

Where the Wall Will Fall First

Most believe that 'generic' biologics are not a question of *if*, but *when*. Just when, though, and which therapies could face a threat in the marketplace, depend on the complexity of the product. Research is far along, indicating that some of today's biggest markets could be exposed when the wall comes tumbling down.

BY JOHN CARROLL

Senior Contributing Editor

As the chief medical officer of Express Scripts, Steve Miller, MD, travels around the country routinely, talking to payers about the trends he sees percolating in the drug market. And one topic is guaranteed to ignite tremendous interest: the prospect that the first generation of "generic" biologics — follow-ons, in the parlance of the industry — may be on the horizon.

"Payers are wildly interested in this," Miller says emphatically.

This is an issue that's hard for anyone paying healthcare bills to ignore. The 200 or so biologic therapies that are on the market already command a significant chunk of overall drug spending, and Miller is tracking another 400 to 600 biologics in clinical trials. Payers believe that the prospect of biogenerics offers them an opportunity for price relief.

For now, as legislators debate the details of a new bill, biologic follow-ons are a Congressional hot potato. There's considerable enthusiasm for new legislation on the subject, but with competing bills and anxious lobbyists on both sides of the issue, it's still anybody's guess as to what will happen.

For market watchers like Miller, it seems clear that after years of talk, something is likely to happen soon. Drug developers, though, aren't about to wait to see the fine print in any bill before they leap into this market.

Global companies like Teva, Barr, and Hospira already have created development programs to design biosimilars of products that are either off patent or facing a loss sometime in the next few years. Kathleen Jaeger, JD, CEO of the Generic Pharmaceutical Association, adds India's Wockhardt and Germany's Stada, among others, to that list of generic companies. In the United States, Jaeger adds, Momenta Pharmaceuticals also has been playing a role in the early stage of biogeneric development.

But some unexpected players also are suiting up to jump into this market, and their arrival could have a noticeable impact on long-term pricing trends.

Big Pharma companies already

No matter where he travels in the United States, the topic of follow-on biologics is guaranteed to spark tremendous feedback, says Steve Miller, MD, chief medical officer of Express Scripts. "Payers are wildly interested in this," he says.

schooled in the art of generic salesmanship — such as Novartis' generic arm Sandoz — are being joined by smaller generic outfits in Europe and the United States, as well as a group of biotech compa-

nies that see this niche as an opportunity to cut risks and boost operating capital.

Barely a week goes by without some new announcement of a biogeneric strategy. India-based Dr. Reddy's, one of the biggest global generic companies, laid out the outline of a business plan when it announced in late June that it was creating a roster of biogeneric programs, including some for complex monoclonal antibodies. That announcement followed another from Avesthagen, a British biotech with lines of business in food and agriculture, which said it has 11 biologic follow-on therapies in devel-

opment for autoimmune disorders, anemia, asthma, blood solid tumors, and sepsis.

With a regulatory pathway in Europe already established, there's a market waiting to be tapped. Many companies are looking toward Europe as the first key market, but eventually, they say, the world's biggest drug market — the United States — will have to join the game.

"Right now, the percentage of overall drugs that are biotech is about 20 percent, but it's increasing every year," says Theresa Gerard, PhD, a former division director for the Division of Cytokine Biology at the U.S. Food and Drug Ad-

ministration, and a former Amgen director. Now a consultant, Gerrard recently testified before Congress on the issue. "The overall drug budget is huge. And where are the new advances coming from? Biologics. This will happen eventually, and companies right now are gearing up."

GAINING EXPERIENCE, QUIETLY

Most of the developers are playing their biogeneric cards very close to their vests. In the drug industry, lawsuits are a commonly used tactic to either delay or advance a generic. Developers also are loath to signal their strategies to the competition.

Barr partnered with Pliva to develop a granulocyte-stimulating factor (G-CSF) product — a generic version of Neupogen — before it finally bought Pliva. That program to design a less expensive, comparable therapy for stimulating white blood cells is headed into clinical trials this year. The company also is willing to acknowledge that there is another biogeneric product in development for North America. But beyond that, says company spokesperson Carol Cox, mum's the word: "Most companies do not disclose their full product pipelines for competitive reasons," she says.

