News Feature

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Biotechs go generic: The same but different

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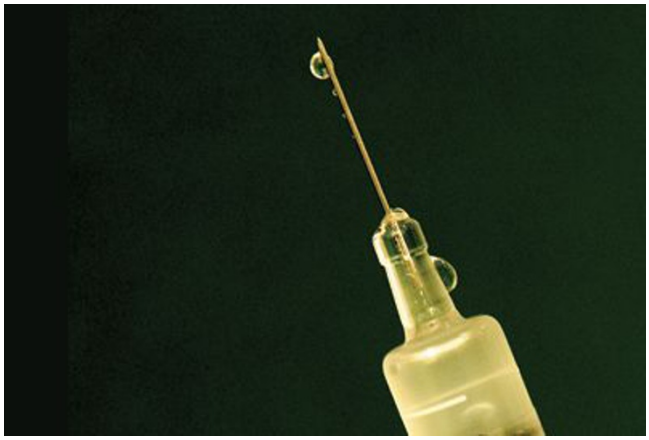
1. Heidi Ledford writes for *Nature* from Boston.

Abstract

As several lucrative protein-based drugs are poised to go off patent, makers of biopharmaceuticals argue that their products are too complex to be reproduced as generics. Heidi Ledford investigates how close 'biosimilar' drugs can get to the original.



D. MARTINEZ/REUTERS/CORBIS

In 2006, Craig Wheeler, then president of Chiron BioPharmaceuticals in Emeryville, California, received a call from across the country that would challenge his perspective on the biotechnology industry. Momenta Pharmaceuticals, a small firm in Cambridge, Massachusetts, was looking for a new chief executive. The company planned to develop new drugs, in part relying on its ability to detect and manipulate the carbohydrate molecules that decorate proteins. But Momenta also intended to create generic versions of therapeutic proteins, something that Wheeler says he thought was impossible.

Unlike the straightforward industrial chemistry techniques used to make small-molecule drugs, the methods of producing and isolating 'biologics' — complex drugs, vaccines or antitoxins made by or from living cells — can be complex and fickle. "The process is the product" was the mantra of the biopharmaceutical world, says Wheeler. Even those who developed drugs in the first place were loath to play around with their methods. "We were deathly afraid of changing anything because we couldn't tell where it would lead," he says.

Debate has flared over whether proteins are too complex to be copied. Even nomenclature for the replicants has changed as a result. Many have discarded the term 'biogenerics' in favour of 'biosimilars', saying that the word 'generic' unfairly implies a perfect replication. And companies and lobbyists on both sides are battling over whether biosimilars should be allowed to follow the fast track to approval available for small-molecule generics, or whether they should undergo expensive clinical trials beforehand. Pending US legislation on the matter could result in billions of dollars being won or lost by companies such as Momenta and the larger biotechnology and pharmaceutical companies that own the ageing patent rights to biologic drugs.

Epoetin alpha or 'EPO', for example, is a recombinant form of the protein erythropoietin used to treat anaemia. It is marketed by several companies under different names, and currently commands a $12-billion market. EPO has already lost patent protection in Europe, and European regulators approved the first epoetin biosimilar in August. EPO and other drugs set to lose patent protection in the near future (see table) are attractive targets for the generics market. Europe has only recently determined a regulatory pathway for such generics, reaching the conclusion that the expedited path for small-molecule drugs is not directly applicable to protein-based therapeutics. Neither the United States nor Japan has a policy in place, and expectations of US legislative action during this session of Congress are fading. Ultimately generics companies want to leave the door open for accelerated reviews that would decide on a case-by-case basis.

Table 1: Patent Expirations For Prominent Biologic Drugs

Full table

Complex challenge

Wheeler certainly had his doubts both about biosimilars and Momenta. The sheer complexity of proteins presents a challenge. For small-molecule drugs, structure can be determined with certainty, and 'the process' is not in itself crucial. As long as the end product is the same as the original and there are no worrisome contaminants, the generic form of a small-molecule drug may often proceed to market without clinical trials.

But proteins are much bigger — sometimes hundreds to thousands of times as large. In some cases the precise structure made by the atoms in the protein and the various chemical adornments it may have picked up cannot be determined. Moreover, the cells that are used to produce the protein sometimes leave a unique fingerprint of sugars and phosphate patterns reflective not only of the cell type but also the conditions under which they are grown (M. Gawlitzek, U. Valley, M. Nimtz, R. Wagner and H. S. Conradt *J. Biotechnol.* **42,** 117–131; 1995). Genzyme for example, another Cambridge biotechnology company with a number of biologic products, recently struggled to gain regulatory approval to scale up production for one of its own drugs. Growing the cells in large tanks was found to change the drug's carbohydrate composition.

