BioCentury
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PAVING THE WAY

BY STEVE USDIN, WASHINGTON EDITOR

Amgen Inc. and the Sandoz unit of Novartis AG are charting a course that could create competitive U.S. markets for two of the biggest prizes in the biosimilars universe, AbbVie Inc.'s Humira adalimumab and Amgen's Enbrel etanercept, which together had U.S. sales of $13.4 billion in 2015.

Unanimous advisory committee endorsements for ABP 501, Amgen's version of adalimumab, and GP2015, Sandoz's etanercept, suggest the two companies have overcome the formidable scientific and regulatory hurdles to gaining the first FDA approvals for self-injectable biosimilars.

The two companies adopted regulatory strategies that went beyond FDA's minimum requirements.

To increase the chances of FDA approval and bolster the confidence of physicians and patients, Amgen gold-plated its development program by conducting a clinical trial that the agency said was unnecessary.

Sandoz, with one eye on a future application for interchangeability and the other looking to persuade physicians to switch patients from branded Enbrel to biosimilar GP2015, incorporated a switching extension in its clinical trial that the agency had not asked for and excluded from its review.

Once they have FDA approval, Amgen and Sandoz will have to bash holes through dense patent thickets, and create and execute commercial and marketing strategies suited to the new competitive landscape.

AbbVie has over 70 Humira patents that it claims will keep biosimilars off the U.S. market until 2022.

Amgen has stated that it could launch its biosimilar Humira "as soon as 2017," but the best-case scenario for launching with minimal IP risk is late 2018 or early 2019.

Sandoz hasn't provided guidance on the launch date for its etanercept, but it must win pending litigation or wait for the expiration of Amgen's Enbrel patents in 2029.

The commercial environment will be complex because AbbVie and Amgen have additional defenses against erosion of the Humira and Enbrel markets, including exploiting physician and patient skepticism about biosimilars, using discounts and rebates to undercut biosimilar pricing and adding new indications.

Marketing and support will be critically important because the products are chronically self-administered, unlike biosimilars of oncology products.

After having overcome all of these challenges, there is also a real risk the biosimilar pioneers could find themselves in a crowded, chaotic marketplace.

Amgen's and Sandoz's success in punching holes in the Humira and Enbrel IP defenses will lower the barriers to market for competitors that are poised to swarm onto the market. At that point, a Darwinian selection based on marketing prowess and manufacturing capacity and costs could determine which biosimilar Humiras and Enbrels survive and thrive (see "Humira Biosimilars" & "Enbrel Biosimilars," page 3).

OVER-STUDYING

FDA staff usually adopt a neutral or even adversarial stance toward drug sponsors at advisory panels. But at the Arthritis Advisory Committee meetings about ABP 501 and GP2015, the agency spent much of its time explaining and defending its approach to regulating biosimilars and bolstering the case for approval of Amgen's and Sandoz's products.

In addition to preclinical analytical comparisons and a 203-person PK similarity study, Amgen conducted two randomized, double-blind active comparator-controlled trials of ABP 501: a 526-patient rheumatoid arthritis (RA) trial and a 350-patient plaque psoriasis trial.

Richard Markus, VP of global biosimilars development at Amgen, told the committee the company "probably could have done one trial" but performed two "for additional comfort." As the first of a planned suite of Amgen biosimilars to reach FDA, the company clearly wasn't willing to take any avoidable risks with adalimumab.

However, FDA took the unusual step of admonishing Amgen for producing more clinical data than was required, and urging future biosimilars applicants to avoid unnecessary trials.

Nikolay Nikolov, clinical team leader in FDA's Division of Pulmonary, Allergy and Rheumatology Products, stressed the primacy of analytic data in establishing similarity. He noted the agency views clinical data as a tool to reduce "residual uncertainty" remaining after analytical characterization, not as a principal source of evidence of safety or efficacy.

It is "almost impossible" to design a clinical study that can detect differences between two very similar molecules, Nikolov said.

"There is no expectation that there will be studies in multiple indications," he added.

