

## BUSINESS

# Path to approval proves rocky for copycat biodrugs

Attempts to copy the first generation of biotechnology drugs are facing fierce resistance, as **Meredith Wadman** reports.

**P**roducers of generic drugs are embarking on an epic battle to win regulatory approval for the first copies of the complex biological drugs that underpin the biotechnology industry.

Next week, a European Union law comes into effect that will define a pathway to the market for generic versions of the drugs, and the European Medicines Agency is expected to give its first approvals of such drugs sometime next year.

These could include a copy of human growth hormone and the hepatitis C treatment interferon- $\alpha$ , made by Swiss company BioPartners. Another possible candidate is a version of California-based Amgen's blockbuster anaemia treatment erythropoietin, made by Croatian drug company Pliva.

But the prospect of biogenerics is viewed by the biotechnology industry as a significant threat now that the patents on the founding generation of its products are expiring. And the industry is using every argument it can find — including possible safety concerns — to press regulators for high hurdles to their approval.

"We believe in biosimilars," says Roger Perlmutter, Amgen's head of research, using a term the industry prefers for generic biopharmaceuticals. "But from a public-health point of view, you don't want to put molecules on the market that are less safe" than the ones they're meant to imitate.

The makers of generics counter-charge that the industry is using scare tactics to protect lucrative markets. "There is no reason to say that these products are any more risky" than standard drugs, says Andreas Rummelt, chief executive of Sandoz, the generics division of Novartis and one of the world's top two generics manufacturers. "Patients and physicians

need to have access to safe and effective follow-on products once patents expire."

But as a regulatory path forward opens in Europe, its US equivalent remains elusive. The Food and Drug Administration (FDA) seems to have stalled in its efforts to find one — prompting Sandoz to sue it a couple of months ago. The company is demanding action on its 28-month-old application to bring a generic version of human growth hormone to market (see *Nature Rev. Drug Discov.* **4**, 798–799; 2005).

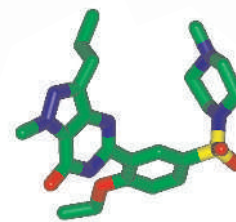
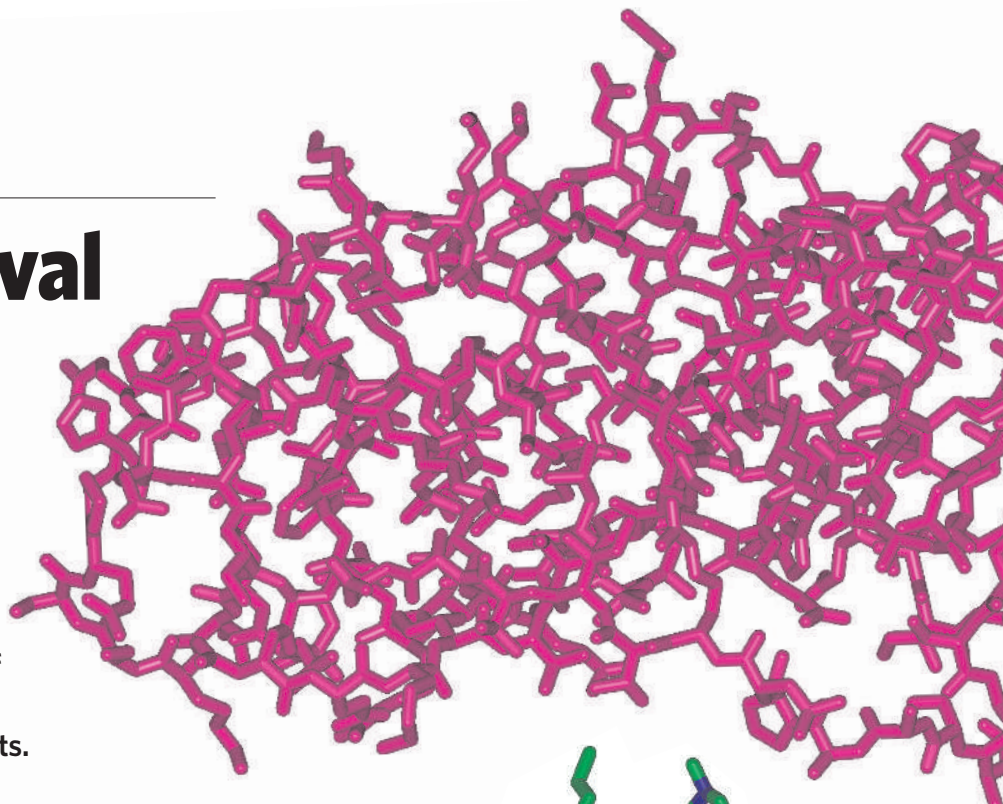
"Scientists at the agency have said the application can be approved," asserts Eric Pomerantz, general counsel at Sandoz. "There are no technical, scientific, regulatory or legal reasons for not approving it."

