference Molecule Market



Source: IQVIA; Bernstein

volumes: since biosimilars of infliximab and etanercept (**Amgen Inc./Pfizer Inc.**'s *Enbrel*) were launched, these medicines have grown at compound annual growth rates of 10% and 4% respectively, having been flat before, according to IQVIA data. And there are signs that biosimilars are opening up use of biologics earlier in the treatment pathway.

So while the nascent US biosimilars market remains hamstrung by patent disputes, topsy-turvy market incentives and a mind-boggling naming policy (*see Box US Biosimilars: Close To Lift-Off?*), Europe is bracing for its biggest biosimilar launch-party yet. An unprecedented number of competitors are vying for a share of Humira's $4.4 billion European sales (over $12 million per day), across its dozen or so indications. Many of Europe's payers have geared up to take full advantage of biosimilar adalimumabs the minute they become available.

There are still challenges. But those challenges have shifted. They are no longer about informing and convincing physicians and other stakeholders of biosimilars' safety and efficacy. They are now about figuring out the pricing and procurement dynamics that enable meaningful health system savings and increased patient access, but which also sustain a vibrant, competitive biosimilar market.

Not Whether, But How

Europe's payers and physicians have cut their teeth on other monoclonal antibody biosimilars, including infliximab, in the same anti-TNF class as Humira and used across a similar range of inflammatory diseases, and, most recently, biosimilar trastuzumab (*Herceptin*) in cancer. There is a strong foundation of clinical and real-world data supporting the equivalence of biosimilars to their originator. "Biosimilars work. They are equivalent enough" to the originator molecule, asserts Justin Stebbing, Professor of Cancer Medicine and Medical Oncology at the Imperial College Healthcare NHS Trust in England. Stebbing is lead author on a Celltrion-funded equivalence study of biosimilar trastuzumab, which showed that the Korean group's biosimilar, now available as *Herzuma*, was therapeutically equal to Herceptin in patients with early-stage HER-2 positive breast cancer. But he suggests that, as comfort with biosimilars grows, full-blown clinical trials may not be necessary across all indications. In some situations, such as metastatic cancer, "we can extrapolate," he says (*see box: Changing Attitudes*).

Indeed, "extrapolation [relying on data in one indication to support use in another] is now better understood, and accepted," says Fraser Cummings, consultant gastroenterologist and Honorary Associate Professor at the University Hospital Southampton NHS Foundation Trust, speaking at SMi's Biosimilars & Biobetters conference in London on September 26, 2018. Cummings acknowledges, though, that some clinicians still want to see clinical data in a relevant population. And indeed, for now, "we still need clinical studies, including combination and switch studies, as well as more long-term data," says Stebbing. Real-world data and pharmacovigilance remain critical: systems must handle growing volumes of data, and be sufficiently sensitive to pick up signals as patients are switched from reference drugs to biosimilars, and, increasingly, between biosimilars.

Yet while these data accumulate, the question for many health systems has moved from whether to use biosimilars, to how to use them. Providers are now grappling

US Biosimilars: Close to Lift Off?

The FDA has approved over a dozen biosimilars, but most are caught up in patent disputes. And even if they were not, the US health system's web of rebates and reimbursement contracts is not designed to encourage more careful purchasing – indeed, many hospital systems benefit from buying more expensive drugs. The result is "anemic" biosimilar competition and a missed opportunity to save what could have been over $4.5 billion in 2017 alone, lamented FDA Commissioner Scott Gottlieb in a July 2018 speech.

Momentum is building behind efforts to boost biosimilar adoption, however. Gottlieb's July speech was to launch the FDA's 11-point plan to promote biosimilar uptake and competition. This included a more efficient approval process, better communication, finalized labeling guidance and steps to tackle anti-competitive behavior.

Forthcoming guidance around interchangeability could be the most important catalyst for change, however. Most US states have passed laws that would allow pharmacists to substitute biosimilars that are designated interchangeable, significantly boosting uptake. Credit Suisse analysts expect the first interchangeable biosimilar to be approved in 2019-2020. Meanwhile, AbbVie's lawyers have held off biosimilar Humira in the US until 2023.

with the practicalities of staffing and setting up patient-switching programs, and working out what, if anything, to tell patients as they move onto a medicine that might look slightly different. They are having to balance budgetary priorities with patients' needs and concerns, and ensure that decisions are understood and supported by all stakeholders.

Biosimilar sponsors, meanwhile, must continue to navigate (and influence) complex, fragmented and fast-evolving procurement systems alongside a growing number of competitors – including the originator.

Payers Poised To Embrace Biosimilar Humira

The onslaught of Humira biosimilars will test how well health systems and sponsors are facing up to those challenges.

As of late September 2018, eight biosimilar brands (five different molecules) had been approved in Europe, with several more in development (*see Exhibit 2*). AbbVie's CEO Rick Gonzalez has predicted that ex-US sales of the drug will fall by no more than 20% by the end of 2019. This may be optimistic (even if ex-US includes other markets where biosimilars are not available, such as Brazil and Japan). Sales of branded Remicade have dropped almost 70%, albeit three years after launch. Humira sales could drop farther and faster, since there are more competitors at the outset, and far more rigorous preparations among some European payers. "I think uptake of [biosimilar] adalimumab will be massive," predicted Michael Muenzberg, biosimilar consultant and former medical director of EU biosimilars for Amgen, at SMi's Biosimilars & Biobetters conference.

Several European health systems, including in the UK and Germany, have increasingly aggressive national or regional biosimilar prescription targets or quotas in place to

Changing Attitudes

Attitudes across professional societies in Europe, too, have evolved to encourage use of better-value medicines. This is critically important in convincing physicians to use biosimilars. The positions of groups such as the Association of German Rheumatologists, the British Society of Gastroenterology, and many others have shifted from cautious skepticism two or three years ago, to positive endorsement today.

Even in France, where strong physician lobbies and a law that prohibits patient switching have slowed biosimilar uptake, things are changing. Marc Bardou, a gastroenterologist and professor of clinical pharmacology at the Centre Hospitalier Universitaire (CHU) Dijon, Northern France, was highly skeptical of using biosimilar infliximab in GI indications when it first became available. Now, reassured by data from a national switching trial, "my and many of my colleagues' attitudes have completely shifted," he says.

Exhibit 2

Biosimilar Humira Products Ready To Launch In The EU In October 2018

Manufacturer	Biosimilar Adalimumab Brand Names (Approval Date)
Amgen	Amgevita and Solymbi (Mar. 2017)
Samsung Bioepis	Imraldi (Aug. 2017)
Boehringer Ingelheim	Cyltezo (Nov. 2017)
Sandoz	Halimatoz, Hefiya and Hymrioz (July 2018)
Fujifilm/Mylan	Hulio (Sept. 2018)

SOURCE: News releases

encourage uptake, sometimes linked to financial or non-financial incentives. In the UK, preparations have gone deeper still. NHS England's Regional Medicines Optimisation Committee, charged with ensuring the national payer obtains good-value medicines, urged local medicines purchasers back in May 2018 to avoid entering into new adalimumab contracts lasting beyond 16 October 2018. Instead, NHS England's Commercial Medicines Unit will use a price-based national tender to select a short-list of adalimumab formulations under a 'framework agreement'. Regional players can then select from and negotiate further discounts around these formulations, according to local priorities.

Importantly, given that adalimumab is often administered at home or in an out-patient setting, shared savings schemes are being set up to ensure that incentives for hospital systems and primary care providers are aligned to use cheaper biosimilars. Advice is also provided to hospitals and general practitioner practices on updating agreements with local homecare providers. Even letter templates are available for providers and clinicians to send to patients, informing them of why they are being switched to a biosimilar medicine and what it means. Online savings calculators will enable regional providers (Trusts) to work out the savings available from switching a certain proportion of their patients.

"I have never seen such a coordinated push for speed, depth and breadth of uptake," says Omar Ali, formulary advisor for Surrey & Sussex Healthcare NHS Trust and visiting lecturer, value based pricing & outcomes based innovative contracting at the University of Portsmouth in the UK. England already has the highest biosimilar penetration across the EU 5 countries, and saved £324 million ($423 million) from biosimilars last year. The NHS hopes to make regular annual savings of £300 million by 2021.

Some German payers have been avoiding high-priced Humira since 2016, even without a biosimilar to that particular molecule. Instead, in areas such as Westfalen-Lippe, physicians and hospitals are encouraged to use biosimilar versions of other anti-TNF medicines such as infliximab or etanercept (*Benepali*) – especially for new patients. Potential annual savings from using cheaper biosimilars – up to 20%, or over €4,000 per patient – are spelled out. The share of infliximab biosimilars in Germany is now about 80%, although regional variation is high.

Speeding Up Switching

Switching is key to biosimilars' success: without it, their markets would be limited to new patients. Here too, attitudes are shifting as savings materialize and study data accumulates to support the safety of switching (*see Exhibit 3 for study examples*).

Many of Europe's healthcare providers are being urged by their funders to prepare for extensive switching from Humira onto biosimilar adalimumabs. Patient switching is already a well-oiled process in many markets and hospital systems, though. In Norway and Denmark, which run nationwide tenders for biosimilars, mandated patient-switching may occur across the entire country. Patients in Sweden's capital, Stockholm, were switched within two months to biosimilar infliximab, with few complaints according to Gustaf Befrits, a health economist with the Stockholm County Council, speaking at a conference earlier in 2018. In June 2018, the European Specialist Nurses Organisation (ESNO) launched a guide on how to support patients switching from reference to biosimilar drugs, or *vice versa*.

The most recent switch underway across many Trusts in England, onto biosimilar trastuzumab, appears to be going smoothly. Patients at the Royal Marsden Hospital in London were switched in September 2018 to a biosimilar trastuzumab that "cost about half the price of the original," says Jatinder Harchowal, chief pharmacist at the Royal Marsden Hospital in London. "We didn't have to do an intense amount of training," he continues, "because people understand and accept" biosimilars. Patients at the Imperial College Healthcare NHS Trust are also being switched to *Ontruzant*, a biosimilar trastuzumab developed by **Samsung Bioepis Co. Ltd.** and marketed by **MSD** in Europe. The switch is mandatory for all patients on the IV formulation of the drug (the branded version is also available in sub-cutaneous form), but patients are informed. The timing and depth of information provided is at the discretion of the Trust and clinicians, however. Some clinicians feel the change should be kept as low-key as possible to avoid unnecessary stress among patients.