But even if they're not providing details, would-be biogeneric manufacturers are touting their plans in broad strokes, and analysts have been able to identify those therapeutics that are



PHOTOGRAPH BY GREG KIGER

likely to be the first to go bi-generic.

“There’s a handful of drugs that already have lost their patents,” notes Miller. “Growth hormones are the one people have the most experience with. They’re the easiest to make a generic for and get a regulatory pathway. It’s a small population, but it will give regulators and the marketplace good experience.”

“Interferons for multiple sclerosis are a much bigger market,” he adds. “There’s human insulin for diabetics, and then the colony stimulating factor for people undergoing chemotherapy. And then, around 2012, erythropoietin and other factors like that could have copies.”

For all those products, there will be multiple manufacturers. “Look at what is going on in Europe right now,” says Miller. “A few weeks ago, Hospira announced it was tackling the European pathway for erythropoietin — which, dollar-wise, is a \$10 billion-a-year product.” Hospira CEO Christopher Begley recently suggested that a generic anemia drug could be launched early next year in Europe — some have speculated at a 15 to 25 percent discount — but Hospira says it’s much too early to discuss pricing because of potential factors beyond its control, such as the competitive landscape.

It’s not easy to map out a precise development timeline over which biologics will lose patent protection. Erythropoietins have been on the market since 1989, with an initial European patent expiration dated in 2004. But for many of their franchises, manufacturers have dozens of patents stretching out over the life of the therapy. Each patent represents a legal line that

can be assaulted or defended in the march to a follow-on product.

\$65 BILLION QUESTION

Citigroup Investment Research recently listed a number of biologic therapies it thinks will butt heads in the marketplace with follow-on products (see “Where the action will be,” page 30). Add up the revenue represented by those drugs alone, and you come up with almost \$14 billion a year — in today’s dollars. Not surprisingly, that kind of money is attracting a long line of potential competitors.

Estimates place the global market for biologics at \$65 billion and growing fast. Ed Ogunro, PhD, Hospira’s chief scientific officer, says that in addition to leveraging the company’s development experience, Hospira is “developing strategic comarketing or in-licensing relationships with companies that have established biogenerics programs — which is reflected in our development, manufacturing, and distribution agreements with Stada and Bioceuticals for a biosimilar version of erythropoietin (EPO).” Hospira also has been “purchasing organizations with key biologic expertise and then building the core competency. For example, we acquired BresaGen, an Australia-based biotechnology company committed to the commercial development of protein and peptide therapeutics.”

“There will be an initial rush, and it will be sustainable,” says Mark Merritt, CEO of the Pharmaceutical Care Management Association. A few big generic companies already have made it clear that they’re ready to go after this market, he says, “but big pharma also would dive into

this space. A lot of them are being awfully quiet, but they have too much capacity, don’t have a pipeline, and don’t have a long-term strategy that seems to be working.”

HOW COMPLEX IS THE SCIENCE?

While Gerrard was at the FDA, she heard plenty from biotech companies about the comparability of biologic products. At the time, they were making a case that would ease their way through a manufacturing change-up.

“They were the ones that came and said, ‘We don’t need to do new clinical trials every time we make a manufacturing change,’ because the therapies were already so well characterized. And we agreed,” says Gerrard. “I worked with a lot of biotech companies on product changes, changes in cell lines, how it’s purified.”

That experience will help set the stage for FDA reviews of follow-on products, she adds. But the agency is nevertheless likely to take a case-by-case approach to any approvals.

“There’s not a one-size-fits-all approach,” says Gerrard. “How much data you would need on a bi-generic depends on product complexity and the clinical indication, which includes what we know about safety and efficacy. By the time products come off patent, with 10 to 20 years of experience, we know a lot about their safety and efficacy. These biotech drugs are different than traditional drugs, larger and more complex, but that is addressed routinely at the FDA. These products are assessed with many more tests than a traditional drug and use far more sophisticated tools.” If the FDA doesn’t feel com-

Where the action will be

In one of the most detailed examinations of biologics likely to face follow-on competition by 2015, Citigroup Investment Research topped its list with these agents:

Epoetin alfa (Epogen), the anemia drug that earned Amgen about \$2.5 billion last year in the United States alone, lost European Union patent protection 3 years ago, and begins to lose U.S. patent protections in 2012.