HUMIRA BIOSIMILARS

At least 16 biosimilars of Humira adalimumab from **AbbVie Inc.** (NYSE:ABBV) have made it into the clinic, including two that are approved in India. A BLA for ABP 501 from **Amgen Inc.** (NASDAQ:AMGN) is under review in the U.S. Two other companies are planning submissions this year. AbbVie has a thicket of patents that it says will keep competitors off the U.S. market until 2020, but a combination of patent challenges and efforts to engineer around AbbVie's patents could bring biosimilars to the U.S. market sooner. Stage of development and disclosed plans for regulatory submissions are shown below. *Source: BCIQ: BioCentury Online Intelligence*

Company	Status (submission plan)
Zydus Cadila Group (NSE:CADILAHC; BSE:532321)	Mkt in India (plans U.S. launch 2019)
Reliance Life Sciences / **Torrent Pharmaceuticals Ltd.** (NSE:TORNTPHARM; BSE:500420)	Mkt in India
Amgen Inc. (NASDAQ:AMGN) / **Daiichi Sankyo Co. Ltd.** (Tokyo:4568)	Registration in U.S., EU
Samsung Group / **Biogen Inc.** (NASDAQ:BIIB) / **Merck & Co. Inc.** (NYSE:MRK)	Registration in EU
Coherus BioSciences Inc. (NASDAQ:CHRS)	Ph III (submit in U.S. 2016, EU 2017)
Biocon Ltd. (NSE:BIOCON; BSE:BIOCON) / **Mylan N.V.** (NASDAQ:MYL)	Ph III (submit in U.S., EU 2016)
Biocad CJSC	Ph III (submit in emerging mkts 2018; U.S., EU 2019)
Boehringer Ingelheim GmbH	Ph III
Kyowa Hakko Kirin Co. Ltd. (Tokyo:4151) / **Fujifilm Holdings Corp.** (Tokyo:4901)	Ph III
LG Life Sciences Ltd. (KSE:068870) / **Mochida Pharmaceutical Co. Ltd.** (Tokyo:4534)	Ph III
Merck KGaA (Xetra:MRK)	Ph III
Momenta Pharmaceuticals Inc. (NASDAQ:MNTA) / **Shire plc** (LSE:SHP; NASDAQ:SHPG)	Ph III
Novartis AG (NYSE:NVS; SIX:NOVN)	Ph III
Pfizer Inc. (NYSE:PFE)	Ph III
Oncobiologics Inc. (NASDAQ:ONS) / **Viropro Inc.** (Pink:VPRO) / **Zhejiang Huahai Pharmaceutical Co. Ltd.** (Shanghai:600521)	Start Ph III 2H16
Walvax Biotechnology Co. Ltd. (SZSE:300142) / **BIOCND Inc.**	Ph I

ENBREL BIOSIMILARS

At least nine programs have made it to the clinic with biosimilars of autoimmune drug Enbrel etanercept from **Amgen Inc.** (NASDAQ:AMGN). While the GP2015 BLA from the Sandoz unit of **Novartis AG** (NYSE:NVS; SIX:NOVN) is first to be reviewed by FDA, at least four are on the market outside the U.S. Stage of development and any disclosed plans for regulatory submissions are shown below. *Source: BCIQ: BioCentury Online Intelligence*

Company	Status (submission plan)
3SBio Inc. (HKSE:1530) / **Cipla Ltd.** (NSE:CIPLA; BSE:CIPLA)	Mkt in China, India
Samsung Group / **Biogen Inc.** (NASDAQ:BIIB) / **Merck & Co. Inc.** (NYSE:MRK)	Mkt in EU, South Korea
Hanwha Chemical Corp. (KSE:009830)	Mkt in South Korea
Intas Pharmaceuticals Ltd.	Mkt in India
Novartis AG (NYSE:NVS; SIX:NOVN)	Registration in U.S., EU
Mycenax Biotech Inc. (TPEx:4726) / **TSH Biopharm Co. Ltd.**	Registration in Taiwan
Coherus BioSciences Inc. (NASDAQ:CHRS) / **Daiichi Sankyo Co. Ltd.** (Tokyo:4568) / **Shire plc** (LSE:SHP; NASDAQ:SHPG)	Ph III (submit in EU, Japan 2016)
LG Life Sciences Ltd. (KSE:068870) / **Mochida Pharmaceutical Co. Ltd.** (Tokyo:4534)	Ph III
Lupin Ltd. (NSE:LUPIN; BSE:500257) / **Yoshindo Inc.**	Ph III

Nikolov said FDA "acknowledges the community's nervousness and need for reassurance that these products will work in different indications. Unfortunately, we are seeing biosimilar sponsors seeking to do multiple studies in multiple indications, which for us is not the right way to approach biosimilars."

For its etanercept, Sandoz supplemented its analytic characterization with PK studies and a switching study in which 531 plaque psoriasis patients were randomized to receive either GP2015 or Enbrel for 12 weeks, and then were switched between the two treatments at six-week intervals through week 30.