Switching is likely to become more frequent as more biosimilars reach the market, each offering payers a better price. The limiting factor in many systems will be clinical and nursing resources. "We have over 600 patients on Humira" across our hospitals, says Southampton NHS Foundation's Cummings. "Even with the slickest switch, each

patient will need 30 minutes at least." He predicts no more than one switch per year in any given indication as a result.

Doctors Take A Back Seat

In future, doctors in UK hospitals may play even less of a role in determining which version of a particular biologic patients actually receive. "It is going to be the Trust's decision," predicts Imperial's Stebbing. For him, that is fine. "We're busy. We don't have time to ask where the trastuzumab comes from."

Hospital physicians in Norway and Denmark have already relinquished such decisions. These markets use price-based tendering to select a single winner, which becomes the preferred medicine across the entire country. According to IQVIA, this system has led to biosimilar penetration of 98% and 100% for biosimilar infliximab in Norway and Denmark, respectively – and some of the fastest and strongest price erosion. (Physicians can prescribe an alternative, but may face financial penalties for doing so.)

The picture is less clear-cut in other markets. In France, hospital doctors can still specify a particular brand if they wish. And although hospitals are offered incentives to use cheaper medicines if they fall within a diagnosis related group (DRG) tariff, which provides fixed payments for certain activities and procedures, many expensive medicines, including biologics, are reimbursed separately. In Germany, hospitals in some regions may still profit from using innovator biologics, because of contracts with insurers that simply reimburse list price minus a fixed percentage discount. So they have little interest in changing doctors' behavior. But the hospital-insurer contracts are evolving to encourage greater biosimilar uptake, including through introducing flat-funding for all products with the same international non-proprietary name (INN), set at the level of the cheapest drug in that category.

Retail Versus Hospital

Biosimilar uptake also varies widely across the hospital and retail (community) settings. Some biologics, particularly those for chronic conditions, are administered and paid for outside hospitals (even if they are prescribed by hospital doctors). Humira is one example: in most indications, it is administered at home or at least in the community setting. In the retail sector, choice of medicine is often less constrained by institutional practices and policies, and some analysts predict a slower-than-anticipated uptake of biosimilar adalimumab as a result. They speculate that patients in the home setting may be more resistant to switching from a more familiar reference product.

But the influence of many of Europe's payers is spreading into retail, where incentives for using biosimilars are evolving fast. In Germany, insurance funds run 'open-house' contracts for biosimilars in the retail setting, with conditions such as minimum list-price discounts or maximum prices pegged to that of the cheapest or second-cheapest candidate. As biosimilar competition increases, the screws are being tightened, notes Pro-Biosimilars, a national industry association. Even in France, economic pressures compelled the health ministry in August 2018 to call for proposals for new ways to encourage uptake of biosimilar etanercept and insulin glargine in the community setting. Meanwhile, biosimilar sponsors are bending over backwards to support education and uptake in these retail settings, too. Chrys Kokino, head of biologics at **Mylan NV**, whose biosimilar adalimumab *Hulio* is the most recent to gain European approval, is not concerned about the retail versus hospital distinction, given the overall variation between European markets. "Every European market is different. As long as we are able to improve patient access, we are not as concerned about where the prescription originates as uptake will be dependent on recognition of the product's efficacy, safety and utility," he says.

How Low Is Too Low? The Sustainability Question

Biosimilar sponsors have spent over a decade trying to persuade Europe's payers to use biosimilars. Now they are worried that those payers, in their new-found enthusiasm, might become too aggressive in pushing down prices. Sponsors are now worried about sustainability. "The way things are going right now, driven only by price, will mean less competition, less choice, and patients will lose as a result," warns Paul Harmon, senior director and oncology biologics lead at Mylan Europe.

With so many adalimumab competitors, the risk is that prices dive deeply and rapidly, making it un-economic for some players to remain in the game. Already, biosimilar discounts have reached depths that few thought possible – like Denmark's 70% discount on branded Herceptin, or Norway's 72% discount on branded Remicade in 2015.

At what point the price becomes un-economic will vary by company, molecule and market. "I don't know what the ap-

propriate price is. Is it 10%, 20%, 30% less than the originator? I don't know. But it definitely isn't 90%," says Harmon.

The Humira gold-rush will begin to force answers to this question, and others around what a healthy and sustainable biosimilar marketplace looks like. Granted, it costs a considerable amount – in the $100 million to $200 million range – to bring a biosimilar to market, and it can take 10 years. If prices drop too low, there could be fewer competitors, which, as well as restricting choice, could also potentially threaten supply.

The huge margins on biologics mean there is plenty of scope for generous discounts, however. Modern manufacturing technologies are pushing down unit production costs. "They might make gross margins that are less than 80-90%, but there's no reason [profit] margins won't still be in the 30-50% range in five years' time," making it a nice business still, says Bernstein's Gal. Muenzberg also dismisses sponsors' sustainability concerns. "There's a lot of room for profit," he says. And indeed companies like **Orion Pharma**, distributing biosimilars in the Nordic countries, are doing nicely on their formula of large discounts and large market share.

Europe's patchwork of national and regional reimbursement policies, procurement processes, cultures and even intellectual property protection mean prices are not going to fall by the same degree all at once. Despite a common quest for value, biosimilar uptake and utilization is highly variable across different molecules and markets. Indeed, the region offers a convenient suite of case studies showing the impact of different biosimilar procurement strategies and physician incentives. Although no single country provides a perfect example of a healthy biosimilars market – if indeed anyone knows what that is – "there are lots of individual best-practices you can learn from specific markets, regions, even specific hospitals," says Florian Turk, head global payer, marketing, sales and relations at **Sandoz International GmbH**.

And worst practice: many biosimilar sponsors hate the aggressively price-focused, single-winner national tenders seen in some Nordic countries, that cut out all but one player. Such tenders "are negative for both originator and biosimilar manufacturers…and may eliminate manufacturers' incentives to innovate in areas of added value, such as administration route, device design, patient support programs," declare the authors of a **Pfizer Inc.**-sponsored IQVIA report, *Advancing Biosimilar Sustainability in Europe,* published in September 2018.

Multiple Winners

They instead favor multi-winner tenders, and/or sub-national tendering (at the hospital or regional level) based on other criteria as well as price, that may sustain several competitors – including potentially the originator – and offer patients and prescribers a range of options. Such systems are in place in the UK and Germany, and in France, where, according to Sandoz' Turk, "only 40% of the decision is based on price; 50% is qualitative criteria." Those qualitative criteria extend to education, support and logistics, inventory management and even environmental impact of production, as well as excipients, delivery device and administration mode.

The weighting of such criteria varies by country and region and even, in some markets, by individual insurers or even hospitals. Price predominates in most cases. But once a certain level of discount is achieved – for instance, in the UK framework agreements – there is room around the edges. Priorities will be based on individual institutions' patient numbers, storage capacity, resources and more. "Some [biosimilar trastuzumabs] have longer stability data than others," illustrates Royal Marsden's Harchowal. That can help avoid wastage. For other hospitals, guarantee of supply may be a priority, for example when usage is high and/or in acute settings. (Sandoz hit capacity issues for its *Rixathon* [biosimilar rituximab] after its mid-2017 launch, giving the lead in some markets to rival **Celltrion Inc./Mundipharma International Corp. Ltd.**'s Truxima.)

Not all formulations of a given molecule are available as biosimilars: Roche's sub-cutaneous MabThera (rituximab) has seen minimal sales erosion from biosimilars, according to IQVIA data. Roche also has a (still-patented) sub-cutaneous version of Herceptin, which is much quicker and cheaper to administer than the intravenous version. In England, patients on sub-cutaneous Herceptin are, for now, allowed to remain on it. There is even reverse-switching in some English Trusts: patients may be started on biosimilar trastuzumab by infusion, but once they are stable, they are sent home with a prescription for sub-cutaneous Herceptin. "It actually saves money to keep them out of hospital, even with the more expensive formulation," says Omar Ali.

Exhibit 3

Switching Studies Show Few Concerns

The Norwegian government-sponsored NOR-SWITCH trial of infliximab found the biosimilar to be non-inferior to the reference molecule.	See The Lancet, June 2017 for study results. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2817%2930068-5/fulltext
A Danish study of over 800 patients with inflammatory arthritis, switched from Remicade to Celltrion's biosimilar Remsima, also showed non-inferiority.	See Annals of the Rheumatic Diseases, 2016 for full study results. https://ard.bmj.com/content/76/8/1426.long
A Sandoz-sponsored systematic literature review of switching studies, published in March 2018, found no differences in immunogenicity, safety or efficacy following switching.	See Drugs, March 2018 Vol. 78 (4), for full study results. https://link.springer.com/article/10.1007%2Fs40265-%2018-0881-y

These dynamics allow innovators to hold onto a slice of the market; they also drive innovation among the followers. Celltrion is working on a sub-cutaneous form of infliximab, for example. Others are finding new, more convenient and faster ways to deliver I.V. medicines, and to offer support. "We are looking at patient services, devices and other means to further differentiate ourselves in the marketplace," says Mylan's Kokino.

Thriving In Complexity

Europe's biosimilar practices will continue to evolve, but they will not harmonize. Optimal procurement systems, number of competitors, average price drops and the extent to which factors like product stability, dosage, formulation and delivery trump pricing will continue to vary by molecule, indication, country and even region. This fragmentation may be precisely what allows the biosimilar market to thrive, sustaining multiple competitors across the region as a whole, and a wide choice for patients.

Europe's complexity has played directly into the hands of groups like Mundipharma, which commercializes three of Celltrion's biosimilars across several European markets. Mundipharma is a network of associated, yet independent organisations across Europe (and beyond). Each has deep knowledge of local systems, stakeholders, priorities and culture, and each has the freedom to use that expertise to maximize patient access. This local-first philosophy and structure is particularly well-suited for biosimilars. After extensive education campaigns, working closely with stakeholders, and sharing early lessons, "we understand how biosimilars are procured and how physicians prescribe them" in each market, says Warren Cook, senior commercial lead, biosimilars at Mundipharma.