A change in the arrangement or type of these sugars can profoundly affect protein activity, directing it to a new tissue, altering its function or alerting the immune system to its presence. Momenta claims that its generics will be aided by new methods to precisely monitor the sugars that decorate many protein surfaces. Understanding the arrangement of these sugars can be crucial to creating a copy of a protein that bears them, but they have been notoriously difficult to study, says Wheeler. "I said, 'They can't know this stuff'." Nevertheless, on a whim, he decided to pay the company a visit.

> “The generics people still really hate me because I was on the other side.”
>
> Craig Wheeler

Wheeler studied the approach, toured the laboratories and came away convinced. Having made the leap to become Momenta's chief executive, he knows he is a rarity among his peers. "The generics people still really hate me because I was on the other side," says Wheeler with a laugh. "I know all the counter arguments."

The dangers of change

The arguments can be compelling, as even small changes in biopharmaceutical production have resulted in tragic consequences. In 1998, European regulators asked Johnson & Johnson, based in New Jersey, to remove human serum albumin from its brand of EPO, called Eprex. Serum albumin, which was purified from human blood at the time, was there only to stabilize the protein during storage, and regulators wanted to eliminate the risk that Eprex might spread infectious agents. So Johnson & Johnson replaced it with polysorbate 80 (also known as Tween 80), a detergent and emulsifier commonly used to keep proteins in solution. Around the same time, the company also introduced a line of pre-loaded syringes.

Nicole Casadevall, a haematologist at Hôtel-Dieu Hospital in Paris, remembers when the first Eprex patients began to get sick. Doctors shipped blood samples to her so that she could test for antibodies against the drug. "I began to see one case, then another, and then I was receiving cases from all of Europe," says Casadevall. In some patients, the immune system branded Eprex a foreign invader and produced antibodies to neutralize the drug. The antibodies not only rendered the therapy useless, they also attacked the endogenous protein — erythropoietin — causing a life-threatening anaemia in at least 200 patients.

It has taken years to determine just what went wrong with Eprex. Johnson & Johnson says that polysorbate 80 caused compounds to leach from rubber stoppers in some of the pre-loaded syringes. Those compounds, the company argued, may have served as an adjuvant, boosting the recipients' immune response to the protein.

In the United States, the original legislation covering generic drugs simply did not anticipate biological therapies, says Janice Reichert, a research fellow at Tufts Center for the Study of Drug Development in Boston, Massachusetts. The only protein therapeutics on the market in that era were insulin and growth hormone. "There was no reason to believe that they would have EPO on the market," says Reichert. "Now we're sort of reaching a critical mass." Biopharmaceuticals represented a $30-billion market in 2005 and are expected to net $70 billion by the end of this decade.

The US Congress introduced legislation to carve out a regulatory path for biosimilars but has been slow to act on it. Patent-holding companies have vigorously opposed the legislation, which is intended to assess biosimilars on a case-by-case basis rather than require trials for every drug. Meanwhile, Europe has approved only two drugs, EPO and human growth hormone, via its biosimilars pathway. Insulin and growth hormone, the only biosimilars marketed in the United States, are covered under present generics legislation because of their long history of use and their relative structural simplicity. All eyes are looking to companies such as Momenta to see what will happen to their first applications for approval in Europe and, eventually, the United States.

Three steps

R. PERACHIO

Creating the impossible: Ganesh Venkataraman (left) and Craig Wheeler of Momenta.

Momenta Pharmaceuticals occupies a building in Cambridge's Kendall Square, just a stone's throw from the Massachusetts Institute of Technology, where the company's founders first developed the carbohydrate technology.

On a recent summer afternoon, one of those founders, senior vice-president of research Ganesh Venkataraman, leans against a fume hood and outlines the company's three-step plan to introduce its technology to the US Food and Drug Administration.

The first step is M-Enoxaparin, he explains, a generic form of Sanofi-Aventis's Lovenox. Lovenox is a complex mixture of sugars — but no protein — produced when the long carbohydrate polymer heparin is isolated from pig intestines and chemically shattered into short sugar chains. The resulting fragments are used to treat deep-vein thrombosis and pulmonary embolism, and Lovenox pulled in €2.4 billion in sales in 2006. Venkataraman says that Sanofi-Aventis declared it impossible to determine more than 70% of the carbohydrate composition of Lovenox. "We can account for every species in that mixture," says Venkataraman. Momenta chemically recreated that blend, and submitted the drug for approval in August 2005. Lovenox is not considered a biopharmaceutical, however. So Momenta's partner, Sandoz — the biogenerics arm of the Swiss pharmaceutical company Novartis — based in Holzkirchen, Germany, has filed for approval under the standard, existing generics pathway. That application, originally projected to take two years or less, is still pending.