Rachel Glaser, an FDA medical officer, told the advisory committee that switching is not a requirement for approval and FDA has not yet released interchangeability guidance, so the agency's analysis of the GP2015 data was based on the initial 12-week treatment period.

WHAT'S THE DIFFERENCE?

Although the advisory committee voted unanimously to recommend approval of indications Amgen and Sandoz had not studied in the clinic, their queasiness about approvals of biosimilars based primarily on analytical data suggests manufacturers will need to launch aggressive marketing campaigns to persuade physicians and patients to switch from Enbrel and Humira.

"I'm always going to be uncomfortable extrapolating to indications without clinical data," said Erica Brittain, deputy branch chief and mathematical statistician at the National Institute of Allergy and Infectious Diseases' Biostatistics Research Branch. Brittain served as a temporary member of the committee.

She and other panel members said they were not absolutely confident FDA could be sure that apparently minor differences between biosimilar and reference molecules would not lead to differences in safety or efficacy.

For ABP 501, the concerns focused on extrapolation of the indication to inflammatory bowel conditions, while for GP2015 the issue was differences between the biosimilar and the reference molecules.

Enbrel has 10-18% misfolded proteins, while GP2015 has 9-12% misfolded proteins, according to Sandoz and FDA. Misfolding reduces the drug's potency, said Steven Kozlowski, director of the Office of Biotechnology Products in the Office of Pharmaceutical Quality (OPQ) at FDA's Center for Drug Evaluation and Research (CDER).

This difference posed a difficulty for the regulator. "We don't expect companies making biosimilars to intentionally maintain impurities in the reference product. That doesn't seem like a laudable goal," said Kozlowski.

He concluded the difference in the rate of misfolding in GP2015 is acceptable because "it was never outside the range of the reference product."

Clinicians on the committee were hesitant about extrapolating for ABP 501 from arthritis indications that are mediated by TNF-alpha to inflammatory bowel conditions because the mechanism of action in the latter is unknown.

Nikolov told the committee FDA is confident that Humira and ABP 501 are "so similar that we can rely on the safety and efficacy of the original product."

He added: "We think they are similar enough to give us confidence that the mechanism of action would be the same for all indications they are seeking approvals for."

Kozlowski tried to assuage the concerns of clinicians who have been trained to rely on clinical data. He told physicians on the committee that they had been unknowingly relying on FDA to make similar determinations for decades because biologics vary from lot to lot, and because the agency routinely reviews and allows manufacturing changes that result in slight modifications to the products.

"I'M ALWAYS GOING TO BE UNCOMFORTABLE EXTRAPOLATING TO INDICATIONS WITHOUT CLINICAL DATA."

ERICA BRITTAIN, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES

"Every time you use a different lot you are using a slightly different product," Kozlowski said.

He added the "vast majority" of manufacturing changes have no clinical effects, and that FDA has learned to detect variations that could result in meaningful differences. "We use this judgment all the time and we've used it for decades since biologics started," he said.

HUMIRA IP

Before Amgen and Sandoz get to work persuading physicians to use their biosimilars, they'll have to get past the IP hurdles.

Humira was first approved in 2002. The portfolio of patents AbbVie has constructed around adalimumab will keep competitors off the U.S. market until 2022, EVP and CFO William Chase told the Barclays Global Healthcare Conference in March.

Amgen and AbbVie are engaged in the formal patent notification and litigation process outlined in the U.S. biosimilars law.

Amgen declined to discuss the timing, but the CEOs of two other Humira biosimilars developers, Momenta Pharmaceuticals Inc. and Coherus BioSciences Inc., told BioCentury the litigation is likely to be completed near the end of 2018 or the beginning of 2019.

In addition, the U.S. Patent and Trademark Office's Patent Trial and Appeal Board (PTAB) has accepted *inter partes* review (IPR) challenges Coherus filed against three Humira patents. Results are expected in the same time frame as completion of the Amgen litigation, Coherus Chairman, President and CEO Denny Lanfear told BioCentury.

Coherus started developing an IP strategy for Humira five years ago, including plans to invalidate some AbbVie patents, and creating its own formulation IP, Lanfear told BioCentury. The USPTO has awarded the company one adalimumab formulation patent and two are pending.

"AbbVie's IP strategy will be effective in blocking most competitors," said Lanfear, who predicted about 75% of the biosimilar versions of Humira under development will fail the IP tests.

He believes Coherus "should have a clear shot to launch in mid-2018."