Today, infliximab biosimlar *Remsima* remains the number one infliximab brand in Mundipharma's seven territories, which include Germany, Italy, the UK and the Netherlands. Mundipharma also sells Celltrion's rituximab (Truxima), which grabbed 75% market share in the Netherlands six months post-launch, and trastuzumab (Herzuma), launched in May 2018. As In Vivo went to press, Mundipharma announced plans to acquire **Cinfa Biotech**, which received a positive recommendation in Europe last month for approval of its biosimilar version of Amgen's *Neulasta* (pegfilgrastim).

Celltrion and other biosimilar-makers are also using multi-branding strategies to address (and benefit from) Europe's complexities. Multi-branding refers to marketing the same molecule under distinct brand names. The eight brands of adalimumab biosimilar are in part about overcoming divergent national patent constraints (patents are national affairs; the concept of an EU-wide patent extends to name only). Molecules like adalimumab, approved for a dozen or more indications, are more likely to bump up against such patent barriers. Amgen's biosimilar adalimumabs *Amgevita* and *Solymbic* are identical other than in one of the nine indications each is indicated for.

Multiple brands may also enable sponsors to hand out distribution rights to different partners, and increase their share of voice through having two sales forces. They may position one brand more aggressively to compete in government-backed tender processes, for instance, reserving another for commercial contracts, which may include a ser-

vice element (e.g. home-care). There may also be cultural nuances around particular brand names. In short, sponsors are "playing with patents, and pricing to different games" in a bid to maximize market share, says Bernstein's Gal.

Are Biosimilars Changing Treatment Pathways?

Biosimilars are already saving health systems money and enabling more people to access specialist treatments that they may not otherwise have been able to afford. They are expanding treatment choice as competition forces biosimilar and originator sponsors to differentiate their medicines, for instance through new more convenient formulations, delivery devices or dosages.

But so far, there is only limited evidence that biosimilars are actually changing treatment pathways through allowing earlier use of biologics. UK guidelines around the use of filgrastim (granulocyte-colony stimulating factor, G-CSF) in chemotherapy patients changed to include first-line/prophylactic use following the introduction in 2008 of biosimilar versions of Amgen's original, *Neupogen*. Other than that, "the evidence is mostly only anecdotal," says Turk.

It is a start, though. As biosimilars savings accumulate, specialists are likely to push for a loosening of treatment guidelines, narrowed over recent decades by increasingly widespread health technology assessment amid soaring drug costs. "We have no data to support changes in treatment pathways, but we do see faster [volume] growth among biologics with biosimilar competition than those without," says Pontus Johansson, head of unit at Sweden's medicines reimbursement agency, TLV. "This could be due to lower prices. But it could also indicate that patients are being put on the treatment earlier, because of affordability."

In future, "I can see the availability of biosimilars changing the sequence of drugs we use, and how we use them," says Cummings. Cost-driven restrictions on the use of drugs like infliximab, now baked into treatment pathways, should gradually lift. Meanwhile, adoption of new biologics may slow further, certainly in the first-line setting. "It will be [even] tougher for originator drugs to access biologic-naïve patients," says Southampton's Cummings.

The arrival of biosimilar adalimumabs in Europe marks the end of a decade-long transition period as these medicines proved their therapeutic equivalence, and their potential to help save costs while driving access. The next phase will see greater penetration of biosimilars in the slower-adopting European markets. Dynamics among front-runner regions such as the Nordic countries, the UK and some parts of Germany will begin to determine whether sponsors' sustainability fears are justified, and how many competitors the region's disparate – yet increasingly value-seeking-- markets can sustain.

There are further biosimilars to come, including a handful of copies of Amgen's long-acting Neulasta in Europe, likely to see rapid uptake given the high adoption of biosimilar filgrastims. A further $52 billion (€44 billion) of biologics are expected to go off patent in the top ten developed markets between 2019 and 2022. As the category matures, biosimilars' impact will likely stretch beyond pricing and volumes, potentially changing how patients are treated, and raising entry thresholds for novel biologics. First, though, comes the battle for Humira's billions and the many lessons from that. "I'm fascinated to see what's going to happen," says Cummings. "Hold onto your hats."

Published October 26, 2018 in Generics Bulletin

Humira Under Pressure As NHS England Invites 'Competitive Prices' For Biosimilars

By Ian Schofield

Companies wanting a share of the lucrative adalimumab market in England following the expiry of patent protection on **AbbVie Inc.**'s *Humira* will need to offer a "competitive price". They have just a few days in which to do so.

Biosimilar versions of adalimumab are expected to be made available under the National Health Service in England starting on Dec. 1 this year. An invitation to tender for adalimumab supply to the NHS was launched on Sept. 19, and companies, including AbbVie, have until Oct. 22 to submit their bids. NHS England says that no supplier will be awarded the whole market, and that the highest shares will go to products with the most "competitive prices."

Competition will be keen, and NHS trusts and clinical commissioning groups are being warned not to accept discounted interim offers from suppliers seeking to get a foot in the door as quickly as possible.

Although prices for biosimilar versions of adalimumab have not yet been confirmed, NHS England estimates their use should help save it "at least £150m" a year, depending on the prices that are agreed for the products. In 2017/18 the NHS spent around $400m on Humira, "the highest spend on any medicine used in our hospitals."

NHS England mentions four biosimilars that have been authorized in the EU and may soon be competing to take market share from Humira: *Imraldi* from **Samsung Bioepis Co. Ltd.**, *Hyrimoz* from **Sandoz International GMBH**, *Amgevita* from **Amgen Inc.**, and *Hulio* from **Mylan NV**/**Fujifilm Kyowa Kirin Biologics Co. Ltd.**. It also points out that "ongoing use of Humira may also continue where clinically appropriate and where it is best value."

Biogen and Samsung Bioepis (a joint venture between Biogen and Samsung Biologics) said they would begin launching Imraldi in major European markets from Oct. 17. Ian Henshaw, global head of biosimilars at Biogen, told *Pink Sheet*: "You've got four or five competitors entering the market at pretty much the same time. This is the first time this has happened [entry of infliximab and etanercept biosimilar products has been gradual]. So we're going to see a lot of competition."

NHS England also notes that "at least two" further biosimilars are expected to become available in the UK during 2019. It names them as **Boehringer Ingelheim GMBH**'s *Cyltezo* and **Fresenius Kabi AG**'s MSB11022. Cyltezo already has an EU marketing authorization, while MSB11022 was filed with the EMA in December 2017. However, Boehringer Ingelheim told *Pink Sheet* that it does not plan to launch Cyltezo in the EU and will concentrate on US launch plans. While four companies have reached a patent settlement with AbbVie in the US, allowing them to launch their biosimilar versions there in 2023, BI said it was not in settlement discussions and was "now the only company with an approved biosimilar to Humira that has not settled with AbbVie." It said it was committed to making Cyltezo available in the US "as soon as possible and certainly before 2023 when these settling companies are allowed to launch their products."

"No supplier of adalimumab will be awarded the whole market but will have a strong incentive to offer their best price at the point of tender" – NHS England

Any additional biosimilars in the UK would be included in an NHS re-tender next year.

'Sustainable Market'

The tender strategy for adalimumab is "a first step towards development of a sustainable market" for adalimumab with the aim of achieving "the best possible value for the NHS while also maintaining plurality of supply," NHS England says.

The biosimilars will initially be introduced under a framework supply agree-

ment lasting 12 months from Dec. 1, 2018 to Nov. 30, 2019, with options to extend for up to two more years.

Tenders for the biosimilars will be awarded as four lots, "based on the assumption that there will be four biosimilar products and four bids by 1 December." If only three offers are received, "then three lots will be awarded as three distinct lots and so on. The size and shape of each lot will depend on the offers received and the relative prices." Humira will be a separate line in the tender.

Under the tender strategy, "no supplier of adalimumab will be awarded the whole market but will have a strong incentive to offer their best price at the point of tender," according to an October 2018 document produced by the four English Regional Medicines Optimisation Committees (RMOCs). RMOCs make recommendations, provide resources and coordinate activities to ensure the "optimal use of medicine" in the NHS.

> **"If there are price differentials, awarded shares will be higher for the most competitively priced suppliers, but all suppliers will get access to at least some of the market upon receipt of a compliant bid to avoid dominance."**

"If all tendered prices are similar, the shares awarded will on an equitable basis," the document says. "If there are price differentials, awarded shares will be higher for the most competitively priced suppliers, but all suppliers will get access to at least some of the market upon receipt of a compliant bid to avoid dominance."

A separate "commissioning intentions" document issued by NHS England in September says that the adalimumab market will be split into 11 hospital groups. NHS England framework prices for adalimumab "will be live" from Dec. 1, and hospital groups will be notified which adalimumab products are available to them.

The groups will each be awarded access to either Humira, a first-line biosimilar (either citrate-containing or citrate-free) or a second-line biosimilar (citrate-free if the first line is not citrate-free).

"Patient groups and clinicians told us that the availability of a citrate-free biosimilar was important to them as citrate can sometimes be associated with discomfort on injection," NHS England said. "The procurement strategy ensures that each hospital group has access to a citrate-free formulation for situations where this is required." Imraldi and Hyrimoz both contain citrate; the other three do not.

As part of the tender award process, companies will be told which supply regions they have been awarded, a process that is expected to be completed by Nov. 1. "After a mandatory 10-day standstill period, the details of the awards will be shared with the wider NHS (around 11 November)."

Direct Approaches Expected

NHS England has warned trusts and clinical commissioning groups that they "may be directly approached by suppliers of adalimumab and offered interim prices which offer significant initial discounts". It says that CCGs and trusts "are advised to do nothing at this stage and to not sign up to any proposal, or make any firm commitments (regardless of how large the discount is) until the planned tender model is confirmed as we expect improved prices as part of that process."

From April 2019, NHS England is planning to set a national reference price for adalimumab to "incentivise the system to uptake best value adalimumab products at scale and pace." NHS providers and commissioners "will be expected to make commissioning arrangements" that "reflect the national reference price for adalimumab."

Switching

NHS England has also produced a "Toolkit for implementing best-value adalimumab" to help organizations to implement a biosimilar switching program, which it says will also apply to other biologics with biosimilar versions.

The toolkit shows NHS trusts how to agree the switching process, review which patients are eligible for a switch and the relative timescales for both newly diagnosed and existing patients, and decide whether switching will happen at the same time for all indications or just specific ones.