Filgrastim (Neupogen), another Amgen anemia therapy worth \$827 million in U.S. sales, went off patent last year. With Epogen, the two drugs account for about a quarter of Amgen's annual revenue.

Somatropin rDNA (Nutropin) and **somatrem** (Protropin), Genentech's growth hormones, command a \$370 million U.S. market. Genentech's patents expire in 2009.

Human insulin and related products from Novo Nordisk, which, with Norditropin human growth hormone, gained \$897 million in U.S. income. Novo Nordisk's patents expired years ago.

Citigroup followed with an even longer list of biologics that face a moderate threat from generic competition by 2015. That tally includes these blockbusters:

Darbepoetin alfa (Aranesp, Amgen)
Etanercept (Enbrel, Amgen)
Interferon beta 1a (Avonex, Biogen Idec)
Alteplase (Activase, Genentech)
Dornase alfa (Pulmozyme, Genentech)
Imiglucerase for injection (Cerezyme, Genzyme)
Hylan GF-20 (Synvisc, Genzyme)
Algalsidase beta (Fabrazyme, Genzyme)

portable, it will ask for additional data from analytical tests, animal studies, or human clinical studies.

The FDA is getting support from payers and generic players for its position that biologics should be sized up one therapy at a time.

As FDA Chief Medical Officer Janet Woodcock, MD, explained to Congress last March, regulators have been comfortable establishing the comparability of biologics that undergo manufacturing changes. But the complexity of proteins

makes it unlikely that manufacturers, in most cases, could show that their follow-ons are identical to the therapies that they mimic. In other words, it's unlikely they would be AB rated.

"Typically, demonstrating the similarity of a follow-on protein product to a reference product will be more complex, and thus [will] require more new data, than assessing the similarity of products before and after manufacturing changes made by the approved

product's sponsor," Woodcock told the House Committee on Oversight and Government Reform. The amount of data needed, she says, will vary according to its similarity to the approved proteins.

"It is the combination of the protein's amino acid sequence and its structural modifications that give a protein its unique functional characteristics," Woodcock said. "Therefore, the ability to predict the clinical comparability of two products depends on our understanding of the relationship between the structural characteristics of the protein and its function, as well as on our ability to demonstrate structural similarity between the follow-on protein and the reference product."

That may be possible for some relatively simple protein products, she added, but "technology is not yet sufficiently advanced to allow this type of comparison" for more complex products.

That science, though, is advancing, and the agency has signaled its willingness to advance its guidelines with the technology.

"This is a much different industry than chemical drugs, which is why the FDA needs flexibility," says Miller. "You shouldn't look at this as a single entity. It's uniquely different. Monoclonal antibodies, for example, will present a huge challenge to anyone looking to manufacture similar products because of their extraordinary complexity."

"There is no one-size-fits-all approach," agrees Cox at Barr. "On a scale of 1 to 10, G-CSF is a 3 or 4 in terms of complexity. There's science in the public domain to assist in the development of a generic version of G-CSF. We will be proving that our product works the same way in

the body as the brand does."

For now, Barr sees enough opportunity in the field to get its programs underway even before the FDA and Congress lay out the rules. In the meantime, they're not exactly stumbling around in the regulatory dark.

"You've probably got a flashlight," says Cox wryly, "but having a pathway makes it a lot more beneficial."

THE DISCOUNTS

One of the other reasons why so many companies are interested in this field is that it's likely to get started with some relatively high pricing.

"The rationale is that it will cost more to bring these products to market, and that may be true," says Jaeger. "These products are priced exceedingly high and their margins are staggering — 70, 80, 90 percent margins. When you consider these margins, even after investing a few more dollars, this is still quite lucrative."

"Once one generic alternative is out there," says Merritt, "then there will be a host of other generic alternatives, driving prices even lower. Certainly, this will be a system that snowballs into bigger and bigger discounts."

Miller agrees. "When you have a lot of manufacturers, the [price of the] product drops 60 to 90 percent. Because you'll have fewer companies involved initially, we believe the discount will be more like 25 percent. But when you consider that the average prescription for a biologic is \$1,500 for a month's supply, that's about \$400 a month."

