

Box 1 US follow-ons without a follow-on pathway

A few follow-on biologics have found a regulatory loophole in the US, which originated from some early confusion about which drugs should be regarded as biologics. Historically, most biological products, such as vaccines, blood products, blood derivatives, serums and antitoxins, were regulated under the Public Health Service Act.

Some early biologic-like products, such as animal-derived insulin and human growth hormone derived from cadaver pituitaries, didn't fit in with the vaccines and blood derivatives, so they were lumped in with chemical drugs under the Federal Food Drug and Cosmetic Act (FD&C).

As the biotech revolution arrived in the early 1980s, scientists began making recombinant insulin and human growth hormone. As the nonrecombinant version of these drugs had been approved under the FD&C Act, the new recombinant versions were also approved under this Act. When the first recombinant alpha interferon products were approved, however, they were regulated under the Public Health Service Act. To try and clear up the confusion, in 1991, the FDA sent most biologics—though not all—to be regulated by the Public Health Service Act.

When Congress created an abbreviated pathway for generic drugs, it applied the pathway to products regulated under the FD&C Act only. As a few biologics had slipped into FD&C, a narrow pathway was created for those types of drugs to enjoy an abbreviated approval. *EW*

bars approval of a follow-on biologic for the first 14 years of a brand product's life on the market. A bill introduced by Rep. Henry Waxman proposed no exclusivity period. The European Medicines Agency (EMA), a body of the EU responsible for evaluating drug applications, requires generics companies to wait 10 years before marketing their drug, plus another year if any additional disease indications were approved for the brand drug.

Some groups say the FDA should emulate the EMA and publish guidance documents on each product class before drugs in those classes can be approved. The European agency has issued specific guidance documents for insulins, growth hormones, erythropoietins and G-CSF products.

With so many heated questions, it's difficult to predict the kinds of data the FDA might require. As a basic first step, Insmmed is characterizing its drug, INS-19, to determine if it is similar enough to Neupogen. The company chose a battery of tests based on its past experience and scientific judgment, says Allan at Insmmed.

Insmmed's recent clinical study administered INS-19 and Neupogen to 32 volunteers and found the two drugs to be 'bioequivalent'. Bioequivalence is a term to denote that the rate and extent of bioavailability as well as the efficacy and safety of two products are the same. Demonstration of bioequivalence is a primary clinical requirement for FDA approval of chemical generics. But experts say bioequivalence studies aren't enough to demonstrate safety and efficacy of most follow-on biologics.

Insmmed plans to request a meeting with the FDA to discuss additional studies. "We won't talk [with the FDA] about anything specific to

regulatory pathways, because the pathway hasn't been put in place," says Allan at Insmmed. "We'll tell them who we are and what we're doing, and we'll talk about what we think is a reasonable development program for this product." These are reasonable steps to take in preparation for a regulatory pathway, some experts note. "To run all the technical studies and to run a bioequivalence study is certainly not taking too much risk," says Andreas Rummelt, CEO of Sandoz. "To go further is taking more risk," he says.

Of the traditional generics companies, several are taking a proactive approach to follow-on biologics. Sandoz began developing Omnitrope in 1997, more than a year before it received confirmation from the FDA that a regulatory pathway would be possible under the loophole in US laws. The FDA and the EMA approved the drug in 2006. Jerusalem-based Teva Pharmaceuticals started developing its biosimilar G-CSF product more than two years before European legislation was finalized, according to Debra Barrett, vice president of government affairs at Teva. The company received a positive opinion from the EMA in February.

Some companies are finding themselves on both the innovator and the generic sides of the issue. Seattle-based Cell Therapeutics' pipeline includes an innovative commercial product as well as a potential follow-on G-CSF product.

If Congress doesn't pass legislation—unlikely, but possible—Insmmed could always seek approval through the full, innovative route, which may or may not be cost effective. "I haven't made that decision. It will depend on the nature of the studies," says Allan. The company doesn't plan on marketing INS-19 in Europe.

Emily Waltz New York

IN brief

SBIR boost

Congress gave small biotech businesses cause for celebration by approving a bill to extend the Small Business Innovation Research (SBIR) and Small Business Technology transfer programs by another fourteen years. The programs were due to 'sunset' in September of this year but a Senate committee has now raised funding levels for these grants to \$150,000 for phase 1 grants and \$1 million for phase 2 grants. In addition, a new SBIR bridge-grant program from the National Cancer Institute (NCI) offers up to \$3 million in funding to boost small companies from phase 2 to successful commercialization. This transition has been referred to as the 'valley of death' because many companies fail from a lack of cash flow after they have graduated from the phase 2 grant, but not yet achieved commercial profitability. The bridge funds will help companies like NovaRx of San Diego, who developed their cell-based vaccine for lung cancer under an SBIR fast-track phase 1/2 grant, to move forward with commercialization of their product. Says Habib Fakhrai, president of NovaRx, "The results of the trial were so stellar, so good, that we were able to use those results to procure further funding...Without that SBIR grant, it would have been extremely difficult." The NCI will require bridge-grant applicants to raise matching funds from private investors—a tough test for a new company, but one that the NCI believes will separate the wheat from the chaff. Small venture capital firms would also be eligible for funding under the new agreement. *—Catherine Shaffer*

Startups lure oil giants

Cellulosic ethanol developer Verenium has partnered with British petroleum company BP in a \$90 million deal—a sign that next-generation biofuels companies are increasingly looking to oil giants for funding. Over the next 18 months, London-based BP will pay Verenium, of Cambridge, Massachusetts, \$45 million for broad access to its technology, facilities and expertise, and an additional \$45 million to co-fund technical initiatives. Verenium currently operates a pilot plant and is completing a demonstration-scale facility, but as Peter Nieh, a managing director at Menlo Park, California-based Lightspeed Venture Partners points out, "Biofuels startups typically need distribution partners. They can't put fuel into the marketplace by themselves." As part of the deal announced in August, the companies will equally own any jointly developed intellectual property. Partnerships with large oil companies can be beneficial particularly in later stages of development as they bring refining and market expertise. "These partnerships are new enough that there are a lot of unknowns," cautions Nieh. Virent Energy Systems of Madison, Wisconsin, in May partnered with Royal Dutch Shell to develop technologies for converting plant sugars into gasoline-like products. Mascoma, a Boston-based cellulosic ethanol company, also in May, closed a round of equity investment that included \$10 million from Marathon Oil of Houston. *—Emily Waltz*