SPECIALTY PHARMACY NEWS

FDA Looks at Biogeneric Issue, but Action Unlikely in Near Term

Payers are looking at applying formulary strategies such as generic substitution to many injectable drugs, but the biggest cost savings from generic substitution will be out of reach until generic standards are developed for biologically based products. FDA is moving ahead with the preliminary research needed to determine a regulatory framework for approval of bio-generics, but stakeholders involved in the debate say that the United States' first approved biogeneric product still is several years away at best.

That's because of the difficulty involved in proving biosimilarity in biologics, and because the name-brand pharmaceutical industry is arguing for a tough standard. FDA — although it has held one workshop on the issue and will hold another next January — is unlikely to act until it gets legislative guidance from Congress. And Congress is unlikely to act until it sees a "critical mass" develop — which may not come until the Medicare prescription drug benefit takes full effect and begins to take its toll on the federal budget, says Washington, D.C.-based Foley & Lardner attorney Stephen Bent, who has been involved in the issue of generic drugs from the beginning.

Big Difference From Chemical Drugs

Biogenerics are generally large protein molecules derived from living cells, as opposed to smaller, chemical molecules derived from a chemical process that can be precisely controlled. For chemical products, proving the essential similarity of the active ingredient and the bioequivalence of the drug to the brand-name product is pretty straightforward, because a small molecule can be precisely characterized.

But proteins are more difficult to characterize than small molecules. And consequently, pharmaceutical regulatory agencies in North America, Europe, Australia and New Zealand have been debating how best to determine bioequivalency or biosimilarity.

Meanwhile, in the unregulated markets, which include Korea, India, China and South America, several companies already are selling epoetin and human growth hormone (HGH), with more products to come, says Richard DiCicco, president of Technology Catalysts Inc., a consulting firm in Falls Church, VA.

But in the regulated markets, only one biogeneric has been approved: Omnitrop, an HGH from Novartis' Sandoz unit, was okayed for sale in Australia earlier this year. But $10 billion worth of biologics will go off patent between now and 2011, which means that the issue is coming to a head, says Bent.

"There's plenty in the pipeline," adds DiCicco. Epogen (epoetin alfa) comes off patent this year, Novolin (insulin), Protropin (somatrem) and Activase (alteplase) come off patent in 2005, while Neupogen (filgrastim) comes off patent in 2006. Humulin (insulin) already is off patent, as are Avonex (interferon beta-1a) and Humatrope (somatropin).

Twenty years ago, at the time that Congress developed a framework for approval of generic drugs produced by the fledgling generic industry, biologics were barely a blip on the horizon, says

Bent. Because the issues involved were so difficult — techniques for determining biosimilarity hadn't been created — lawmakers chose not to deal with biologics at all, he says.

Premarin is not a specialty drug, but the saga surrounding Barr Laboratories' efforts to win FDA approval for a generic version of Premarin foreshadow the difficulties surrounding biologics. Barr Laboratories has tried repeatedly to market a generic version of Wyeth's Premarin, which contains more than 50 estrogens isolated from pregnant mares, but has been forestalled because of FDA's delays in determining how to prove bioequivalency.

FDA is forging ahead to gather the information it eventually will need for its regulatory standard. The agency held a workshop on Sept. 14-15 in order to gather information from the various stakeholders in the debate, and pledged to hold a second two-day seminar in January. After that, FDA promises to begin to consider guidelines for approval of these products.

Some companies already have filed for approval of their products under existing guidelines for New Drug Applications or Abbreviated New Drug Applications. Novartis, for example, has filed for approval of its HGH product, Omnitrop, while Teva Pharmaceutical Industries Ltd. has filed for a version of insulin. However, FDA hasn't given any indication of whether it will consider these products without an existing regulatory framework.

Bent says that FDA won't act without guidance from Congress. "Right now, there's simply no basis for negotiated settlement — the two sides don't have anything to negotiate with," asserts Bent. It's possible that Congress might offer the pharmaceutical industry an additional patent extension in exchange for support on generic biologics, but it's not going to happen quickly, he says.

The new Medicare drug benefit — which doesn't take full effect until 2007 — could in fact be the catalyst for action on this issue, Bent says, adding, "I don't think Congress will act until the prescription drug benefit costs click in in three or four years."

BIO, PhRMA Argue for Tough Standard

Biotech industry officials argue that the agency must impose a far more stringent standard than the one it uses for chemically based generics. "The people who like to make the case that there's no consensus [in how to regulate these drugs] say that the product is the process," says Bent. He adds that in the case of biologics, the response that a biologic product creates in a patient "isn't always a very well-understood process," and can be difficult to determine via assays.

This is exactly what the Washington, D.C.-based Biotechnology Industry Organization is arguing. In testimony before the FDA workshop in September, BIO's managing director for scientific and regulatory affairs, Sara Radcliffe, argued that protein products are more complicated and more fragile than are most traditional "small molecule" drugs, and that the nature of a protein product is closely dependent on the starting materials and processes used to make that product.