Coherus is also developing a biosimilar Enbrel for the European market. It plans to file an MAA this half.

Momenta President and CEO Craig Wheeler told BioCentury the "most significant" Humira patents are being attacked through IPR. These include dosing patents because FDA requires biosimilars to mimic the reference product's dosing.

Biosimilars companies will be able to engineer around some of AbbVie's patents, especially its formulation patents, according to Wheeler, and those that remain in force after early 2019 are likely to be "minor process patents."

He speculated that if a court determined "minor" patents were being infringed, it would impose "reasonable royalties."

However, the courts' approach to royalties remains uncertain, along with other factors that will shape the Humira biosimilars market.

Summing up the uncertainties at the Goldman Sachs Global Healthcare Conference in June, Wheeler said: "We can't predict — no company can predict — when Humira is going to truly launch, how many competitors are going to be there, what price point it's going to be, [or] what share you're going to have."

ENBREL IP

Enbrel was first approved by FDA in 1998, and prior to the winter of 2011 it looked like the IP pathway for a biosimilar etanercept in the U.S. was clear. The barriers included a process patent that expired in 2013, a method of use patent for Enbrel in psoriasis that expires in August 2019 and a patent covering an aqueous formulation that expires in November 2023. To market a biosimilar in the U.S., companies could wait for these patents to expire, attempt to engineer around them or seek to have the PTAB or a court invalidate them.

The situation changed in December 2011 when PTO issued two Enbrel patents that originally were filed in 1995. Today, patent terms are limited to 20 years from the date they are filed, but when the Amgen patents were filed, U.S. law granted 17 years starting from approval of the patent.

Because they are grandfathered under the old rules, Amgen's patents on the etanercept fusion protein and on DNA encoding the fusion protein and methods of making the fusion protein expire in 2028 and 2029.

In 2013, Sandoz sought a declaratory judgment of non-infringement against the two patents, but a federal court ruled the company could not sue until it had filed a marketing application with FDA.

In February this year, Amgen beat Sandoz to the punch, suing to block entry of a biosimilar Enbrel until 2029.

Speaking at a healthcare conference in May, Amgen EVP and CFO David Meline said the company has continued to invest in Enbrel because it is "an important product for the company and we have exclusivity through 2029."

Sandoz declined to respond to questions about the timing of the lawsuit or whether it would launch a biosimilar Enbrel in the U.S. prior to resolution of the litigation.

COMMERCIAL PROTECTIONS

AbbVie and Amgen can be expected to deploy a variety of weapons to avoid the calamitous loss in market share that typically accompanies expiration of small molecule patents.

"Even when a biosimilar competitor comes to market, we've got commercial strategies that we think can do a very, very good job of ensuring long-term durability of Humira in the U.S.," AbbVie's Chase told investors in May. "That has to do with our preferred position with payers, and the difficulty in switching a well-controlled patient and the familiarity that the Humira brand has from a safety standpoint, from a halo of indications."

Because of some overlap in their labels, the approval of a biosimilar Enbrel in Europe will have a modest effect on Humira sales as patients are steered to the lower-priced product, according to Chase.

"Enbrel does not have the suite of indications that Humira has, but there is a little bit more read-through and, therefore, as we've modeled the year, we expect about a 2% headwind on our international growth rates in Humira relative to what we've historically seen. We see an international growth rate of Humira now in the mid-single digits, and we think that's still the right way to model it," he said.

Pfizer Inc., which markets Enbrel outside the U.S., believes market erosion will be slow. Speaking at an investor conference in June, Chairman and CEO Ian Read said, "Right now, I don't think you're going to see substitution of existing patients. I think you're going to see new patients being taken up by the biosimilars."

He said switching existing patients to biosimilars is "a longer term play."

The European experience with etanercept and other biosimilars varies, however, and there are signs that switching to a biosimilar, and high market penetration for biosimilars, can be rapid (see "Eurosimilars," page 7).

Like Amgen, Pfizer is now competing on both sides of the fray, as it is marketing and developing a suite of biosimilars as a result of its acquisition of Hospira Inc. in September 2015.

AbbVie and other manufacturers of original biologics can fend off competition by providing rebates that reduce incentives to switch, according to Roger Longman, CEO of consultancy Real Endpoints LLC.

"My bet is that the brands will lower their net-rebate prices to just above the biosimilar price because it will still be highly profitable for the brands to maintain their market share at those prices," he told BioCentury.

He noted AbbVie has increased Humira's price continually, so even a 30% rebate would yield a higher price than Humira was selling for in 2009.

