Western biotechs ponder follow-on possibilities

US biotech company Insmed claims to have replicated one of Amgen's blockbuster drugs Neupogen (filgrastim) for treating neutropenia. With no viable, abbreviated regulatory route for obtaining market approval for most generic biologic drugs in the US, the Richmond, Virginia–based biotech's announcement in July that it had proven 'bioequivalence' appears a PR-savvy statement of intent rather than anything more definitive. In the meantime, as the long-awaited US legislation to create a regulatory pathway for follow-on biologics apparently remains in limbo until 2009, in addition to traditional generics companies, several other North American biotech companies are ramping up preparations to produce copies of recombinant drugs.

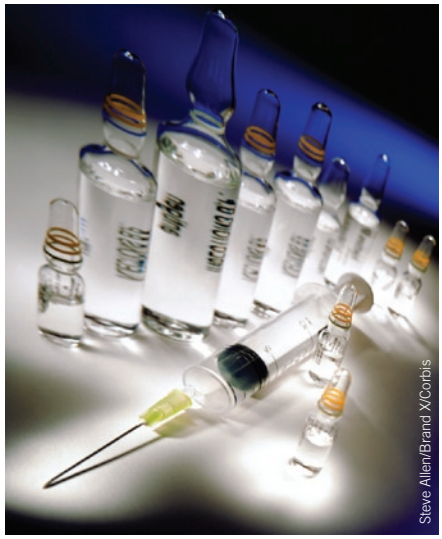
Insmed is trying to position itself to be one of the first to put a generic biologic of this type on the US market. The company's strategy depends on Congress passing a law that gives the US Food and Drug Administration (FDA) the power to approve such drugs through an abbreviated route. "You have to have faith that they'll pass it eventually," says Geoffrey Allan, CEO of Insmed. "If you haven't started today developing these products, you're not going to be the first man in the marketplace when the time comes."

"I speculate that there are a number of companies doing the same thing," adds Jacqueline Wright Bonilla, a senior counsel at Foley & Lardner in Washington, DC. "Insmed chose to go public."

For nearly 25 years, the FDA has exercised its power to quickly approve generic small molecules, or chemical drugs. This abbreviated regulatory route allows generics companies to skip much of the costly clinical trials that innovator companies endure, and charge less for their drugs. But no such route exists for generic versions of biologics dubbed 'biogenerics' or 'follow-on' biologics.

A loophole in US laws, however, has allowed the FDA to apply an abbreviated process to a handful of follow-on biologics (**Box 1**). Sandoz, the generics arm of Novartis based in Holzkirchen, Germany, brought its recombinant human growth hormone Omnitrope (somatropin) to market through this pathway. This loophole, however, does not apply to most biologics—drugs produced through biotech or derived from natural sources—including Insmed's product.

With no official guidance from the FDA, Insmed is developing its product based on its best guess as to what the agency might require. The potential requirements are no secret:



Given the complexity of biologics, minor differences between biosimilars and brand products are to be expected.

Europe has been approving what they call 'biosimilars' through a streamlined process since 2005 (*Nat. Biotechnol.* **26**, 5–6, 2008). Specific guidelines for the type of product Insmed is developing, a recombinant granulocyte colony stimulating factor (G-CSF), were published by European regulatory authorities in 2006. The first biosimilar G-CSF product in Europe is pending final approval.

European regulations recognize that minor differences between a biosimilar and a brand product are expected given the variability of biologics, and require companies to justify those differences on a case-by-case basis. But how closely US legislation will resemble Europe's is unclear. Congress in the past has remained hesitant about those differences. Biologics are more structurally complex than small molecules and can vary depending on the manufacturing process and the source of the material. Unlike small molecules whose chemical composition can easily be determined and compared with an innovator product, biologics are difficult to characterize and comparisons are more challenging. It is unlikely, the US federal government has argued, that a manufacturer could make a product identical to an innovative biologic. 'Similar' is the closest most follow-on biologics are going to get, and further studies to test safety and efficacy may be required.

But companies such as Cambridge, Massachusetts–based Momenta, which specializes in characterization, say they have the expertise to identify any differences between a biogeneric and its reference product, and that these data can be used to direct further development and review of the drug. "What we're doing is what Congress says can't be done," says Craig Wheeler, CEO of Momenta.

Weston, Ontario–based Apotex is developing a follow-on G-CSF product with the intention of marketing it in Canada and the US once regulatory pathways are established. Canada has issued a draft set of rules for the approval of subsequent entry biologics (SEBs) (*Nat. Biotechnol.* **26**, 599, 2008). Under the proposal put forward by Canada's regulatory agency Health Canada, manufacturers seeking approval for generic versions of biologics, on patent expiry, would be allowed to incorporate publicly available information, but must show that the quality, safety and efficacy of the SEB is comparable to the original biologic. Apotex plans to look into additional follow-on biologic products once legislation is approved, according to press releases. Elsewhere, Cangene of Mississauga, Ontario, is developing a follow-on granulocyte-macrophage (GM)-CSF. Neither company would comment further on their follow-on products.

Of course, biosimilars companies with approved products in Europe are closely watching the development of US legislation. "I know those companies are all thinking of those products as being applicable in the US once there is a pathway," says Wheeler.

In addition to science questions, policy debates in the US have further delayed legislation. The first proposed bill on the topic was introduced in September 2006. A handful of bills have been introduced since then, but none will pass before the November election, say experts. "In the absence of a consensus I think Chairman [John] Dingell has been reluctant to take the bill up," says Jim Greenwood, president of the Biotechnology Industry Organization (BIO) in Washington, DC.

Senators from states such as Massachusetts, California and Maryland—where the country's largest biotech clusters are based—recognize the economic benefits of high-paying jobs at innovative companies, and tend to support measures that don't penalize them, says Ira Loss, a founder of Washington Analysis in Washington, DC. Others are pushing hard for healthcare reform and ways to get cheaper drugs to patients. The Congressional Budget Office in June estimated that follow-on biologics will cost up to 40% less than innovator drugs, although it is not clear what set of biologics they included in their analysis.

How long brand products should be protected from generic competition remains a contentious issue. A bill proposed by Rep. Jay Inslee

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 (EMEA), 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 EMEA 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, Insmed 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 Insmed.

Insmed'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.

Insmed 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 Insmed. "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 EMEA 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 EMEA 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—Insmed 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*