Generic Biologics Still on Congress' Radar Screen

A bill that would allow for the production of generic insulin likely would not affect most insulin users.

BY JOHN R. BELL
Associate Editor

A Congressional push for fast-track approval of generic biologics likely won't have any effect on insulin costs for most patients with diabetes, mainly because the types of insulins most patients use now are still on patent, according to an expert.

Patents for several insulin formulations—both regular and NPH—have expired in this decade: for example, Humulin (Eli Lilly & Co.) in 2001 and Novo-Nordisk's Novolin in 2005. However, the Food and Drug Administration has not issued its in-progress guidelines for approval of several new follow-on biologics, each of which is claimed by its manufacturer to contain the identical active ingredient as the approved product and therefore, they argue, should not need additional testing.

Debate remains as to whether existing regulations should allow for approval of such products. Applications for new biologics are regulated by the 1944 Public Health Service Act. However, small-molecule drug products are instead regulated by the Food, Drug, and Cosmetic Act of 1938, which allows the accelerated approval of new drugs based on prior evidence. In 2006, the FDA approved a follow-on of the recombinant human growth hormone Omnitrope, manufactured by Sandoz, but the agency said it considered that product to be not a generic but instead a "follow-on protein product," because it had made no determination of therapeutic equivalence.

According to the FDA, other proteins that have received fast-track approval in this manner include GlucaGen (glucagon recombinant for injection), Hylenex (hyaluronidase recombinant human), Hydase and Amphadase (hyaluronidase), and Fortical (calcitonin salmon recombinant) nasal spray.

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While the argument over existing regulations continues, some members of Congress are pushing forward with new proposals. A member of his staff confirmed that Rep. Henry Waxman (D-Calif.) will reintroduce a bill submitted last session, H.R. 6257, that would effectively force the FDA to fast-track approvals of follow-on generic biologics—a bill that some believe will lead to the production of generic insulins and thus lower costs for state governments and insurers. The date of reintroduction has not been determined, the staff member said.

A Senate version of the same bill, S. 4016, was sponsored by Sen. Hillary Clinton (D-N.Y.), with Sen. Charles Schumer (D-N.Y.), Sen. Patrick Leahy (D-Vt.), and Sen. Debbie Stabenow (D-Mich.) as cosponsors. In each house of Congress, the bill was referred to committee but expired in December, when the 109th Congress ended, as do all pending bills not passed before the end of a session.

On another front, two Democratic Congressmen from Michigan, John Dingell and Bart Stupak, wrote to FDA Commissioner Dr. Andrew von Eschenbach at the end of January, lamenting the "failure of FDA to use its existing authority to approve generic biopharmaceutical drugs." The Congressmen also requested a list of the follow-on biologics for which the FDA has received abbreviated approval applications. The letter noted that the House Energy and Commerce Committee, which Rep. Dingell chairs, would use the requested information in its ongoing investigation into the overall generic drug approval process.

Dr. Bill Law Jr., immediate past president of the American Association of Clinical Endocrinologists, said in an interview that confusion in the lay media about the difference between nonanalogue human insulins and analogue human insulins has ended up helping these legislative efforts. "It's only after the 20-year patent law has expired [on a human analogue insulin] that it would be eligible for a generic company to come in and make one," said Dr. Law, an endocrinologist in private practice in Knoxville, Tenn. As to the nonanalogue varieties, "unless the companies can sell one for less than $16 a vial, it's not going to change the cost" to the patient, he said. This confusion has given rise to false hopes for a drastic reduction in insulin costs for most patients, according to Dr. Law.

Regarding approval of follow-on biologics, "it's totally different from making a pill, where you have complete control over what goes in that pill," he said. "Everything else that's in that pill was specifically added by the manufacturer of that pill, whereas the analog insulin we're talking about making is created in a biologic system, like a yeast cell or bacterium, and then has to be highly purified to eliminate the cellular contaminants."

Thus, the safety of a generic biologic cannot be established as easily as that of a drug, Dr. Law said. "Good science requires proof of safety. From my standpoint as a doctor treating patients, it's not enough just to show that in that bottle there's a certain amount of insulin. I want to know what else is in that bottle that came from a bunch of yeast and bacteria."