In contrast, said Longman, "the biosimilar will have a lot of start-up and manufacturing costs yet to amortize, so they'll be loath to discount too much."

According to Longman, pricing by biosimilar manufacturers is constrained not by cost of goods sold (COGS), but rather by the need to recoup sunk costs. Discussing the barriers to entering the biosimilars market at an investor meeting in May, Sandoz CFO Tobias Hestler said it costs over $200 million to develop a biosimilar and build a manufacturing facility.

"WE ARE SEEING BIOSIMILAR SPONSORS SEEKING TO DO MULTIPLE STUDIES IN MULTIPLE INDICATIONS, WHICH FOR US IS NOT THE RIGHT WAY TO APPROACH BIOSIMILARS."

NIKOLAY NIKOLOV, FDA

Models by market analyst Evercore ISI also project gradual biosimilar uptake. Based on biosimilar entry in 2018-19, the firm estimates U.S. sales of AbbVie's Humira increasing from $10 billion in 2016 to a peak of $11.9 billion in 2019. Evercore then projects single-digit annual declines that will bring Humira revenues in the U.S. down from $11.7 billion in 2020 to $8.9 billion in 2024. In 2030, 28 years after its approval, AbbVie will be bringing in $5 billion annually from Humira, according to the model.

Evercore ISI's model for Enbrel predicts peak U.S. sales of $5.65 billion in 2017, declining to $4.32 billion in 2022, and exceeding $3 billion through 2027.

OPENING THE DOOR

By the time Amgen and Sandoz have breached the IP walls around Humira and Enbrel, it is very likely FDA will have approved other biosimilars of the drugs.

Because Humira and Enbrel are sold at retail pharmacies and are used chronically, sales support and building brand loyalty will be important.

Amgen is positioning itself as a well-known, reliable manufacturer whose brand will extend into the biosimilars space. At the advisory committee meeting for its version of Humira, the company highlighted its 35 years of biologics manufacturing experience. It has a commercial team that markets Enbrel and can leverage a large product portfolio to make deals with or apply pressure to payers and physicians to prefer its products.

Speaking on an earnings call in April, Amgen's Meline said the company believes the biosimilars "market is going to develop more as a branded market," with the reputation of the manufacturer being the "most important consideration for adoption of a biosimilar product for patients and physicians."

Amgen is also assuming that its experience in navigating the U.S. drug acquisition system will be a competitive advantage.

Pharmacy benefit managers (PBMs) and large payers have a great deal of leverage over pricing and formularies in the outpatient market. In its 2015 annual report, Amgen noted that marketing of products like Enbrel are contingent on making deals with "three PBMs overseeing approximately 75% and three insurers overseeing approximately 43%, respectively, of total covered lives in the United States."

Coherus intends to license its Humira and Enbrel biosimilars to a company that has the marketing muscle required to persuade physicians and patients who are stable on an anti-TNF biologic to switch to a biosimilar, Lanfear told BioCentury.

"We will announce a strategic deal for Humira in the first half of 2017," he said. "It is a better market for a larger company with a bigger sales force."

Momenta's Wheeler has a different view of the market from Amgen.

> **"WE DON'T EXPECT COMPANIES MAKING BIOSIMILARS TO INTENTIONALLY MAINTAIN IMPURITIES IN THE REFERENCE PRODUCT."**
>
> STEVEN KOZLOWSKI, FDA

"We think it's going to be a more competitive business," he said at the Deutsche Bank Health Care Conference in May. He said a "brand-like business strategy" for biosimilars will not succeed in the long term.

Instead, Wheeler told BioCentury, prices will be determined by the number of competitors and the behavior of the branded originator.

"This is a market that will be done through contracting, and a lot depends on what the brand does," he said. "What triggers markets to collapse is bad behavior," which he said would include brand companies setting "market-killing" prices that make it impossible for competitors to recoup sunk costs.

This kind of behavior is unlikely, Wheeler said. Brand "companies that keep products in the marketplace can keep at least some market by keeping the price high. Particularly here, because some physicians haven't accepted biosimilars, they'll make more money by keeping the price at a reasonable level."

At some point, Wheeler said, there may be enough competitors to create a generic-like biosimilars market, and low-cost manufacturing will be key to survival in that environment.

"In the more generic phase of the market, manufacturing cost will be critical," he said. "Companies that are thinking carefully about low-cost manufacturing can make money in a low-cost biosimilars market."