"Successful approaches have been demonstrated where the hospital department(s) have been supported to reinvest some of the savings into additional clinical capac-

ity to address the needs of patients," it notes. However, it adds that some clinicians "may be reluctant to use a biosimilar and consideration should be given how to address their concerns and how best to respond to patient concerns and objections."

Where the HTA body NICE has already recommended the originator biological medicine, the same guidance will normally apply to the biosimilar, "so biosimilars do not require a separate or additional technology appraisal," the toolkit says. "The choice of whether a patient receives a biosimilar or originator biological medicine should be made after using shared decision making principles between the responsible clinician and the patient."

Patient Engagement

NHS England said it has been working closely with the national groups that represent the majority of patients who are being treated with adalimumab, including the National Rheumatoid Arthritis Society, the National Ankylosing Spondylitis Society, the Psoriasis Association, and Crohn's & Colitis UK.

The four groups issued a joint statement in which they welcomed the introduction of biosimilar adalimumab, but said it was "vital that patients are fully informed about all the treatment options available to them and commissioners and health professionals adopt the principles of shared decision-making."

They also said they would like to see "an appropriate share of savings" being ploughed back into rheumatology departments to "improve service and patient care."

While NHS England has said that more patients are getting access to high-quality, effective care due to the uptake of existing biosimilars, this is "not the case in rheumatoid arthritis," where NICE eligibility criteria for accessing biologics/biosimilars have "remained the same for the last 17 years" and are "now out of date by comparison to access to such medicines across many other European countries," they declared.

Published October 17, 2018 in Pink Sheet

One-Third Of Payers Preferred Biosimilars Over Reference Drug in 2017

By Cathy Kelly

Only 32% of payers gave biosimilars preferential formulary coverage with lower cost sharing versus their reference drug in 2017, according to the medical benefit pharmacy trend report released recently by PBM MagellanRx.

Even fewer payers, just about one-quarter, required plan members to step through a biosimilar before covering the innovator product, the report says. And it doesn't appear that many more will be adopting that policy soon. Of those who did not require step therapy favoring biosimilars, only 31% plan to implement the strategy in the future.

Magellan's analysis is based on a survey of medical, pharmacy and network directors at 46 commercial insurance plans covering more than 128 million medical pharmacy lives. It also relies on medical benefit claims from commercial and Medicare Advantage plans.

Payers indicated that a significant cost differential between the biosimilar and reference drugs – a 27% discount – would be needed for them to implement step therapy. FDA designation of interchangeability or provider network acceptance are other factors that could encourage implementation.

At the same time, the amount of negotiated rebates obtained by payers is trending upward, the report notes. The average rebate required by payers to prefer a drug reimbursed under the medical benefit increased from 18% of the price in 2018 to 21% in 2017.

The findings are in line with market reports indicating the allure of higher rebates for innovator drugs has hampered uptake of biosimilars to date.

Pfizer Inc.'s lawsuit against **Janssen Pharmaceuticals Inc.** over rebating deals for *Remicade* (infliximab) that blocked coverage for Pfizer's biosimilar, *Inflectra*, highlights the challenge for biosimilars. *(Also see "Pfizer v. J&J Sets Stage For Biosimilar Showdown Over Exclusive Contracts" - Pink Sheet, 20 Sep, 2017.)*

Half of payers "always" or "usually" required a rebate to implement a product preferencing strategy last year, the report said. About one-third "seldom" or "never" did.

Rebates are more commonly used for pharmacy benefit drugs but the data indicate the practice is also gaining more traction for medical benefit drugs, particularly in competitive categories such as autoimmune disease and erythropoiesis stimulating agents.

Prior authorization and step therapy are the most common utilization management tools for medical benefit drugs, with 75% of commercial plans and 64% of Medicare plans using them in 2017. However, nearly one-quarter (22%) of Medicare plans and 13% of commercial plans do not employ utilization management at all for medical benefit drugs.

Vial Rounding and Value Frameworks

Payers are working to address drug waste by policies targeting therapies packaged in vials, particular single-use units.

Magellan noted more than 40% of commercial and Medicare payers are promoting use of vial rounding by providers. The practice involves identifying doses that use less than half of the "next vial" and could be reduced by 5% or 10%

to eliminate use of the additional vial.

About one-quarter of plans with vial rounding policies make the practice mandatory for providers and the remainder make it voluntary. Policymakers have criticized manufacturers' use of "oversized" vials as a cause of significant waste and unnecessary cost for payers. *(Also see "Cancer Drug "Oversized" Single-Dose Vials Waste Money, Need Rethinking – Article" - Pink Sheet, 2 Mar, 2016.)*

Very few payers reported using value frameworks for oncology drugs in 2017. Frameworks developed by the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) have been available since 2015. Both are geared toward assisting prescribing decisions.

Just 2% of payers said they are currently using the ASCO tool and 11% said they are using the NCCN "evidence blocks." More payers indicated they may be using the ASCO and NCCN tools in the future (11% and 16%, respectively). And 14% of payers said they would use other value frameworks in the future. *(Also see "Valuing Drugs In The US: How We're Doing And What's Ahead" - Pink Sheet, 22 Jan, 2018.)*

Published March 19, 2018 in Pink Sheet

Biosimilar Switching Studies Show No Adverse Efficacy Or Safety Effects, Researchers Say

▶ By Sue Sutter

A new **Sandoz Inc.**-led literature review finding a lack of ad Biosimilar Switching Studies Show No Adverse Efficacy Or Safety Effects, Researchers Say

Adverse effects from switching between a reference biologic and a biosimilar could reduce the importance of an interchangeability designation from the US FDA.

The act of switching between innovator biologics and their biosimilars has not been associated with altered immunologic response, efficacy or safety concerns, according to a systematic review of 90 switching studies published online March 3 in the journal Drugs.

The paper's lead author is Hillel Cohen, executive director of scientific affairs at **Novartis AG**'s Sandoz division.

> **"The extensive data collected to date suggest that the act of switching from a reference medicine to a biosimilar is not inherently dangerous, and that patients, healthcare professionals, and the public should not assume that it is problematic."**
> **– Sandoz's Cohen, et al.**

"There is a large body of published evidence for biologic medicines evaluating the impact of switching from reference medicines to biosimilars that assesses immunogenicity, efficacy and safety," the authors say. "The cumulative results of these published data do not show significant differences" in anti-drug antibodies (ADAs) or neutralizing antibodies (NABs) after switching "compared to subjects that were not switched. There were also no reported increases in treatment-related safety events, including loss of efficacy, that were related to the act of switching from reference

medicines to corresponding biosimilars."

"The extensive data collected to date suggest that the act of switching from a reference medicine to a biosimilar is not inherently dangerous, and that patients, healthcare professionals, and the public should not assume that it is problematic," the authors conclude.

In the nascent US biosimilar market, where only nine 351(k) applications have been approved to date and three products have launched, the study could provide some comfort to patients and clinicians who have voiced safety and efficacy concerns about so-called "non-medical switching," in which patients are moved from reference products to biosimilars for nonclinical reasons, such as insurance coverage. *(Also see "Biosimilar Non-Medical Switching: Advocacy Groups, FDA Advisors Push For Action" - Pink Sheet, 14 Jul, 2016.)*

A biosimilar would need an interchangeability designation from FDA before it can be automatically substituted for a reference product at the pharmacy level. However, none of the biosimilars approved to date has been designated as interchangeable.

It's unclear when the US might see its first interchangeable biosimilar, particularly given what biosimilar developers say are hurdles erected by FDA in a January 2017 draft guidance that recommended sponsors use only US-licensed reference products in multiple-switch studies conducted to support an interchangeability designation. *(Also see "US Comparator Requirement For Interchangeable Biosimilars Would Hurt Industry" - Pink Sheet, 31 May, 2017.)*

The agency has subsequently suggested it may not stick to such a hardline view against the use of foreign comparator products for multiple-switch studies. *(Also see "Interchangeable Biosimilars: FDA Clarifies US Reference Not Mandatory For Studies" - Pink Sheet, 27 Oct, 2017.)*

Sandoz's Cohen has publicly spoken about the industry's concerns that the lack of an interchangeability designation would be used by reference product sponsors to limit uptake of biosimilars and raised doubts about their quality. *(Also see "Biosimilar Firms Fight Against 'Whisper Campaign' On Interchangeability" - Pink Sheet, 22 Oct, 2017.)*

However, if the American public can be sufficiently persuaded as to the efficacy and safety of switching between reference products and their biosimilars, interchangeability designations may become less important for market uptake.

90 Studies Analyzed

In their article, "Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes," Cohen, et al., note that "concerns have been raised that switching patients from reference medicines to biosimilars, or other structurally-related biologics, may lead to increased immunogenicity and consequential safety problems, or even a loss of efficacy. A review of switching studies reported in the literature is an important first step to confirm or deny any existing pattern that may exist related to biologic switching."

The authors conducted a search through June 30, 2017 of all published studies, including randomized trials and observational studies, involving switches between a reference product and a biosimilar. Studies involving switches from erythropoietin to darbepoetin or pegylated-erythropoietin, and between insulin products, were excluded as being outside the scope of the review.

"Altogether, there were 90 studies of both smaller and larger proteins that enrolled 14,225 unique individuals and that contained primary switching data," the authors state. "They included seven different molecular entities used to treat 14 diseases. Safety, efficacy, or immunogenicity endpoints were incorporated into all studies, but only a limited number of studies included all three categories." There were no published reports of switches between biosimilars.

Overall, 36 publications provided primary efficacy data on the larger biologics after switching from reference products to their corresponding biosimilars; 12 of these were single-arm studies, and the other 24 were cohort studies comparing switched versus non-switched patients.

"In the vast majority of these studies, overall efficacy was comparable in maintenance versus the switched groups, or was maintained before and after the switching event in the 'cohort studies,'" the authors state. While there were "sporadic observations of loss of responses" reported in a few studies, "no consistent pattern occurred."

The percentage of treatment-emergent adverse events and treatment-emergent serious adverse events in the

reference product and switched arms were comparable across disease indications for larger biologics. In addition, ADA and NAB levels were comparable at baseline and end of study across all disease indications and treatment groups for those studies that reported immunogenicity data.

