DRUG DEVELOPMENT

‘Biosimilar’ drugs poised to penetrate market

Draft regulations will pave the way for copycat antibodies and other large molecules.

BY HEIDI LEDFORD

When is a copy good enough to be treated as the real thing? In recent days, regulators on both sides of the Atlantic have been grappling with the question as they try to develop guidelines that will expand the development of ‘biosimilar’ drugs: copycat versions of complex biological drugs, such as antibodies and other therapeutic proteins.

Biosimilars differ from generic drugs because their active ingredients are huge molecules with intricate structures. Such molecules are nearly impossible to replicate in every detail — even in the hands of the original manufacturer, minute variations in production yield slight differences. Unlike the relatively simple construction of a small-molecule drug, making a biosimilar is more like placing a complicated family recipe in the hands of a new chef. The overall result may be roughly the same, but it is not exactly how mother used to make it — and it may not precisely match the safety and therapeutic effects of the original.

SANDOZ

Growth medium: Sandoz hopes to benefit from biosimilars.

Biosimilar medicines already have a toehold in Europe, but last week regulators there at the European Medicines Agency (EMA) hammered out draft guidelines that could drastically expand the market for these compounds. And in Washington DC, the US Food and Drug Administration (FDA), which in March received the authority to approve biosimilars as part of President Barack Obama’s health-care reforms, is holding a public meeting this week to gather opinions on how it should evaluate such drugs. The new health-care act defines biosimilars as ‘highly similar’ to the original product; the FDA must now decide what that means, and how much extra testing will be required of a biosimilar before it can be marketed.

“This legislation was anticipated for so many years,” says Deborah Shelton, a partner at the law firm Sheppard Mullin Richter & Hampton in Washington DC. “Now it’s here and we’re still in a black hole.”

Meanwhile, some companies see biosimilars as a low-risk way to bolster dwindling drug pipelines. Biological drugs are expensive, and even with a 20–30% reduction in the original price, biosimilars can still pull in a huge profit. “Not a day goes by when you don’t read a press release saying some company is getting into biosimilars,” says Michael Malecki, head of the biosimilars group at Decision Resources, a market-research firm based in Burlington, Massachusetts. But if regulators require extensive testing, biosimilars could falter. For example, in 2006, the Croatian drug maker Pliva decided to abandon its copy of the best-selling anaemia drug erythropoietin after learning that the EMA would require more clinical trials than the company had anticipated.

Europe’s framework for approving biosimilars was established in 2004, and copies of three drugs have already hit the European market. Some observers expect the FDA guidelines to be broadly similar to the European ones, which generally require clinical tests of biosimilars, but the extent and nature of the tests depends on the class of drugs being copied. A relatively simple and familiar molecule such as insulin, for example, may require less testing than a complex protein carrying several chemical modifications.

Yet biosimilars have had a slow start in Europe, says Huub Schellekens, who studies pharmaceutical development at Utrecht University in the Netherlands. The three drugs copied in Europe — human growth hormone, erythropoietin and granulocyte colony-stimulating factor, another treatment for anaemia — were selected because they command a huge market, their patents had expired, and they are relatively simple to make. But these drugs were already embroiled in a price war with second-generation longer-acting versions. Furthermore, the inability to tap the US drug market may ultimately have stifled industry enthusiasm. North America accounted for 39.8% of world pharmaceutical sales in 2009 compared with 30.6% for Europe.

At a meeting on 27–28 October in London, regulators at the EMA worked to finalize draft recommendations for biosimilar versions of the biggest moneymakers of the biological world: highly specific

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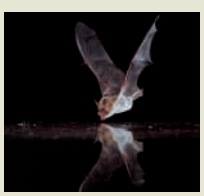

D. NILL

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TOP FIVE BEST-SELLING MONOCLONAL ANTIBODIES IN 2009

Once these biological drugs go off patent, they may inspire a wave of biosimilar imitations.

Name	Brand name	Target	Primary indication	2009 sales (US$)	Estimated patent expiry
Infliximab	Remicade	TNFα antagonist	Rheumatoid arthritis	5.98 billion	2011 (US) 2014 (5 EU countries, Japan, global)
Bevacizumab	Avastin	VEGF	Colorectal cancer	5.73 billion	2019 (US) 2018 (EU) 2020 (Japan)
Rituximab	Rituxan/MabThera	CD20	Non-Hodgkin's lymphoma	5.61 billion	2016 (global)
Adalimumab	Humira	TNFα antagonist	Rheumatoid arthritis	5.49 billion	2016 (US) 2018 (5 EU countries, Japan, global)
Trastuzumab	Herceptin	HER2/neu receptor	Breast cancer	4.85 billion	2015 (US) 2014 (EU, global) 2016 (Japan)

antibodies called monoclonal antibodies. In 2009, monoclonal antibodies brought in US$36.4 billion in sales worldwide. "These are blockbusters," says Falk Ehmann, the scientific secretariat for the Working Party for Biosimilar Medicinal Products at the EMA. "They are the hot molecules." The prospect of copying them — and selling the copies on the lucrative US market — could finally animate European biosimilars efforts, says Schellekens. The guidelines will be presented to the EMA's Committee for Medicinal Products for Human Use next week and, if accepted, will then be posted for public comment.

The first biosimilar monoclonal antibody is likely to be a copy of the cancer drug rituximab. Initially developed by Biogen Idec in Cambridge, Massachusetts, rituximab is expected to be one of the first monoclonal antibody therapies to go off patent, which Malecki says it may do in Europe as early as 2013. It is also one of the best-sellers: in 2009 the drug earned about $5.61 billion worldwide (see 'Top five best-selling monoclonal antibodies in 2009'). In May, the Israeli generics maker Teva Pharmaceuticals announced that its biosimilar version of rituximab is ready for clinical trials, which are now expected to conclude in August 2011.

All biosimilars will probably require some clinical trials in the United States, says Mark McCamish, head of global biopharmaceutical development at Sandoz, a generics company based in Holzkirchen, Germany, but the FDA should expect a lively debate about how extensive those clinical trials must be.

On one side of this debate will be companies such as Denmark's Novo Nordisk, which derives at least 90% of its income from biologics and has no biosimilar programme. Jim Shehan, the company's general counsel for North America, urges stringent clinical trials that pit a biosimilar head-to-head with the product it aims to replace.

Meanwhile, McCamish and others with a vested interest in marketing biosimilars — Sandoz already sells three in Europe and is developing about a dozen more — will argue that the FDA should use the variation in the original drug as a guide. Biologics are so complex that minor manufacturing changes often change the properties of the drug.

"There's going to be a range of how much a biosimilar company would have to do," says McCamish. "If the biosimilar falls within the goalposts of the originator's own changes, then you should have very abbreviated clinical testing." ■