The second step is a generic version of Copaxone, a complex peptide mix marketed by Teva Pharmaceuticals in Petach Tikva, Israel for the treatment of multiple sclerosis. Momenta, together with Sandoz, will also file for approval of its version of Copaxone under the existing generics pathway. But after that comes the challenge: the third step involves two protein biologics, still in development, both of them complex proteins, complete with their adorning sugars and other modifications. By then Momenta will have walked through the entire regulatory process, says Venkataraman.

For now, the researchers are working on characterizing complex mixtures and proteins. Using enzymes that cut sugars in specific places, they feed the fragments into one of the whirring mass spectrometers scattered throughout the lab, ready to pick apart a protein's knots of amino acids and forking carbohydrate chains. "These instruments can give you femtomolar resolution," says Venkataraman, proudly indicating the mass spectrometers. Momenta has also developed a computer algorithm that allows its researchers to feed in results as they are revealed. The algorithm then calculates all the structural possibilities, which can then be narrowed down and confirmed through additional experiments.

Momenta is counting on its in-depth structural analysis to promote acceptance of its biosimilars. "We think that chemical characterization is a door opener," says Venkataraman."You first need to establish that you at least chemically understand the molecule." Both Wheeler and Venkataraman are quick to note that they are not opposed to clinical trials of biosimilars. But whether a trial is necessary and what form that trial must take should be decided on a case-by-case basis, they say, not made mandatory.

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Original variability

Biopharmaceuticals are often a mixture of protein variants, differing from batch to batch. "One of the key things that one has to do is to accumulate enough information on the original product to understand its own variability," says Cartikeya Reddy, head of the biologics division at Dr Reddy's Laboratories, a pharmaceutical company based in Hyderabad, India. Since 2001, Dr Reddy's has been producing a biosimilar version of granulocyte-colony stimulating factor (G-CSF), a protein drug used primarily to stimulate white blood cell production after chemotherapy or bone-marrow transplants.

Understanding the variability in the original product is crucial but reproducing the precise mixture poses another challenge. Generics companies may know only the sequence of the protein of interest, and what they can glean from published material, says Reddy. Whenever possible, Reddy says his company uses the same cell line, or another cell line from the same species used by the innovator.

Wheeler says that Momenta's intensive characterization ahead of time gives it a competitive advantage when it comes to making the drug. "We would have a far greater ability to design a work-around than others because of our analytical capability," he says. But Venkataraman admits that the company has not yet worked out a rational design for how to, for example, force a cell to reproduce a particular sugar pattern once it has been identified. "We're trying to get to it," says Venkataraman. "It's a frontier that hasn't been tackled."

Venkataraman's ultimate goal is to use the structural information about a product and its biosimilars to rationally predict whether the differences between the two are likely to have an impact on toxicity or efficacy. Nevertheless Momenta's analyses will easily be overshadowed by real-world examples of the dangers involved. Johnson & Johnson's Eprex is so often cited in reference to biosimilars that the details of the incident sometimes get forgotten. Eprex was not a biosimilar, and problems associated with manufacturing changes are endemic to all biopharmaceuticals, not just biosimilars. Moreover, a clinical trial wouldn't have revealed Eprex's problems. But a simple chemical analysis might have shown the presence of the leachates in the syringes. "Eprex is an example that's good to scare people," says Venkataraman. "It raises this fear of the unknown."

But the tale of Eprex also highlights the unpredictability of the human immune system. With the exception of G-CSF, every known protein-based drug tested prompts antibody production, usually at a subclinical level. Models that aim to determine whether a particular change in protein structure will tip the immune response from subclinical, to clinical, have performed poorly. "There doesn't seem to be any underlying pattern to what's immunogenic and what's not," says Robin Thorpe, head of the biotherapeutics group at the National Institute for Biological Standards and Control in Potters Bar, UK. "You're going to have to do some kind of study in humans." Because of the low frequency of immunogenic responses, as seen in the Eprex case, such trials are likely to include post-marketing surveillance.

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Venkataraman agrees that post-marketing surveillance will be important for biosimilars. "There are still several leaps that have to happen to get to the same level as small molecules," says Venkataraman. "The science is evolving to get there, but the lawmakers need to create the incentives. They shouldn't base legislation on today's technology."

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