The authors cite a report, based on a Turkish claims database, that raised safety concerns about switching from a reference infliximab to a biosimilar version, with a reported 82% drop-out rate in switched arm compared to a 24% drop-out rate in the control group that remained on reference product. "It is possible that these were chance results because no such large differences in drop-out rates were seen in switched versus control patients in the 46 other studies that evaluated switching between these same biologics," the authors write.

Scarcity Of Multiple Switch Studies

The authors identified only three published studies that involved multiple switches back and forth between a reference product and a biosimilar. All three involved Sandoz biosimilars: *Zarxio* (filgrastim-sndz), which references **Amgen Inc.**'s *Neupogen* (filgrastim); *Erelzi* (etanercept-szzs), which references Amgen's *Enbrel* (etanercept); and GP2017, which references **AbbVie Inc.**'s *Humira* (adalimumab). Zarxio and Erelzi are licensed in the US, while GP2017 is under FDA review with a November user fee goal date.

The GP2017 study data were published after the November 2018 data cut-off for the systematic review. "However, given the paucity of published multiple switching studies and the importance of such studies to questions related to switching and immunogenicity, we elected to include the third multiple switching study in the description of results," the authors say.

In all three multiple-switch studies, there were no differences in efficacy, safety or immunogenicity between the switched and non-switched arms.

Cohen, et al., observe that patients already have been exposed to "de facto multiple switches for many originator biologics when product quality attributes changed after one or more manufacturing process modifications were introduced."

While additional, multiple-switch studies with biosimilars will directly address the theoretical safety concerns about switching back and forth multiple times, "at present there is no evidence available that such switches will impact either safety or efficacy," the authors conclude.

Published March 8, 2018 in Pink Sheet

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Novartis Gives Up On Rituxan Biosimilar For US Market

By Kevin Grogan and Alex Shimmings

Novartis AG has thrown in the towel on getting US approval for a biosimilar of **Roche**'s lymphoma, leukemia and rheumatoid arthritis drug *Rituxan* (rituximab), after the FDA asked for more information on the company's version of the drug, which is approved already in Europe and elsewhere.

In May, Novartis generics unit Sandoz received a complete response letter from the FDA for its Rituxan biosimilar and no reasons for the rejection were disclosed, nor were any timelines mentioned for a potential refiling. At the time, the company limited itself to saying that it "stands behind the robust body of evidence included in the regulatory submission."

Now, following an evaluation of the FDA's request for additional information "to complement the filing," Sandoz said it will not pursue a re-application for a Rituxan biosimilar stateside. Instead, the firm will focus on "progressing its biosimilar pipeline in areas of greatest unmet access needs."

Sandoz global head of biopharmaceuticals Stefan Hendriks said in a statement that "we appreciate the important conversations with the FDA, which have provided specific requirements for our potential US biosimilar rituximab, but believe the patient and marketplace needs in the US will be satisfied before we can generate the data required."

He went on to say that "we are disappointed to have to make this decision and stand behind the safety, efficacy and quality of our medicine, which met the stringent criteria for approval in the European Union, Switzerland, Japan, New Zealand and Australia."

Speaking to *Scrip* at the company's R&D day in London, Novartis CEO Vas Narasimhan said that when it comes to biosimilars, "the US is very complex – almost product by product, I was going to say 'adventure' but I'm not sure that's the right word!" He added that with *Zarxio*, its version of **Amgen Inc.**'s *Neupogen* (filgrastim) and other biosimilars, the company has enjoyed successful launches but now with rituximab "we have hit some bumps with the FDA obviously...that's been an interesting experience because we are approved in Europe, Japan, Australia, Canada and a bunch of other countries."

Narasimhan noted that the FDA had actually asked Novartis to repeat the pivotal study for its version of Rituxan and "in my judgement, it is not a good investment of our investors' dollars to repeat a study that will be many years...we walk away at this point rather than continuing to throw money into it."

Tale Of Two Continents

Biosimilars "has been a tale of two continents in my mind," he told *Scrip*, as Europe "has been extraordinarily successful. It's where we have had great launches, we have a broad portfolio and most of the uptake is faster than we would have expected." He pointed out that Novartis has been in biosimilars in Europe since 2010 and the experience gained has made it easier to get approvals and rapidly get to the market.

Narasimhan stressed that the experience with rituximab in the US "doesn't signal a strategic shift in our focus" and while there is still a lot to work to do there, "I think there is a lot of goodwill among all policy makers who agree biosimilars could reduce a lot of waste..but it's looking to be a few more years before it fully materializes."

The decision to give up on biosimilar Rituxan in the US will be welcomed by Roche and co-marketing partner **Biogen Inc.** Sales of the branded blockbuster, which is sold as *MabThera* outside the US and Japan, have been battered by biosimilars in Europe, down 48% to CHF731m for the first

nine months of 2018, but are still rising in the US, up 4% from January to September to CHF3.19bn.

However, there is likely to be some competition soon across the Atlantic in the form of **Celltrion Inc.** and **Teva Pharmaceutical Industries Ltd.**'s *Truxima*, also known as CT-P10. Last month, the FDA's Oncologic Drugs Advisory Committee voted 16-0 that the totality of evidence supports licensure of CT-P10 as a biosimilar to Rituxan for three non-Hodgkin's lymphoma (NHL) indications, with panel members concluding that small analytical differences between the products were not clinically meaningful.

The Celltrion case is especially interesting, given that the South Korean firm is only seeking approval in the US for three of Rituxan's eight labeled indications due to "the current intellectual property and exclusivity landscape."

The Celltrion case is especially interesting, given that the South Korean firm is only seeking approval in the US for three of Rituxan's eight labeled indications due to "the current intellectual property and exclusivity landscape." Missing from the biosimilar's proposed label are a fourth NHL indication, as well as indications for chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis and pemphigus vulgaris. *(Also see "Celltrion's Biosimilar Rituximab Brings Indication Carve Outs To US FDA Panel Review" - Pink Sheet, 12 Sep, 2018.)*

In Europe, however, Truxima was approved in February 2017 for all MabThera indications. Quoting IQVIA data last month, Celltrion said Truxima's market share in the five major European countries (the UK, Germany, France, Italy and Spain) averaged 34% - 64% for the UK alone.

Commenting on Novartis' decision, Bernstein analyst Ronny Gal issued a note saying "this should be viewed as a rebuke to the FDA requirement bar in terms of preclinical characterization. We are hearing the echoes of internal debate within the agency as preclinical guidance is being re-examined." He added that "this leaves Teva/Celltrion with a material lead," noting that **Amgen Inc.** and **Pfizer Inc.** are yet to submit their Rituxan biosimilar "and it may end up being a very limited market."

As for Sandoz, which has seven approved biosimilars worldwide, three of which have the green light in the US, Hendriks stated that "we believe we should now focus on opportunities in the US and around the world where we can best meet rapidly evolving patient and healthcare system needs."

Sandoz, like a host of other companies, has decided that a version of the world's best-selling drug – **AbbVie Inc.**'s *Humira* (adalimumab) – meets those criteria. At the end of last month, the FDA approved *Hyrimoz*, Sandoz's biosimilar of the mega-blockbuster and despite a patent settlement recently agreed with AbbVie, it will not be launched in the US until September 2023. However, it was launched in Europe in October immediately after the Humira patent expiry. *(Also see "Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?" - Scrip, 12 Oct, 2018.) (Also see "AbbVie Defends Humira With Aggressive Discount In First EU Tender " - Scrip, 1 Nov, 2018.)*

Published November 5, 2018 in Scrip

AbbVie Defends Humira With Aggressive Discount In First EU Tender

By Jo Shorthouse

AbbVie Inc. is ready for a fight to keep rivals away from having their piece of the biosimilar adalimumab market if reports of a price cut of 80% are anything to go by.

The discount in an, as yet, unknown market, is not expected to hurt AbbVie much financially. Even with the 80% discount, the gross margin on manufacturing Humira would be above 75%.

The news was broken in an analyst note by Bernstein's Ronny Gal. He said: "We expect the biosimilar players who are not up to scale yet and need to recoup their initial investment would not bid that low."

At the time of writing, details of the tender process are scarce. When approached for comment, AbbVie has declined to confirm or discuss the matter.

But this is the first solid indication of how AbbVie may defend its share of the Humira market in Europe, worth $4.4bn per year. Rivals bidding on the European adalimumab market are **Sandoz International GMBH** (*Hyrimoz*), **Samsung Bioepis Co. Ltd.** and its European partner **Biogen Inc.** (*Imraldi*), **Amgen Inc.** (*Amgevita*), **Mylan NV** and **Fujifilm Kyowa Kirin Biologics Co. Ltd.** (*Hulio*) and **Boehringer Ingelheim GMBH**, which has told *Scrip* it will not be launching *Cyltezo* in Europe to enable it to concentrate on the US market.

Pricing information, from the association of statutory health insurance doctors for the North Rhine region in Germany, the KVNO, shows six syringes of Humira at a list price cost €5,300. Amgen's Amgevita is listed at €4,533, while Hyrimoz and Imraldi are priced at €4,206 and €3,354 respectively, offering a discount of 15%, 21% and 37% on Humira.

"Not all buyers will achieve the kind of discount achievable by a national tender. However, the band of pricing will move lower. We would expect average discount would have to be above 50%," elaborated Gal.

"The adalimumab situation is a reflection of the challenge posed by biological medicines, and how patent expiration does not automatically translate in the marketing of cheaper biosimilars," commented Jaume Vidal, European policy advisor to the NGO Health Action International. "What we have here is a pharmaceutical company protecting an already blockbuster product by gaming the IP protection system."

HAI's Vidal told *Scrip:* "AbbVie is taking advantage of a regulatory framework that makes it very difficult for other pharmaceutical companies to develop and market their biosimilar products. At the core of it is an all-too-familiar problem: the abuse of the IP protection system and lack of transparency on the purported development costs that are used to justify exorbitant prices."

US Implications

Gal says he suspects that the AbbVie strategy is "in-effect targeting the US market."

AbbVie "will hold the EU volume despite very large discounts. The objective is to defend the US market by denying the biosimilars in-market experience and then arguing the European 'chose' Humira over the biosimilars for quality reasons beyond price," he said.

