IN brief

Three deaths sink Affymax

In February, Affymax of Palo Alto, California, and its partner Takeda of Osaka voluntarily withdrew Omontys, the peptide erythropoietin mimetic, from the market following 19 serious hypersensitivity reactions, including three deaths. Omontys was approved by the US Food and Drug Administration (FDA) in March of 2012 for treating anemia in patients on dialysis with chronic kidney disease (CKD). With the loss of its only product, Affymax has cut its workforce by 75% and is “evaluating strategic alternatives” according to a company press release. The cause of the severe reaction, which occurred within 30 minutes of the first dose of the drug, remains mysterious. According to Affymax’s chief medical officer Anne-Marie Duliege, the incidence of hypersensitivity reactions was the same before and after marketing (0.2%), but the reactions observed after approval, when one-third of patients required immediate medical intervention, were more severe than during clinical trials. Erythropoietin stimulating agents (ESA) have been under increased scrutiny since 2011 when their use linked to cardiovascular problems; Affymax did scale back its target population in its new drug application, eliminating patients with less severe kidney dysfunction, who showed a greater incidence of cardiovascular reactions than with its competitor Amgen’s long-acting EPO, Aranesp (darbepoetin alfa). This raised a red flag for Steven Nissen of Cleveland Clinic, in Ohio, the one dissenting vote of the 16-member FDA Oncologic Drugs Advisory Committee panel that reviewed Omontys. “There’s no reason to believe that the drug would be helpful in the group that had a little worse kidney function and harmful in the group that had a little bit better kidney function,” he said.

Laura DeFrancesco

Monsanto buys microbes

On January 30 Monsanto acquired select assets from Agradis. The purchase includes Agradis’s large collection of plant-associated microbes and screening processes focused on sustainable solutions to boost crop health and productivity, as well as its R&D site in La Jolla, California. Agradis’ assets fit with the St. Louis-based Monsanto’s relatively new push into agricultural biologicals. “We see ag biologicals as a very exciting area, complementing breeding and biotechnology as part of a total system, but again it’s early days,” says Monsanto spokesperson Sara Miller. Monsanto also announced in January a multi-year research collaboration with La Jolla-based Synthetic Genomics, led by Craig Venter, which spun out Agradis, to analyze plant microbe communities and screen for beneficial microorganisms. Monsanto is one of several agribusiness companies to gain a foothold into the \$1.7-billion ag biologicals market. In September 2012 Basel-based Syngenta paid \$113 million for Pasteuria Bioscience, a startup in Alachua, Florida, with a novel biological process to control nematode pests in plants (*Nat. Biotechnol.* 30, 1158, 2012), and chemicals maker BASF in Ludwigshafen, Germany, forged a \$1-billion deal for Becker Underwood, a global provider of biological crop protection products based in Ames, Iowa.

Emily Waltz

Box 1 Europe follows US lead on heparins

The EMA opened a public consultation in February to revise the guidelines for its biosimilar LMWHs. Europe is already ahead of the US when it comes to biosimilars, with over a dozen biosimilars on the market. But when it comes to LMWH—fragments of heparin, typically sourced from pig intestinal mucosa, that act as anticoagulants—it is the FDA that is ahead. There are two FDA-approved copies of Paris-based Sanofi’s Lovenox (enoxaparin), but none in Europe.

LMWHs—though larger and more complex than small-molecule drugs—are not proteins, but rather short polysaccharide chains. Sandoz-Momenta’s copy, m-enoxaparin, was approved in 2010 with an abbreviated new drug application (ANDA), a pathway traditionally used for small-molecule generic drugs. Amphastar-Actavis’ ANDA-approved version of LMWH followed a year later, after lengthy discussions and a lawsuit.

With its recent proposed revisions to its biosimilar LMWH guidelines, the EMA will in theory allow “convincing” and “considerable” analytical data to replace a dedicated clinical efficacy trial in some circumstances. The EMA is thus acknowledging that analytical characterization techniques have improved substantially in recent years. It is also tacitly accepting that its clinical demands were deterring generic enoxaparin applicants in Europe.

Some biosimilar proponents suggest that EMA leans more toward clinical proof of similarity, whereas FDA appears more open to analytics. “I wouldn’t be surprised if European regulators beef up analytic characterization requirements across the board,” says Momenta’s CEO Craig Wheeler. Revisions to EMA’s insulin biosimilar guidelines are also out for review, though in this case driven by the need to include guidance on insulin analogs and long-acting insulins. The deadlines for comments on the LMWH and insulin guidelines are July 31, 2013, and June 30, 2013, respectively.

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The most important lesson from Europe, though, is that despite continued hurdles, such as physician lack of trust in biosimilars, the slow ramp-up is gaining momentum. Biosimilar erythropoietin products already enjoy over a 50% share by volume of some markets. Holzkirchen, Germany-based Sandoz’s Omnitrope (somatotropin) growth hormone has grabbed over half the Danish market, thanks to hospital tenders for growth hormone.

And there are signs of regulatory adaptation, too—nationally and across Europe. The Norwegian Medicines Agency, having been blocked in the courts by Amgen from putting biosimilar filgrastim (Neulasta and Neupogen brands; G-CSF) on the pharmacists’ automatic substitution list, is proposing to change the country’s laws to permit pharmacists to substitute biologics just like small-molecule generics. At the same time, the European Medicines Agency (EMA) is revising its guidance for biosimilar low-molecular-weight heparins (LMWHs), opening the door for fuller analytical data to reduce clinical data requirements (Box 1).

As a host of far more expensive, complex biologics, including monoclonal antibodies, approach patent expiry, the biosimilar stakes are heating up on both sides of the Atlantic. EMA has already received two submissions of biosimilar Remicade (infliximab) made by Johnson & Johnson of New Brunswick, New Jersey, the first of which, from Incheon, Korea-based Celltrion, is under review. Approval is possible this year, although a member of EMA’s medicines committee cautions that discussions are “still difficult.”

They will continue to be. Further adjustments and friction are likely as experience builds. There will be more safety scare-mongering by brand manufacturers, even though, seven years after biosimilars arrived in the EU, these products haven’t thrown up any notable safety issues.

Indeed, potential warning flags from biologics other than biosimilars may affect the latter. Thus, the withdrawal in late February of anemia drug Omontys (peginesatide) from Palo Alto, California-based Affymax (and its partner Takeda Pharmaceuticals of Osaka), due to 19 cases of severe allergic reactions (see DeFrancesco p. 270), could spark a debate around the safety of mimetics and analogs of large-molecule drugs. Omontys is not a biosimilar but rather a long-acting erythropoietin (EPO) analog (specifically a PEGylated synthetic dimeric form of an EPO mimetic peptide comprising two 21-residue identical peptide chains coupled by a linker derived from iminodiacetic acid and beta alanine). Because Omontys’ adverse events were unexpected based on preregistration trial data, FDA may be more cautious in biosimilar approvals based on clinical trial data, rather than data from the general population.

However cautious the FDA finally is in determining interchangeability for biosimilars when it announces its final pathway, many are still upbeat about the prospects for biosimilars, for one simple reason—in the end, declares Craig Wheeler, CEO of Momenta Pharmaceuticals, Cambridge, Massachusetts developer of complex generics and biosimilars, “payer pressure will win.”

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