At a May investor meeting, Sandoz Division Head Richard Francis challenged the idea that biologics originators have a cost advantage and emphasized the difference in cost culture between a company focused on bringing new products to market compared to a generics company.

"I look at the COGS of the top products we have every month, and I plan for what it is going to be over a 10-year period, and I look at procurement spend and at API costs," Francis said. "I didn't do any of that in my previous company."

Francis was SVP for US commercial at Biogen Inc. before joining Sandoz.

INTERCHANGEABILITY

Because Humira and Enbrel are distributed through retail pharmacies, an FDA interchangeability designation, and associated automatic substitution by pharmacists, could provide a huge boost to a biosimilars manufacturer.

Sandoz conducted switching studies and believes GP2015 is interchangeable with Enbrel. The company did not request an interchangeability designation, but it plans to, according to Mark McCamish, global head of biopharmaceutical development at Sandoz.

"From a development perspective, we don't make a non-interchangeable biosimilar," he told BioCentury.

While FDA has not released interchangeability guidance, McCamish noted it has described a two-step process, with companies first applying for approval as a biosimilar and later seeking interchangeable status. He said Sandoz may seek an interchangeability designation from FDA some time after GP2015 is approved as a biosimilar.

FDA has completed draft interchangeability guidance but cannot release it until HHS and White House reviews are completed. However, Momenta's Wheeler said companies do not have to wait for guidance. "As a sponsor, you can ask and FDA will tell you exactly what you need to do," he said.

The bigger problem, he said, is FDA's two-step interchangeable dance.

Because head-to-head tests will be required, biosimilar manufacturers are likely to seek to demonstrate interchangeability with the original biologic, but not with other biosimilars. This means that interchangeability will be most valuable when it can be obtained on first approval, and before other biosimilars have achieved market share, Wheeler said.

"Our view scientifically is we should have interchangeability at the time of approval," Wheeler said. He added that "there is an openness to thinking about it" at FDA, but "they are not there yet." bc

COMPANIES AND INSTITUTIONS MENTIONED

AbbVie Inc. (NYSE:ABBV), Chicago, Ill.
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.
Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Coherus BioSciences Inc. (NASDAQ:CHRS), Redwood City, Calif.
Momenta Pharmaceuticals Inc. (NASDAQ:MNTA), Cambridge, Mass.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
U.S. Department of Health and Human Services, Washington, D.C.
U.S. Food and Drug Administration (FDA), Silver Spring, Md.
U.S. Patent and Trademark Office (USPTO), Alexandria, Va.

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STRATEGY

EUROSIMILARS

BY STEVE USDIN, WASHINGTON EDITOR

The complex European biosimilars landscape makes it hard to extrapolate pricing, market share and switching trends to the U.S.

Across Europe, price reductions following biosimilar introduction vary widely. For example, according to IMS Health Inc., the introduction of biosimilar epoetin products led to prices decreasing 55% in Germany, 39% in France, 24% in Spain and 18% in the U.K.

Penetration also varies widely depending on policies on switching patients from original biologics, contracting policies and incentives for biosimilars. For example, biosimilar versions of Johnson & Johnson's Remicade infliximab range from single digits to 97% across the EU.

Celltrion Inc. markets its biosimilar version of Remicade in Europe as Inflectra, and Pfizer Inc. has rights to market the same product in Europe as Remsima. The product was approved in 2013.

Pfizer won a tender to sell Remsima in Norway in 2014 by offering a 39% discount relative to Remicade, and won the tender again in 2015 with a 69% discount. This year Celltrion took the prize with a 61% discount.

The market share for biosimilar infliximab in Norway shot up from about 9% in February 2014 to 93% in April 2016. Regulators encouraged switching patients from Remicade, and there have been no adverse medical effects from switching, according to Steiner Madsen, medical director of the Department of Drug Information at the Norwegian Medicines Agency.

In a conference presentation in May, Madsen noted market share for biosimilar infliximab varies widely even within Nordic countries, from 97% in Denmark and 88% in Finland, where regulatory authorities strongly encourage switching, to 33.5% in Sweden, where regulators discourage it.

He reported that physicians tend to be more positive about switching than patients, but that payers and healthcare managers must be actively involved to drive rapid uptake of biosimilars.

A May 2015 Finnish Medicines Agency position paper states that switches between biological products are common and usually not problematic, and that there is no evidence for adverse effects due to switching from a reference product to a biosimilar, Madsen noted.

Biosimilars account for 11% of the infliximab market in France, 14% in Germany, and 27% in the Netherlands, according to Madsen. IMS data indicate a 30% biosimilar share of the infliximab market in the U.K. as of February.