A 25 percent initial drop would



PHOTOGRAPH BY JOSHUA CARPENTER

One size fits all won't suffice when the U.S. Food and Drug Administration reviews follow-on products, says Theresa Gerrard, PhD, a former division director for the Division of Cytokine Biology at the FDA. "The agency is likely to take a case-by-case approach."

fit the pattern established by somatropin rDNA (Omnitrope), an FDA-approved growth hormone that Miller calls a "true follow-on." Some monoclonal antibodies "are really complex, immunosuppressing drugs," he adds. "Those will be the most complex" to imitate.

But Jaeger would add that a 25 percent discount is likely to be just the initial bid. Bring in multiple players, and that could swiftly become a 50 percent discount, with even bigger price drops later as the market matures. Ample manufacturing capacity also could help to

drive down the price of these agents.

THE CASE AGAINST COMPARABLES

In this debate, a contrary opinion is never hard to find. Most agree that the level of complexity involved in each development program is likely to play a role in determining just what kind of discounts a new generation of biosimilars would have to offer. To critics of biosimilars, though, the complexity of these therapies is so extraordinary that no significantly less expensive comparable therapeutic can be expected to arrive on the market.

Henry Grabowski, PhD, and several of his colleagues at Duke University's Fuqua School of Business, say the additional clinical research needed to establish the effectiveness of a copycat product is likely to make them considerably more expensive than traditional generics, relative to the innovator product, when they hit the market.¹

Further, for products that are not AB rated, pharmacists couldn't offer them as a substitute of a branded drug, and physicians would specifically have to prescribe them. Under those circumstances, manufacturers also would have to promote them as new therapies rather than biogenerics, making them far more expensive to launch.

"If the discount is small, and patients are achieving good outcomes with the branded product, then generics might get only a small market share," Grabowski said when Duke released his study in May.

¹Grabowski HG, Ridley DB, Schulman KA. Entry and competition in generic biologics. *Managerial and Decision Economics*. 2007 (in press).

Just as big pharmaceutical companies have become more ambitious about rolling out branded generics, some smaller biotech companies, too, see this trend as a good bet. For biotechs — which specialize in high-risk gambles in drug development — tackling follow-ons offers a low-risk approach that can gin some much-needed capital.

Besides, asks Insmmed CEO Geoffrey Allan, PhD, who would be better at understanding the kind of regulatory pathway the FDA is likely to follow in biogenerics than a biotech company?

"If you look at the way a generic company is configured," says Allan, "these guys have been working on small molecules for 20 years. Follow-ons are very complex, living cell systems, and the manufacturing process has a very, very different set of requirements." And a different skill set.

Which is exactly where a company like Insmmed can come in.

MADE IN THE USA

"We have some very early-stage lab bench work going on to characterize these proteins," says Allan. "We would like four to five proteins in IND development in the early part of next year."

For now, Allen is deliberately vague about exactly what he will shoot for, but he has little doubt that the biogeneric revolution is at hand.

"In the early days, the proteins will require clinical trials," says Allan. "In years to come, we'll feel more comfortable about characterizing these proteins, and the requirements for clinical trials will become less and less, depending on the complexity of the protein. There are proteins today that are fairly

simple to characterize, and the FDA would be very responsive to a more limited package of information. And then there are proteins made in mammalian cells that are more complex, and they'll want more information" about toxicology and efficacy.

Biotech companies that offer more precise protein characterizations and a better cost of manufacturing are likely to emerge as important players, says Allan. "Momenta has a set of skills in the characterization of complex molecules, which is at the center of FDA requirements. Can you clearly characterize these proteins to prove you have matched the innovators? As that technology gets more and more sophisticated, platforms and companies that can support that process will play an important role in the future."

It also makes sense for developers like Insmmed to collaborate with the big generic companies, matching biotech's scientific prowess with the bigger players' sales forces.

Allan has heard plenty about the Indian and Chinese generic companies, but he isn't buying the argument that they will be a significant force in the United States. For complex proteins like these, he says, patients will demand nothing but the best — and that means products that are tested, proven, and regulated in the United States.

No one, though, is going to wait until a patent expires to get started.

Says Allan: "You have to get the ball rolling now if you're going to be a player in this market." **BH**

Senior contributing editor John Carroll is a freelance writer and is the editor of Fierce Biotech.