## Plan goes slow

Almost three years ago, then-FDA commissioner Mark McClellan pledged to move ahead with biogenerics, but this hasn't happened yet. Helen Winkle, director of the agency's Office of Pharmaceutical Science, told a generics industry meeting in Washington DC last month that the agency is "struggling" with the issues raised by biogenerics approvals.

It is not hard to see why. The distinctive feature of biological drugs is their size and complexity. Most are large proteins with appended sugar groups — such as erythropoietin and the multiple sclerosis treatment interferon- $\beta$ . They are typically 100 to 1,000 times larger than traditional drugs (see above), and are produced in cultured mammalian cell lines, with their inherent variability, rather than in test tubes.

Because of the compounds' chemical and biological complexity, their purification can involve hundreds of steps, rather than the couple of dozen often required for conventional drugs. Furthermore, almost all



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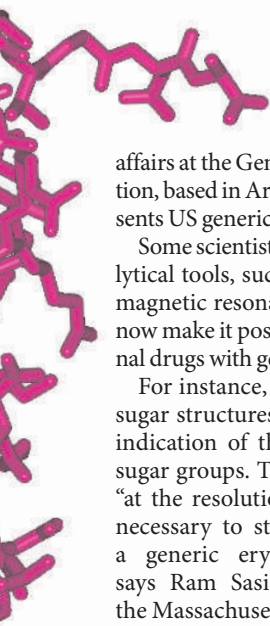
**Little and large:** biological drugs such as erythropoietin (purple), used to treat anaemia, are far larger and more complex than standard drugs such as the impotence treatment sildenafil (Viagra).

biological compounds may provoke rare but serious immune reactions. This immunogenicity adds another layer to the safety assessment required for both innovative and imitative biological drugs.

That has strengthened the hand of the biotechnology industry, which is arguing in the United States that generics makers should be required to go through many of the costly clinical trials demanded of innovator companies when they first bring biological drugs onto the market.

In the case of traditional chemical compounds, "the generic drug is the same as the original, and will behave the same way as the original," argues Amgen's Perlmutter. "You can't do that with biosimilars. Every product is different. And you must test that product [in people] to ensure efficacy and safety. You can't assess that product by any physical test."

The generics industry hotly disputes this last contention, and is calling for a "flexible, abbreviated, approval process" similar to the speedier approval process created for standard generic drugs in the United States by a 1984 law. "An abbreviated approval process is clearly within the scope of current science," says Gordon Johnston, vice-president for regulatory



affairs at the Generic Pharmaceutical Association, based in Arlington, Virginia, which represents US generics makers.

Some scientists concur, saying that new analytical tools, such as high-resolution nuclear magnetic resonance and mass spectrometry, now make it possible to closely compare original drugs with generics, at least in some cases.

For instance, mass spectrometry can map sugar structures on proteins, giving a better indication of the locations and identity of sugar groups. This mapping is now possible "at the resolution that the FDA would feel necessary to study the difference between a generic erythropoietin and Amgen's", says Ram Sasisekharan, a bioengineer at the Massachusetts Institute of Technology in Cambridge, who has studied the feasibility of such comparisons.

And just as biological drugs vary greatly, so too does the range of analytical tools available to establish the bioequivalence of a generic to its original patented analogue. Thus it is widely accepted that the regulatory requirements for biogenerics will have to be assessed on a case-by-case basis.

### Money matters

But if these requirements become too onerous, generics makers may walk away. Already the cost, risk and skill required to enter the area makes biogenerics a challenging target for all but a few companies, says David Evans of Data-monitor, a London-based business information company.

There is one other thing that all sides agree on: plenty of money is at stake. For instance, Pfizer, the original maker of human growth hormone, had \$239 million in US sales of the drug last year according to data firm IMS Health — even though the key patent on the drug has long since expired. Those sales could be seriously eroded if the US District Court rules in favour of Sandoz in the current lawsuit, and the FDA approves Sandoz's generic version.