In the US, Humira made $12.4bn in sales in 2017, making it Humira's biggest market by far. AbbVie has recently settled legislation with Sandoz over the timing of the latter's Hyrimoz launch in the US, with the Novartis company agreeing to delay launch until September 2023, as well as paying royalties to AbbVie of any Hyrimoz sales in Europe. Three other companies have already signed similar agreements with AbbVie. *(Also see "Sandoz And AbbVie Biosimilar Humira Settlement: What Does It Mean?" - Scrip, 12 Oct, 2018.)*

In a previous analyst note on the subject of the European defense of Humira, Gal had noted that "AbbVie appears much more prepared than prior defenders and their key objective is to prevent the creation of large patient databases ahead of US biosimilar introduction. AbbVie is much more likely to give up price than volume." *(Also see "Biosimilar Infliximab Success Paves The Way For Adalimumab In Europe" - Scrip, 16 Aug, 2018.)*

Tendering Strategy

One market where AbbVie may find it difficult to cut out its biosimilar competitors is the UK. NHS England has changed its procurement mechanism for biosimilar adalimumab to encourage competition and sustainability. The tender process will award contracts in lots; this is based on the assumption that there will be four biosimilar products and four bids by Dec. 1. If only three offers are received, then three lots will be awarded as three distinct lots, and so on. The size and shape of each lot will depend on the offers received and the relative prices, the NHS England Specialist Pharmacy Service (SPS) said in a strategy document.

"The strategy means that no supplier of adalimumab will be awarded the whole market but will have a strong incentive to offer their best price at the point of tender. If all tendered prices are similar, the shares awarded will on an equitable basis. If there are price differentials, awarded shares will be higher for the most competitively priced suppliers, but all suppliers will get access to at least some of the market upon receipt of a compliant bid to avoid dominance."

Humira will be a separate line in the tender. Humira is approved for use in Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, and ankylosing spondylitis.

AbbVie announces its Q3 results on Nov. 2.

Additional reporting by Ian Schofield.

Published November 1, 2018 in Scrip

Payers Like Biosimilars, But Rebates Remain The Bottom Line (For Now)

▶ By Jessica Merrill

The launch of the first biosimilar monoclonal antibody in the US, **Pfizer Inc./Celltrion Inc.**'s *Inflectra* (infliximab-dyyb), is raising questions about how biosimilar manufacturers can gain traction in the market when the innovator is willing to compete on price and play hard ball in contract negotiations with insurers – and payers are willing to shake on the deal.

Nearly one year after the launch of Inflectra, **Johnson & Johnson**'s *Remicade* (infliximab) has held onto to the lion's share of the market despite the entry of what is positioned as a cheaper competitor. J&J has successfully defended Remicade by offering steep rebates and discounts, tying rebates in some cases to other important portfolio products and, according to a lawsuit filed by Pfizer in September, coercing payers into agreeing not to reimburse Inflectra in exchange.

"Payers are all looking at the dollars and cents, and the dollars and cents for biosimilars don't make sense right now," said Roger Longman, the CEO of Real Endpoints, a reimbursement intelligence firm. "There's got to be something else that encourages the use of biosimilars."

Aggressive contracting along the lines of the tactics being used by J&J happen in the brand market, with drug manufacturers looking to block their competitors' access to the market, but what's unique in this instance is that Inflectra and other biosimilars to follow are intended to act more like a generic competitor, with the aim of lowering overall healthcare spend.

Exclusive contracts involving brand products usually include a provision that voids the agreement if and when a generic comes to market, but that language doesn't exist for biosimilars, which are harder to replicate and manufacture than small molecule generic drugs and are expected to have less price erosion.

Pfizer has turned to the courts for relief, arguing that J&J's contracting tactics are anti-competitive and could set a worrisome precedent for how innovators respond to the launch of a biosimilar rival. *(Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" - Scrip, 20 Sep, 2017.)* But Pfizer isn't the only stakeholder concerned about the long-term impact on what is an emerging new business area. At a presentation in September, FDA Commissioner Scott Gottlieb acknowledged that the adoption of early biosimilars had been slow and wondered if biosimilar manufacturers might dismiss the viability of the

products if adoption rates don't improve. *(Also see "Payers Could Guarantee Biosimilar Market Share, FDA's Gottlieb Suggests" - Pink Sheet, 22 Sep, 2017.)*

Kaiser Permanente's national pharmaceutical contracting leader Ambrose Carrejo said the market access challenges would be concerning if they persisted. "If [the US market is] not able to produce movement ... to the biosimilars and generate a return for those manufacturers that have gone down this biosimilar pathway and invested in those molecules I think they will just realize over time that they have to close up shop and move on," he said in an interview. "America would have missed a very significant opportunity." Kaiser is one of the few payers that has put Inflectra on its formulary in place of Remicade.

Mylan NV president Rajiv Malik said the company was optimistic about the biosimilar opportunity but closely watching the market. "We are placing bets that rationality will prevail," he said. "Otherwise, people will run out of the stamina to invest the significant dollars required to bring these products to the market, if they don't see the return, and then you will see no one investing in this space and the costs to the healthcare system will continue to go through the roof."

Novartis AG's **Sandoz International GMBH** is not particularly worried by the early challenges, and the generic drug group has experience selling several biosimilars in Europe as well as *Zarxio* in the US, the first biosimilar version of **Amgen Inc.**'s *Neupogen* (filgrastim). "We believe our healthcare system will ultimately embrace biosimilars," head of biopharmaceuticals-North America Sheila Frame said. "We've already seen formularies prioritizing biosimilars. Biosimilars acceptance will come with additional physician and patient experience and payer savings."

High Prescription Volume Equals Leverage

J&J has an upper hand in contract negotiations with payers when it comes to Remicade because the infused anti-TNF is so entrenched in the market and so many patients are already taking it for a range of autoimmune conditions. The high prescription volume gives J&J leverage to hand-tie payers into accepting the contract terms because Inflectra, being new, is not as frequently used. Lower prescription volume means the potential cost-savings in the form of rebates will be lower no matter what discount Pfizer offers. Patients, physicians and payers are still benefiting from a steeper discount and they get the product they know and want, so J&J says its strategy is a win-win, and payers, for now, are mostly accepting J&J's offer. The concern is if the market for biosimilars fizzles over the long-term.

Pfizer said it had expected J&J to aggressively defend its blockbuster franchise, but that it had been taken aback by J&J's effort to block Inflectra from the market entirely.

"We were surprised that J&J would seek to abuse its dominant market position to thwart competition," a Pfizer insider said.

J&J, for its part, eschews the allegations, arguing that Pfizer just hasn't demonstrated a strong enough value proposition for Inflectra. In an interview, Janssen Biotech immunology president Scott White insisted the company hadn't significantly changed its contracting strategy since the launch of Inflectra, other than to offer steeper discounts.

"When we provide a contract with a payer, we provide a bid, and the bid looks at different contracting or pricing terms for a preferred position, a parity position, a step-through position in terms of a variety of discounts we provide," White said.

Competing against an entrenched and trusted product like Remicade isn't easy for any new entrant, he said, noting that he expects it will take time before biosimilars gain more traction in the market. "I wonder if the effort was premature," he said of Pfizer's lawsuit.

Payers Play The Rebate Card

For now, some payers are siding with J&J, despite their enthusiasm for biosimilars to help lower their specialty health care spend.

"If you talk to payers and various folks within payer organizations about can we be doing something to promote the use of biosimlars, most payers will say that makes sense but then do whatever is the most tactical thing at the moment," said Edmund Pezalla, formerly national medical director for pharmaceutical policy and strategy at **Aetna Inc.**

"It's hard to have a long-term strategy, and part of the problem is that the price of the biosimilars isn't low enough yet," he said.

Express Scripts Holding Co.'s chief medical officer Steve Miller agreed. "One problem is that the discounts have been relatively shallow," he said. "We've told all the main actors that shallow discounts aren't going to be adequate. The discounts are going to have to become greater."

The pharmacy benefit manager isn't in the middle of the Remicade debate specifically because the drug is administered in physician's offices and mostly reimbursed through insurers' medical benefit rather than the pharmacy benefit. Bigger discounts are expected to become more commonplace when more than one biosimilar in a category reaches the market. Ironically, that is the case with infliximab, as **Merck & Co. Inc.**'s *Renflexis* (infliximab-abda) launched in July. *(Also see "Merck's Second-To-Market Renflexis Biosimilar Priced Below The First" - Scrip, 24 Jul, 2017.)*

Merck hasn't commented much on the initial uptake but said in an email, "We expected that the first months of our launch would be used to educate customers about the product and for negotiations with them."

Pfizer insists the size of the discount is not the reason for excluding Inflectra from the market altogether. "We know clearly that our ASP [average sales price] is lower than J&J's Remicade, which continued to rise since Inflectra's launch without a substantial loss in volume or share of sales – counter to what should occur in a truly competitive market," Pfizer said. J&J's White confirmed that the ASP for Remicade under Medicare had increased this year, but also pointed out that reporting of ASP has a time delay, so it is not necessarily reflective of what is currently going on in the market.

Kaiser's Carrejo said the decision to put Inflectra on Kaiser's formulary was financially motivated after the payer's physician review board agreed the safety and efficacy data supported adoption. "It became a financial decision much like therapeutic alternatives or generic alternatives," he said.

He acknowledged the decision to switch might be "untenable" for some payers. "Your business has to come in on budget. Taking a significant loss on a biosimilar that could be a $100m or $200m part of your business, taking a 10% cut, could mean not making budget."

It's impossible to know exactly what discounts Pfizer and J&J are offering on their products since that information is closely guarded. Pfizer set the wholesale acquisition of Inflectra at a 15% discount to Remicade at launch in November 2016, but offered rebates and discounts to payers on top of that discount. In its lawsuit, Pfizer said it offered to guarantee payers that the price would be less than the price of Remicade. J&J has said the actual cost of Remicade after rebates and discounts is about 30% below the WAC, though that was prior to the entry of biosimilar competition. Merck's Renflexis also launched at a 35% discount to the Remicade WAC. *(Also see "Merck's Second-To-Market Renflexis Biosimilar Priced Below The First" - Scrip, 24 Jul, 2017.)*

The reality is that J&J can offer substantially greater value to payers through steep discounts on a widely used product like Remicade, at least as long as automatic switching is not an option.