"To ensure consistency in the characteristics of the final product, and to ensure consistent safety and effectiveness, the source material, manufacturing process, formulation and storage conditions must be carefully kept within specifications and control limits that have been empirically determined by the manufacturer and presented for regulatory approval," said Radcliffe. In addition, she said, protein products are difficult to characterize.

BIO argues that — because a follow-on manufacturer can never duplicate exactly the innovator's process — FDA should apply a very stringent standard to such products and require "all of the preclinical and clinical data needed to support the label being claimed."

On the other side, Generic Pharmaceutical Association President and CEO Kathleen Jaeger told FDA at the same hearing that BIO and the Pharmaceutical Research and Manufacturers of

America (PhRMA) are "clearly dragging their feet into the world of competition by undertaking efforts to block consumers' timely access to affordable biopharmaceuticals."

Jaeger said that the science exists now to determine bioequivalency of some biopharmaceuticals, and that because of the cost of these drugs — more than $10,000 a year in many cases — the agency should move quickly to build a framework for approval of generic versions.

"The FDA has said [to those fighting for a strict standard]: 'Put up or shut up. If there's a real risk, give us some examples of what you're talking about'," says Bent, who adds that the federal agency is looking for specifics on what the "parade of horribles" claimed by the branded biologics industry would look like. BIO and PhRMA have promised to provide these examples in time for the next FDA workshop on this topic, and "the rubber's going to meet the road then," says Bent.

EU Already Has Framework in Place

The European Union this year laid out a regulatory framework for what a generic manufacturer must do in terms of studies and findings to win approval of its generic biotech drug, says DiCicco. This information must include "a full characterization of the molecule as 'biosimilar'," he says. In addition, the company must perform a small study with a specified number of patients — for example, for EPO a company must include 500 patients — in order to show biosimilarity, he notes.

This process takes about one year from application to approval, according to DiCicco.

Bent notes that this process "isn't going to make it all that much easier for follow-on biologics to come on the market. If you're doing a clinical trial, it's not a generic anymore. You're talking some money and a lot of time." FDA has considered this same type of framework for approving generic biologics, and may well adopt something similar, says Bent.

The European Commission in April turned down Novartis AG's application for approval of Omnitrop, its generic HGH. But that denial was based on filing problems, rather than on issues with the product itself. Although Novartis has filed suit against the commission, most observers expect that the case will not hold up approvals of other biopharmaceuticals.

DiCicco says that — as EPO comes off patent in the next year in the European Union — 13 companies are lined up waiting to file for approval of their biosimilar products within the next year and a half. "Some of these may already have done the characterization of the molecule and the study," he says.

One interesting fact: Three of these 13 companies are specialty pharmacy companies, not generic manufacturers, he says, adding that "the opportunity isn't so much for traditional generic companies. It's more for specialty pharmacy companies."

In the U.S., DiCicco says, "this is an incredible opportunity for specialty pharmacy companies. They can take those European filings and convert them to an NDA [i.e., New Drug Application] practically overnight."

Marketing for Biogenerics Not Traditional

Marketing for biotech generics is likely to present different issues than does marketing for chemically based generics. That's because if a drug is approved as a biosimilar it can't be directly substituted for the name-brand drug that it is seeking to replace. Instead, the situation is more analogous to "me-too" drugs, where a plan will need to consider which of several similar, competing drugs to include on its formulary.

In Europe, generic companies are used to this, says DiCicco. "Every single generic company in Europe has a sales force," he says. "The European generic companies are well equipped to market a biosimilar under their own trade name, just like they would market an aspirin under their own trade name."

But in the U.S., of course, it's a different story. Generic companies don't have tremendous sales forces and are not used to promoting their products through the traditional, name-brand drug channels.

"If we have to adopt the European approach, you'd see a new strata of generics come on the market," says Bent. The drugs couldn't be substituted for brand-name drugs; instead, they'd need to be marketed on their own merits, almost like "me-too" drugs, he says.

Once these generic versions of biologics are finally approved, it will mean a different playing field for the companies that produce them. "If they're not going to be substituted in Europe and not in the U.S., they'll need to compete on price and brand," says DiCicco.

His company, Technology Catalysts, is seeking a third way for biogenerics to compete: on drug delivery method. "All of these drugs are given by injection," he says. "We're developing needle-free biosimilars."

Technology Catalysts, which does no manufacturing itself, has partnered with a manufacturer of needle-free drug delivery devices and with a manufacturer of generic HGH (DiCicco declined to identify either company). The goal, he says, is to file for approval of a needle-free HGH product in November 2005 in Europe, and to file for approval in the U.S. once the regulatory framework becomes better established.

Will the U.S. approve a biological generic in this decade? DiCicco says he believes the answer is yes. "Most of the knowledgeable people in this industry would say it will happen within three years," he says. However, he notes that knowledgeable people said the same thing three years ago.

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