It's too early to tell how the market for biosimilars of Pfizer's Enbrel etanercept will shape up. The EC approved an MAA from Samsung Bioepis Co. Ltd. for Benepali etanercept in January.

Samsung Bioepis is a JV between Biogen Inc. and Samsung Group.

Biogen, which has European rights, reported $15 million in Benepali sales in 2Q16, and $2 million in 1Q16

In March, Biogen won a tender to supply Benepali to Legemiddelinnkjøpssamarbeid (LIS), the Norwegian drug procurement agency, at a 47% discount from the list price for Enbrel, LIS Director Torfinn Aanes told BioCentury. As of June, Benepali had 59% of the Norwegian etanercept market, he said.

As of May, there had been no sales of Benepali in Finland, and the biosimilar had 2.4% of the Swedish market and 20% of the Danish market, according to Madsen.

The European etanercept market may change in the coming months as additional biosimilars are approved.

In December 2015, EMA accepted an MAA from the Sandoz unit of Novartis AG for GP2015, a biosimilar of Enbrel, and several other companies are developing competing products. bc

COMPANIES AND INSTITUTIONS MENTIONED

Biogen Inc. (NASDAQ:BIIB), Cambridge, Mass.
Celltrion Inc. (KOSDAQ:068270), Incheon, South Korea
European Medicines Agency (EMA), London, U.K.
Finnish Medicines Agency, Helsinki, Finland
IMS Health Inc. (NYSE:IMS), Danbury, Conn.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.
Legemiddelinnkjøpssamarbeid (LIS), Oslo, Norway
Norwegian Medicines Agency, Oslo, Norway
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
Samsung Group, Seoul, South Korea

PRODUCT DEVELOPMENT

COLLECTING CAR PARTS

BY VIRGINIA LI, STAFF WRITER

While CAR T cell therapies have produced impressive response rates in blood cancers, the approach has so far shown limited effect in solid tumors, partly due to poor localization of T cells in tumor sites. Cell Medica Ltd. has therefore been assembling a tool kit to develop and improve upon a chimeric antigen receptor natural killer T cell platform.

Unlike T cells, which circulate in the blood, NKT cells localize in solid tumors in response to chemokines produced by tumor cells.

The first step was a June deal with Baylor College of Medicine to co-develop CAR NKT cell therapies to treat cancer.

The second step was the acquisition of antibody fragment company Delenex Therapeutics AG announced July 12. Cell Medica plans to use Delenex's PENTRA antibody fragment platform to develop humanized single-chain variable fragments (scFvs) that will serve as the antigen recognition component of its CAR therapies.

Cell Medica and Baylor already had a 2011 deal to develop baltaleucel-T (CMD-003), a cell therapy comprising autologous cytotoxic T lymphocytes specific for Epstein-Barr virus (EBV) that is in Phase II to treat aggressive EBV-positive extranodal NKT cell lymphoma.

"As we focus on more difficult to treat solid tumors, we want a cell type that finds its home naturally in those types of tissue, and NKT is such a cell," CEO Gregg Sando told BioCentury.

The June deal with Baylor gives Cell Medica an exclusive, worldwide license to an NKT cell immunotherapy platform, three undisclosed targets for CAR NKT cells and a T cell receptor (TCR) candidate targeting survivin (BIRC5). The partners will also collaborate on CAR T therapies, and Cell Medica has an option to license additional product candidates following the completion of a Phase I study.

Baylor is responsible for preclinical and Phase I studies, and Cell Medica will conduct Phase II and Phase III trials and commercialize resulting products. Cell Medica will fund preclinical and clinical development. Further terms are undisclosed.

The deal includes an option to a program of NKT cells engineered to express a CAR against ganglioside GD2 (GD2), which is highly expressed on neuroblastoma cells. In a mouse model of metastatic neuroblastoma, the CAR NKT cells localized to the tumor, demonstrated potent antitumor activity and led to significantly prolonged survival compared to control. Results were published in *Blood* in 2014.

HUMAN TOUCH

Cell Medica hopes that Delenex's humanized scFv technology will reduce the potential for immunogenicity to CARs and increase the persistence of cell therapies, which the company believes will be necessary to have efficacy against solid tumors.