Some payers say they want to see discounts of up to 40% versus the original brand, but Real Endpoints' Longman pointed out that a race to the bottom on price could present a business conundrum for biosimilar manufacturers because the originator company can compete effectively with a goal of retaining some value from its franchise. "Remicade has very low cost of goods right now. Their unit cost is relatively low. That gives [J&J] significant margin to increase their rebates or increase the discounts," Longman said. "They might not be growing the brand, but they are keeping the competitors from coming in."

Sandoz's Frame also urged against a race to the bottom on price. "If prices drop too quickly, there is no incentive for biosimilar competitors to join the marketplace, leaving room for reference product manufacturers to increase prices indiscriminately," she said. "Additional discounts will happen naturally as new biosimilar competition enters the market."

It's still early days and some payers are likely taking time to survey the landscape, measuring their patient and provider community's willingness to accept biosimilars and watching to see how the discounts will shake out over the long term. But the pharma industry is investing in biosimilars – sometimes hundreds of millions of dollars – for the promise of seeing a return on that investment. That promise will have to be fulfilled if the biosimilar market is going to flourish.

Published November 29, 2017 in Scrip

What's Behind The Success Of Korean Biosimilars?

By Jung Won Shin

South Korean biosimilar companies are entering their prime. One after another, **Celltrion Inc.** and **Samsung Bioepis Co. Ltd.** are making headlines and receiving approvals for their biosimilar products in major markets; the products they have launched are leading their markets, or have potential to do so.

This scene was not expected by many industry players several years ago because, at that time, South Korea had a limited focus on innovation and R&D investment, and the country's pharma and biotech companies had not yielded notable outcomes in global markets.

"Celltrion focused on the high growth potential of the antibody biosimilars market, sought development of biosimilars earlier than others, and is now leading the market," said Dong Won Sung, senior analyst at the Export-Import Bank of Korea. "Samsung has entered the market late but it is quickly catching up with Celltrion based on the ample capital and strong drive frequently seen in large conglomerates."

Various factors, including savvy clinical trial and collaboration strategies, have played a part in the recent stellar performance of the two South Korean firms.

"One of the key factors contributing to the success of Samsung Bioepis and Celltrion in the MAb biosimilar space is the fact that they are conducting global clinical trials in key regions of interest such as the US and Europe, and the firms are tailoring their clinical development to the expectations of the regulatory authorities in those respective regions," Datamonitor Healthcare's analyst Hristina Ivanova told *Scrip*.

Celltrion's Early Days

Celltrion started out as a contract manufacturing organization (CMO) in South Korea, but it is now a pioneer in antibody biosimilars. When multinational pharma firms monopolized global markets with antibody drugs, many of them believed development of biosimilars would be difficult. But Celltrion had different thoughts and became the first mover in this field. Celltrion focused on the potential of the biotech industry and the value of biosimilar business, as patents of several blockbuster biologics were set to expire soon.

When Celltrion began global clinical trials of its first biosimilar product *Remsima/Inflectra*, a version of **Janssen Biotech Inc.**'s *Remicade* (infliximab), the concept of biosimilars was still unfamiliar and South Korea was little known in the global biotech industry. The company had to pioneer the process and pave the way for regulatory approval in Europe. "At that time, there were no global guidelines on biosimilars. We had to pioneer the process by persuading the EMA [European Medicines Agency], but our folks continuously challenged and succeeded. This has become the driving force of our first mover and first launch status," said Celltrion CEO Woo Sung Kee in an interview with *Scrip*.

Celltrion's Remsima now controls more than 40% of the European market. The biosimilar product launched in the US late last year and the company expects to repeat its success in the world's biggest market as it has accumulated prescription data and various clinical data needed to earn doctors' trust and boost recognition of its brand name.

Celltrion's biosimilar rituximab, known as *Truxima*, has also launched in various European countries. Truxima and *Herzuma*, its biosimilar version of *Herceptin* (trastuzumab), are undergoing regulatory approval review in the US.

Meanwhile, Celltrion received a US FDA Form 483 in early 2017 after the FDA's regular GMP inspection of the company's biomanufacturing site in South Korea. But by September the company had already completed improvements for the list of demands the US regulator made. It added that none of the issues directly impacted the company's drug quality; as a result, there were no disruptions in its drug production or global supply and there will be no changes in its products' approval schedules.

Samsung Catches Up

Samsung Bioepis entered the biosimilar business several years later than Celltrion but it is quickly catching up. Backed by Samsung Group's ample capital and strong drive for the biotech business, Samsung Bioepis is swiftly progressing global clinical trials of its broad biosimilar candidates.

"When we started out five years ago, biosimilars were still new to many in the industry. We had the confidence that our

development platform and scientists could capitalize on the level playing field, thereby allowing us to compete from the start and positively impact patients' lives sooner rather than later," Samsung Bioepis told *Scrip*. "Since then, we have relied on our agile biologics development platform to transform and enhance the way therapies are brought to patients from conception and development through regulatory approval by replacing legacy processes with new and innovative ones. In so doing, we have been able to develop arguably the industry's most expansive and rapidly advancing biosimilar pipeline."

Samsung has launched its infliximab biosimilar *Renflexis* in the US, only a few months after Celltrion's Inflectra. With the latest EU approval for its adalimumab biosimilar *Imraldi*, Samsung has become the first company to receive EU approvals of three biosimilar anti-tumor necrosis factor products. Samsung is selling *Benepali*, its biosimilar version of *Enbrel* (etanercept), and *Flixabi*, its biosimilar version of Remicade, in Europe, through its partner **Biogen Inc.** Samsung's biosimilar to Herceptin, *Ontruzant*, is also under regulatory review by the EMA. Ontruzant (formerly known as SB3) received a positive recommendation for approval in Europe from the EMA's scientific committee the CHMP in October 2017.

As a late comer, Samsung Bioepis, which is a joint venture between Samsung BioLogics and Biogen Inc., has largely benefited from the pioneering work of Celltrion. While Celltrion had to spend much time in the beginning creating approval guidelines in global markets, Samsung could receive approval in a shorter period. Renflexis could get FDA approval without review by an FDA advisory committee thanks to Inflectra, which had to earn the green light of the advisory committee as the first mover, NH Investment & Securities said.

Unlike the EU market where Remsima had a significant head start and dominated the biosimilar infliximab market, some South Korean analysts predict it could be a closer match between Inflectra and Renflexis in the US where the launch time gap between the two is only several months. In addition, Renflexis's list price was 35% below its reference drug price, while Inflectra's list price was at a 15% discount to the innovator.

Building On Partnerships

Another factor that contributed to the South Korean companies' success is their robust collaborations with global companies. Celltrion and Samsung Bioepis both have created a network of collaborations with a wide range of companies for the development and marketing of their biosimilar MAbs, said Datamonitor's Ivanova.

For example, Celltrion has a partnership with **Hospira Inc.**, now a subsidiary of **Pfizer Inc.**, for the marketing of Inflectra in the US, and has partnered with **Mundipharma International Corp. Ltd.** for the commercialization of Remsima and Truxima in Europe, benefitting from the local presence their partners have in US and Europe, Ivanova noted.

In addition, South Korean companies' ability to construct high quality manufacturing facilities required for manufacturing biosimilars and governmental policy support are likely to have made it easier for them to get a head start in the biosimilar business.

Helped by the South Korean government's policy support, Celltrion and Samsung Group were able to successfully build large-scale bioreactors in the beginning. From the early 2000s, the government has viewed the biotech industry, including biosimilars, as the country's next generation growth engine, while other countries had slightly different visions. For example, Japan focused much more on novel drug development, overlooking the biosimilars sector, while Singapore opted to attract the production facilities of multinational pharmas such as **Roche** and **Lonza Group Ltd.**, according to NH Investment & Securities.

Increasing Global Competition

As South Korea aims to develop global blockbuster drugs in the coming years, its success in biosimilars could serve as a basis for accumulating and building technology and knowhow to reach its goal.

Although the global biosimilars market is poised to grow sharply for now, EXIM Bank of Korea's Sung stressed the importance of novel drug development amid the toughening of competition in the biosimilar space.

Competition in the global biosimilar market is set to become fiercer as multinational pharmas such as **Pfizer Inc.** and **Merck & Co. Inc.** as well as leading generic companies **Teva Pharmaceutical Industries Ltd.** and **Sandoz Inc.** are actively pursuing the development of biosimilar businesses including through M&A. As a result, the global biosimilar market could turn into a "red ocean" with limitations in growth, Sung said.

According to the Informa Pharma's Trialtrove database, in 2017 there were more than 1,060 clinical trials of biosimilars ongoing worldwide and 158 trials in the US alone. By therapeutic area, there were 299 clinical trials of biosimilars in oncology and 291 trials of biosimilars in autoimmune and inflammation.

As part of its overall plans, Celltrion is already progressing a novel antibody drug pipeline including a new antibody influenza drug. It is targeting becoming a global top 10 biopharma after 2020 once it launches three biosimilar products in global markets, and after that plans to aggressively invest in the development of novel drugs.

Samsung is also stepping up efforts to diversify into new drug development. In August, Samsung Bioepis joined with **Takeda Pharmaceutical Co. Ltd.** to develop novel biologics, moving beyond its core focus on biosimilars. The partners will initially focus on acute pancreatitis and jointly develop Takeda's preclinical candidate in the segment.

Published November 15, 2017 in Scrip

FDA's Gottlieb: 'Pricing And Reimbursement Mischief' Holding Back Biosimilar Market

▶ By Jessica Merrill

FDA Commissioner Scott Gottlieb took the stage at America's Health Insurance Plans (AHIP) National Health Policy Conference March 7 with a searing message for insurers: take a more proactive role in fostering the early biosimilar market or else a "rigged" system could scare biosimilar competition out of the market altogether.

The speech was notable for the aggressive tone in which the FDA leader targeted insurers, pharmacy benefit managers and drug manufacturers that participate in what he called "pricing and rebating mischief," which he said could have long-term consequences for the success of the biosimilar market.

> **"You can't have your cake – or in this case, your rebates – and a vibrant market for biosimilar competition too." – FDA Commissioner Scott Gottlieb**

The message seemed targeted specifically at aggressive contracting schemes like the one **Johnson & Johnson** has put in place to defend its blockbuster *Remicade* (infliximab) against biosimilar competition. The tactics have largely worked, with Remicade retaining much of its market share in exchange for some pricing pressure, despite the entry of two biosimilars, **Pfizer Inc./Celltrion Inc.**'s *Inflectra* (infliximab-dyyb) in late 2016 and **Merck & Co. Inc../Samsung Bioepis Co. Ltd.**'s *Renflexis* (infliximab-abda) in 2017.

