Box 1 Joint biosimilar flops

Pursuing biosimilars is risky business. Even well-established partners have stalled, and the list of failed joint ventures continues to grow. Most recently, Petach Tikva–based Teva and Basel-based Lonza in mid-2013 pulled the plug on their 2009 joint venture, following a halt to their phase 3 trial of biosimilar Rituxan. Rituxan also posed problems for two other sets of biosimilar partners. Samsung/Quintiles in late 2012 halted their phase 3 of this drug, saying they wanted to reorganize to meet emerging US regulatory standards; Celltrion/Hospira made a similar argument when they dropped their phase 3 trial in early 2013.

Around the same time, New York–based Pfizer put an end to its three-year-old biosimilar insulin joint venture with India's Biocon. The big pharma was going to commercialize Biocon's three insulin biosimilars in the US and Western Europe, but claimed 'shifting priorities'. It's not hard to see its reasoning: unlike most other biosimilars, insulins are high-volume and low-price products, with slim margins, where branded competition is aggressive, and where delivery devices matter.

Another example is Percivia, formed in 2011 as a joint venture between Dutch biotech firm Crucell NV and Royal DSM to develop biosimilar and bio-better therapeutic proteins using Crucell's PER.C6 human cell line. The partnership fell through when Johnson & Johnson acquired Crucell in early 2011 and didn't want the technology used for mAbs. Antibody-related dealmaking activity in China has also had its casualties. Walvax Biotechnology, currently seeking majority control of Genor Biopharma, attempted in July 2012 to collaborate with mAb developer Shanghai Fengmao Biotechnology. The deal fizzled amid allegations by Walvax of contract fraud.

An earlier generation of biotechs also floundered while chasing the biosimilars opportunity—including in emerging markets. UK-based GeneMedix, founded in 1997, made unsuccessful forays into markets including China and Malaysia. In 2001 it set up in China through a majority stake in Shanghai Dongxin Biotechnology, but sold the facility in 2005. In 2007, India's Reliance took a majority stake in the struggling AIM-listed company, and GeneMedix was de-listed a year after its EPO candidate failed to impress European regulators in 2011. *MS*

and cost-pressure may be prioritized at the expense of safety. It's often the case that biosimilars—including complex mAb biosimilars—are widely available, well ahead of regulatory, legal and safety monitoring infrastructure. China, for instance, has no regulatory pathway for biosimilars, even though they comprise an estimated 40% of the country's $1.5-billion recombinant biologics market, according to London-headquartered Deallus Consulting. It's a huge market for small foreign players to navigate successfully, and murky intellectual property protection has already spelt gold for powerful local firms, who sell biosimilars at prices up to 60% lower than innovators'. Shanghai-based CP Guojian has several mAbs and complex proteins approved or in late-stage development in China, including Yisaipu, its own Enbrel, and Sai Pu Ting, described as a 'recombinant humanized anti-HER2 mAb injection', probably an Herceptin look-alike. Meanwhile, local M&A is heating up. Shanghai-based Genor BioPharma, whose ten-strong mAb pipeline includes four biosimilars, is being courted by Kunming-based Walvax Biotechnology, in a deal that could create one of the country's largest biotech conglomerates. In July 2013 Genor received approval to begin trials of biosimilar trastuzumab (Herceptin) and has copies of Remicade, Humira and Avastin queuing up behind.

In India, where most patents weren't recognized until 2005, local generics giant Hyderabad-based Dr Reddy's has been selling its own version of Rituxan, called Reditux, since 2007. Reditux isn't a biosimilar in Western terms; it's a noncomparable biologic with the same amino-acid sequence. Still, the size of the opportunity led Roche to jump in with its own low-cost copy of its branded MabThera (rituximab); the Swiss group has a 2012 manufacturing deal with Pune-based Emcure Pharmaceuticals for Rituxan and Herceptin. Such innovator defense tactics, increasingly aggressive, mark another uncertainty for the latest generation of biosimilar startups, especially in the more significant emerging markets. So do deals involving deeper-pocketed Western firms like Mylan of Washington County, Pennsylvania, tied-up since 2009 with India's Biocon of Hyderabad, which plans shortly to submit to local regulators its biosimilar Herceptin. On the other hand, quality concerns are starting to be voiced about some local products, and indeed Dr. Reddy has struggled to find approvals for its biosimilars in other markets. The advantage for products meeting Western regulatory standards may grow.

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IN brief

Mesoblast acquires Osiris' stem cell business

Osiris Therapeutics in October offloaded its signature product, Prochymal, one of the first stem cell therapies to win government approval, to Melbourne-based Mesoblast. The Columbia, Maryland–based biotech will receive $50 million for the drug and the technology behind it, plus $50 million more if the drug passes additional clinical trials and regulatory reviews, the companies say. The price tag is "quite a discount," says Lee Buckler, founder of Cell Therapy Group, a consulting firm in Vancouver. Prochymal, a bone marrow–derived mesenchymal stem cell therapy, has seen limited success, but overall has been a disappointment to many people in the regenerative medicine sector. The drug in 2009 failed two phase 3 clinical trials in severe refractory graft-versus-host disease (GvHD) and didn't fare much better in testing in people with Crohn's disease and chronic obstructive pulmonary disease (*Nat. Biotechnol.* **27**, 966–967, 2009). Finally in 2012 the drug received conditional regulatory approval in Canada and New Zealand to treat GvHD in children. Mesoblast's purchase of Prochymal gives the company a new revenue stream and Osiris' entire mesenchymal stem cell intellectual property estate. More importantly, the deal may also give Mesoblast a foot in the door in the US, says Graig Suvannevejh, an analyst at MLV & Co. in New York. Prochymal is available in the US through expanded access programs and has been given fast track designation and orphan drug status by the US Food and Drug Administration (FDA). Phase 3 studies in Crohn's disease and acute GvHD are underway, and Mesoblast intends to move forward on those with the FDA. "There's good data there," says Buckler. "There are pockets of things that work." The value of what's left at Osiris following the sale is a matter of debate. The stem cell company retained biosurgery products Ovation and Grafix, for wound and tissue repair, and Cartiform, for cartilage repair. But on September 26, two weeks before the sale of Prochymal, Osiris received an untitled letter from the FDA saying Ovation and Grafix violated federal regulations, and that valid biologics licenses must be in effect in order to lawfully market the drugs. Osiris withheld the information from the public until, on October 21, it announced it had "reached an agreement" with the FDA that Grafix could continue to be on the market for acute and chronic wounds, including diabetic foot ulcers, its largest market. CEO Randy Mills said the company resolved the Ovation problem by transitioning the product line to a new formulation. FDA said federal rules prohibit it from confirming or denying the company's characterization of the agreement. Analysts say they are not sure how to interpret the news. Says Buckler: "The company has credibility challenges among many analysts and industry insiders because they believe the company has a consistent pattern of putting a spin on its news in ways in which many suggest less transparent or forthright than is expected." *Emily Waltz*