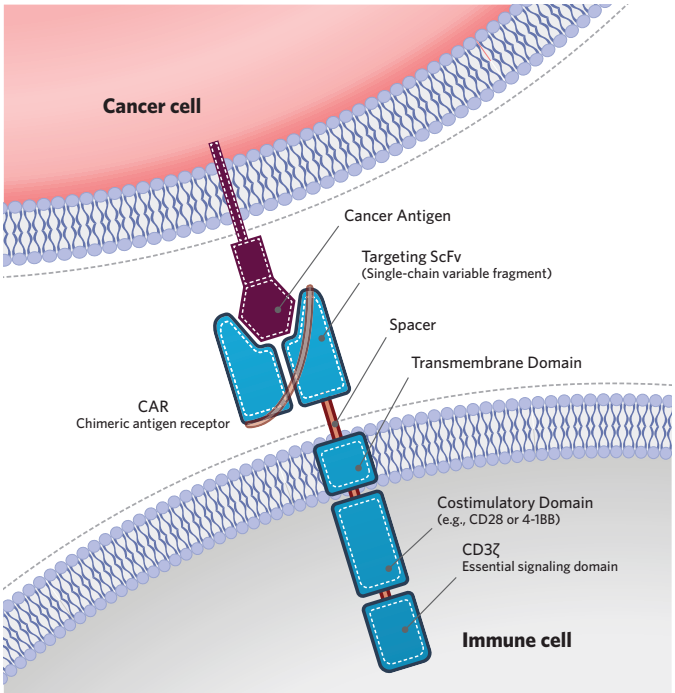
Although the ganglioside GD2 product did not induce graft-versus-host-disease in the *Blood* study, there have been increasing reports of immunogenicity of CAR T cell therapies, according to Leonid Metelitsa, a professor of pediatrics-oncology at Baylor and an author on the *Blood* paper.

"There are more and more recent reports with evidence of limited persistence of CAR T cells and disease recurrence after repeated treatment, even when the first dose led to good clinical responses," said Metelitsa. "Conclusive data is not available, but the indication is that there are T cell responses against CARs, and it would be expected that murine elements of a CAR would be the most immunogenic part."

Sando noted that most CAR therapies in the clinic use non-humanized scFvs.

HUMANIZING CARs

Cell Medica Ltd. acquired **Delenex Therapeutics AG** to gain the PENTRA antibody fragment platform for use in developing humanized single-chain variable fragments (scFvs) that will serve as antigen recognition domains for chimeric antigen receptors (CARs). CARs are composed of an scFv linked to one or more immune cell signaling domains that activate an immune response. The scFv guides the immune cell to the tumor by recognizing and binding a target cancer antigen. *Source: Cell Medica Ltd.*



"When developing CAR products for solid tumors, which may take a longer period to respond to cell immunotherapy, are more difficult to hit, and are not in the bloodstream, you need to be more concerned about persistence, and hence more concerned about making sure all components of the engineered immune cell are humanized," said Sando.

Cell Medica plans to develop CAR NKT therapies for neuroblastoma, small cell lung cancer (SCLC), hepatocellular carcinoma (HCC) and triple-negative breast cancer (TNBC). Sando declined to disclose which cancer antigens the partners will target.

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He said it will take six months to identify antigen-targeting scFvs and an additional six to 12 months to optimize each fragment for a CAR construct. The company hopes to bring three to four CAR therapies into the clinic in 2018.

Sando said Cell Medica also plans to use the Delenex technology to develop next-generation CAR NKT and CAR T cells that secrete scFvs that could serve as local checkpoint inhibitors to counteract the immunosuppressive effects of the tumor microenvironment.

"We will optimize the CAR construct in combination with different local checkpoint inhibitors appropriate for specific cancers depending on the expression of PD-L1 or other inhibitor molecules on the malignant cells," said Sando.

He said the company will explore this approach in the next two years, but would not say whether Cell Medica's first clinical stage CAR therapies would include secreted scFvs.

Within two years, Cell Medica also plans to in-license safety switches and alternative expression systems to enhance its CAR candidates.

Sando said Baylor is currently developing CAR therapies using a retroviral expression system, but Cell Medica hopes to license a lentiviral or transposon system, which he said could be safer and more efficient than the retroviral approach.

The company plans to out-license Delenex's clinical and preclinical programs for further development. Delenex's two most advanced compounds are a topical formulation of DLX105, an anti-TNF alpha mAb fragment that has completed Phase II studies in psoriasis, and an IV formulation of DLX105, which has completed Phase II testing in psoriasis and Behcet's disease. bc

COMPANIES AND INSTITUTIONS MENTIONED

Baylor College of Medicine, Houston, Texas

Cell Medica Ltd., London, U.K.

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