Pfizer has filed a lawsuit against J&J that could set an important precedent for the US biosimilar market, alleging that J&J effectively blocked Inflectra from the market by threatening to withhold all rebates for Remicade if payers reimbursed any Inflectra. *(Also see "Pfizer Sets The Stage For A Biosimilar Showdown Over Exclusive Contracts" - Scrip, 20 Sep, 2017.)* In some instances, J&J has also tied rebates for Remicade to access to other products, a tactic known as bundling.

Payers have argued that their hands are tied because they can't risk losing the millions in rebates they would receive for a high-volume product like Remicade versus what little they would receive for a biosimilar – even if priced lower – that would be prescribed to a significantly smaller number of new patients. *(Also see "Payers Like Biosimilars, But Rebates Remain The Bottom Line (For Now)" - Scrip, 29 Nov, 2017.)* The question is whether payers are putting the long-term health savings that biosimilars could eventually deliver at risk for a short-term gain.

The AHIP meeting is not the first time Gottlieb has spoken out about concerns over the way the US biosimilar market is unfolding. *(Also see "Payers Could Guarantee Biosimilar Market Share, FDA's Gottlieb Suggests" - Pink Sheet, 22 Sep, 2017.)* Lowering drug costs has been one of the commissioner's top priorities, with an emphasis on generics, including complex generics, as a means to that end.

Pay-For-Delay Dressed Nicely

But the speech does represent the most pointed comments the commissioner has made about rebating and contracting practices around biosimilars, which he said are reminiscent of the pay-for-delay tactics used by generic drug manufacturers a decade ago to block generics from entering the market.

"The crux of these pay-for-delay schemes are also taking root in the biologics market, except this time, in these biosimilar pacts, the tactics are dressed in the guise of rebates and contracting provisions between manufacturers and PBMs that discourage biosimilar market entry," Gottlieb said.

PBMs, health plans and the brand drug manufacturer all have an incentive to play into the "rebate trap," he said. Brand biologic sponsors don't have to do more than hold rebates "hostage," he said, or simply lower the wholesale price to match the biosimilar entrant to make the economics of entering the market highly unattractive.

"Everybody wins," he said. "Everyone that is, but the patients, who in the long run don't benefit from the full value of increased competition Congress intended."

The biosimilar manufacturer is another loser under the current scenario, and that could mean drug makers lose interest in investing in the space since biosimilars cost significantly more to develop than generic drugs. Biosimilar manufacturers invest about $100m to $250m to develop the products.

"I fear that is already happening," Gottlieb said, putting some urgency into his commentary. While he said FDA is taking steps to encourage the development of biosimilars, including facilitating a rapid pathway to market and addressing any misconceptions about safety and efficacy, FDA alone can't fix the problems.

The agency has so far approved nine biosimilar products, although only three have reached the market, largely due to ongoing patent litigation between sponsors and brand drug manufacturers. In addition to Inflectra and Renflexis, the only other biosimilar to launch in the US is **Sandoz Inc.**'s *Zarxio* (filgrastim-sndz), a biosimilar version of **Amgen Inc.**'s *Neupogen*.

Sandoz appears to have had more commercial success with Zarxio than Pfizer or Merck have had with their Remicade biosimilars. Gottlieb highlighted the category in his remarks, noting the price has come down 34% since two competitors have launched, capturing nearly 50% of the market and saving payers $150m. In addition to Zarxio, **Teva Pharmaceutical Industries Ltd.** manufacturers another version of filgrastim, *Granix*, which was approved in 2012 through a traditional BLA pathway rather than the pathway for biosimilars.

You Can't Have Your Cake And Eat It Too

Gottlieb said it's time for payers to make a choice between short-term profits and a system that functions better for patients in the long term.

"Do they want to continue to benefit from monopoly rents today, or help generate a vibrant biosimilar market that can help reset biologic pricing – and drug pricing more generally – through competition," he said. "These are binary choices. You can't have your cake – or in this case, your rebates – and a vibrant market for biosimilar competition too."

Gottlieb also recommended a few steps payers could take to incentivize the market, including the adoption of a formulary design that would make biosimilars the default option for newly diagnosed patients. In reality, such a move under the current environment for biosimilars, where interchangeability has not been defined, would probably be viewed as controversial by patients

and physicians, who are not yet entirely comfortable with biosimilars.

Or, he recommended payers share the savings from biosimilars with patients by waiving co-insurance.

"They can reduce administrative barriers when patients and providers use biosimilars, like lifting prior authorization requirements imposed on physicians," he suggested.

Drug makers and payers are likely to take Gottlieb's comments seriously, given the pressure the industry is facing over the high cost of drugs and the way pharmacy benefit managers are taking more heat over the share of costs they take as profit. Industry and those in the supply chain have been pointing a lot of fingers when it comes to talking about who is to blame for the high cost of drugs.

But Gottlieb all but told everyone to grow up. "We have a lot of finger pointing that ignores shared complicity for pricing practices that are eroding trust in both payers and innovators," he said. "I hope that you'll act before that trust is eroded completely."

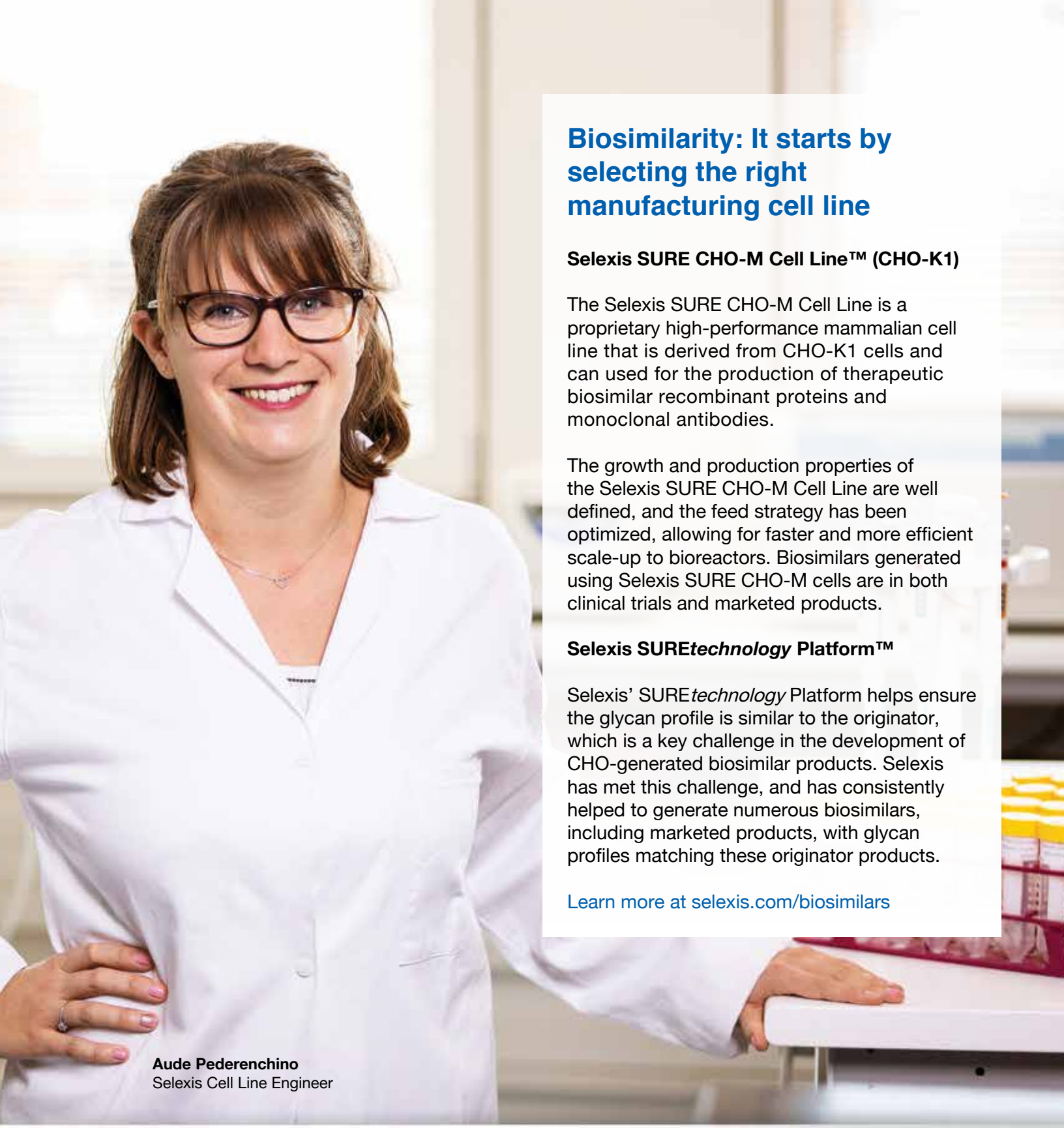
Whether or not industry stakeholders will heed the warning is the question. J&J responded to a request for comment on the speech by claiming it stands by Remicade contracting practices. "In contracting for Remicade, payers and providers have demanded and we have provided aggressive discounts," J&J said. "Competition is doing what competition is meant to do: driving deeper discounts that will lead to overall lower costs for infliximab, including Remicade." The company also pointed out that biosimilars are not identical to Remicade and that FDA has not provided guidance on the risk of switching between two similar products.

Pfizer reiterated its stance. "The promise of biosimilars to help reduce healthcare costs and provide patients access to important medicines is being stymied by anti-competitive barriers such as those established by J&J within insurance companies that have prevented inclusion of biosimilars on formulary and in medical benefit policies."

The Pharmaceutical Care Management Association, which represents PBMs, issued a statement noting, "It's unfair to blame payers - who pay two-thirds the cost of drug benefits - for seeking the lowest cost in a marketplace where they have no control over the prices drug makers set, how quickly FDA approves biosimilars, or when FDA will finalize workable interchangeability guidelines to increase uptake of biosimilars."

Changing attitudes may require policy more than speeches.

Published November 15, 2017 in Scrip



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