In addition to the Congressional bill, a group of governors petitioned the FDA last summer, urging it to release its guidelines for the approval of follow-on biologics, which the agency began in 2002. The petition was supported by various consumer groups and the Generic Pharmaceutical Association, but the agency has not yet responded. ■

Lifestyle, Drug Strategies Found Equal In Preventing Diabetes in IGT Patients

BY JONATHAN GARDNER
London Bureau

Drug and lifestyle interventions reduce the risk of type 2 diabetes among patients with impaired glucose tolerance, and advice on diet and exercise is at least as effective as prescribing medication, Clare L. Gillies and associates reported.

The meta-analysis of 17 randomized controlled trials involving more than 8,000 patients with impaired glucose tolerance showed that pharmacologic and lifestyle (diet and exercise) interventions reduced the risk of progression to diabetes. Pooled hazard ratios were 0.44 for treatment with the antiobesity drug orlistat vs. placebo, 0.51 for lifestyle intervention vs. no intervention, and 0.70 for oral diabetes drugs vs. placebo.

"The increase in obesity and decrease in physical activity in Westernized societies are strongly linked with the increase in the prevalence and incidence of type 2 diabetes," wrote Ms. Gillies, a medical statistician at the University of Leicester (England), and colleagues. "Lifestyle interventions, which aim to reduce obesity and increase physical activity, help to directly address these risk factors."

In the control arms of the studies, the cumulative incidence of diabetes over 5 years was 37.1%. Based on the risk reduction in the intervention groups, the absolute reduction in diabetes incidence was 18.4 percentage points with orlistat, 15.8 percentage points with lifestyle intervention, and 9.3 percentage points with oral diabetes drugs (BMJ 2007 Jan. 19 [Epub doi:10.1136/bmj.39063.689375.55]).

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The number of patients needed to treat to avert or delay one case of diabetes was 5.4 for orlistat, 6.4 for lifestyle, and 10.8 for oral diabetes drugs.

The researchers acknowledged that the results for lifestyle interventions were affected by the baseline body mass index of patients in the trials. For every one unit of mean body mass index of the trial participants, the hazard ratio dropped by 7.3%, which increased the effective risk reduction of the intervention.

Adverse events ranged from 1.2% to 91% in the 10 studies that included pharmaceutical interventions, the researchers wrote.

"For pharmacological interventions, adverse effects need to be fully understood to enable potential harms and benefits to be assessed," they wrote. "Also should what is fundamentally a lifestyle issue really be treated with a lifelong course of medication? As compliance is the key to the success of lifestyle interventions, strategies to assist compliance need to be carefully thought through and implemented." ■

More Complications Seen With Comorbid Apnea

Salt Lake City — Obstructive sleep apnea in patients with well-controlled type 2 diabetes appears to be associated with increased risk of diabetic complications, Dr. Semaan G. Kosseifi said at the annual meeting of the American College of Chest Physicians.

This finding suggests there is merit in routine early screening of diabetic patients for obstructive sleep apnea (OSA). It's possible—although as yet unproven—that treating OSA in diabetic patients will prevent or slow progression of diabetic macrovascular complications, thereby reducing the level of cardiovascular risk, according to Dr. Kosseifi of the Quillen College of Medicine, Johnson City, Tenn.

He presented a retrospective observational study involving 127 patients with well-controlled type 2 diabetes who were referred for sleep studies. Their mean age was 61 years, with a mean hemoglobin A_{1c} of 6.5%. Fifty-six percent had microalbuminuria, and 35% had microvascular complications. Thirty-eight percent had severe OSA.

Severity of OSA as reflected by the apnea-hypopnea index showed a powerfully significant direct relationship to diabetic microvascular and macrovascular complications as well as to microalbuminuria. Moreover, oxygen saturation as measured during sleep studies was inversely related to each of these diabetic complications.

HbA_{1c} level within the favorable range present in the study population wasn't associated with OSA.

"Although obstructive sleep apnea and type 2 diabetes are independent diseases, our study supports the hypothesis that obstructive sleep apnea may contribute to diabetic complications," the physician concluded.

—Bruce Jancin