"This is a huge new opportunity for generics companies — especially as generics growth is slowing in mature markets such as the United States," says Evans. He estimates that the market for drugs that could be replaced by biogenerics was worth \$20 billion last year.

In the meantime, US regulators will have to determine how to handle approval applications. "A lot of these molecules are going off patent," says Sasisekharan. "This is something we need to deal with. We can't avoid it. We can't postpone it. The most important issue is to figure out the path forward." ■

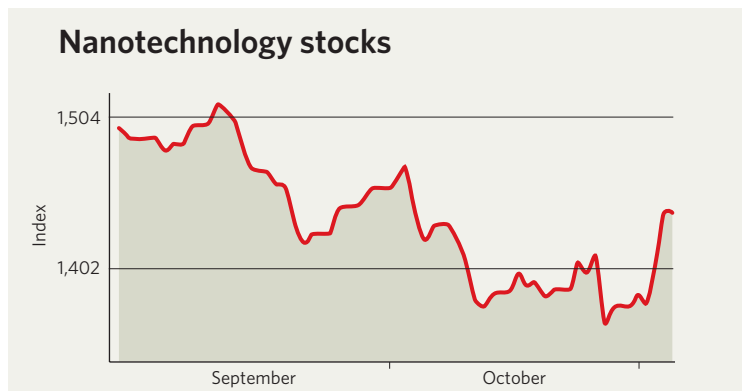
## IN BRIEF

**VIOXX VERDICT 2** Merck scored a major victory in the second US lawsuit brought over the safety of its painkiller Vioxx. A nine-member jury in a New Jersey court found on 3 November that Merck had fairly marketed and fairly represented the risks of the painkiller. Vioxx was withdrawn in September 2004 after it was found that prolonged use increased the risk of heart attack and stroke. The jury concluded that the drug did not cause the heart attack of Frederick Humeston, a 60-year-old postal worker, in 2001. Merck lost the first Vioxx lawsuit in Texas in August (see *Nature* 436, 1070; 2005). Its stock increased by 4% to \$29.48 on the latest news.

**HIRING BINGE** Samsung says it will employ an extra 26,000 researchers in the next five years as part of its drive to consolidate its position as one of the world's largest electronics firms. Lee Yoon-woo, chief technology officer of the Korean company, said that he would double the research and development workforce to 52,000 as the company moved to secure its expansion into areas such as mobile phones and laptop computers. He made his comments at a jamboree on 3–4 November, held for several hundred financial analysts, to discuss Samsung's expansion plans.

**CASH DASH** The average total pay package for research and development chiefs of US biotechnology companies jumped by 12% in 2004, according to an analysis conducted by *BioWorld Today*, a biotechnology newspaper based in Atlanta, Georgia. Vice-presidents of research and development at 145 companies averaged \$366,000 in salary plus bonuses, up from \$326,000 in 2003. Total pay for chief executives rose 5%, to \$596,000, whereas that for chief legal officers at biotech firms dropped a little, to \$242,000.

## MARKET WATCH



Nanotechnology stocks have taken a tumble this autumn, with a couple of particularly troubled stocks compounding the problems of a generally weak market in technology stocks.

The Lux Nanotech Index, which comprises companies supplying nanotechnology products as well as some major industrial companies that rely heavily on nanotechnology, dipped close to its lowest point since 2003 at the end of last month.

"The index has been down, like the broader market," says Peter Hebert of New York-based Lux Research, which compiles the index, adding that he thinks it will rise again soon. Hebert's company has just launched a fund called the PowerShares Lux Nanotech Portfolio, which will allow investors to track the performance of the index.

The weakest performers over the past two months included Skyepharma, a supplier of nanotech-based drug delivery systems based in London, and Headwaters, whose main subsidiary, Nanokinetix of New Jersey, makes catalyst components.

Skyepharma announced "disastrous" first-half results in September, Hebert says, and a share offering failed to attract buyers at the anticipated price, causing its shares to dive. Headwaters fell back sharply from a short-lived summer peak attained on a good set of financial results.

Hebert predicts that stock in the companies represented by the index will move up again "as nanotechnology becomes a significant component of their businesses", and says that subdued stock prices make this a good time to get into the new fund. ■

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