

Legislation Unlikely to Help Most Insulin Users

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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: 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 would or 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), Hy-dase and Amphadase (hyaluronidase), and Fortical (calcitonin salmon recombinant) nasal spray. 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.

Dr. Bill Law Jr., an endocrinologist in private practice in Knoxville, Tenn., said in an interview that confusion in the lay media about the difference between nonanalogue human insulins and analogue human insulins is behind these legislative efforts and public support for them.

"It's only after the 20-year patent law has expired [on a human analogue insulin] that it would be eligible for a generic compa-

ny to come in and make one," he noted. And 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, "the other important thing to understand is, this is not like creating a pill," wherein only the active ingredient is im-

portant, he added. "Everything else that's in that pill was specifically added by the manufacturer of that pill, whereas the insulin we're talking about is a biologic system," and thus cellular byproducts can't be as easily modulated. "It's totally different from making a pill, where you have complete control over what goes in that pill."

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 stand-

point 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."

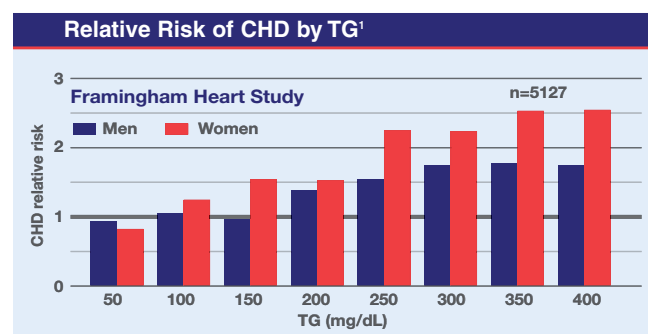
The savings to state Medicaid budgets that fast-track approvals of nonanalogue human rDNA insulins could produce would depend on how much of these traditional insulins a given state purchases in lieu of the more advanced analogues. ■



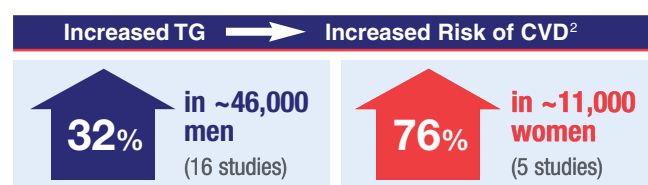
What TG means to a woman's heart

Elevated Triglycerides Make a Difference in Women's Risk of CHD

While great attention and clinical efforts have been directed toward LDL-C-lowering, the Framingham Heart Study 30-year follow-up clearly showed that elevated triglycerides (TG) are also associated with an increased relative risk of coronary heart disease (CHD)—especially in women.¹



In addition, meta-analyses demonstrated that every 1 mmol/L (89 mg/dL) increase in TG increased cardiovascular disease (CVD) risk by:²



CHD is the #1 Killer of Women

The effect of elevated TG in women is important to keep in mind in view of the fact that CHD is the single leading cause of death among American women, claiming nearly 500,000 lives each year.³ Menopausal women are particularly at risk, with CHD rates 2 to 3 times those of women the same age who are premenopausal.³

CHD Risks With Diabetes or Metabolic Syndrome* in Women: Role of TG and HDL-C

Of the estimated 16 million Americans with diabetes, more than half are women.⁴ In women, diabetes is a powerful risk factor for CHD, increasing CHD risk 3-fold to 7-fold compared to a 2-fold to 3-fold increase in men.⁵ It has also been shown that metabolic syndrome is associated with a 2-fold risk of CHD mortality in women.⁶ **It is important to note that the most common pattern of dyslipidemia in patients with type 2 diabetes is elevated TG levels and decreased HDL-C levels.⁷**

*At least 3 of the 5 criteria: abdominal obesity with waist circumference >102 cm in men and >88 cm in women; triglycerides ≥150 mg/dL; HDL-C <40 mg/dL in men and <50 mg/dL in women; blood pressure ≥130/85 mmHg; fasting glucose ≥110 mg/dL.⁸

More Aggressive Guidelines for TG and HDL-C

While LDL-C lowering is recognized as the primary lipid target to reduce CHD morbidity and mortality, it does not remove all risk.⁹ Recent data has shed more light on the role of increased TG and decreased HDL-C in CHD risk. It is critical that these lipid abnormalities be considered and managed, in addition to LDL-C. In fact, the current National Cholesterol Education Program (NCEP) guidelines recommend more aggressive TG and HDL-C target goals.⁸ The American Heart Association (AHA) and American Diabetes Association (ADA) recommend similar aggressive goals for TG (<150 mg/dL) and HDL-C (>50 mg/dL) in CVD prevention for women.^{10,11}

You Can Help Make a Difference

A majority of women are still not aware of the substantial CHD risks posed by abnormal lipid levels.¹² As a physician, you can help make a difference by raising your female patients' awareness of these issues, and by helping them achieve optimal lipid levels, as recommended by the NCEP, the AHA and the ADA.

References: 1. Castelli WP. Epidemiology of triglycerides: a view from Framingham. *Am J Cardiol.* 1992;70:3H-9H. 2. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk.* 1996;3:213-219. 3. American Heart Association. Heart Disease and Stroke Statistics—2006 Update. Available at: <http://www.americanheart.org>. Accessed February 8, 2006. 4. Centers for Disease Control and Prevention. Office of Women's Health. Diabetes. Available at: <http://www.cdc.gov/od/spotlight/nwhw/pubs/diabetes.htm>. Accessed April 11, 2006. 5. Manson JE, Spelsberg A. Risk modification in the diabetic patient. In: Manson JE, Ridker PM, Gaziano JM, Hennekens CH, eds. *Prevention of Myocardial Infarction*. New York, NY: Oxford University Press; 1996:241-273. 6. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation.* 2004;110:1245-1250. 7. American Diabetes Association. Management of dyslipidemia in adults with diabetes. *Diabetes Care.* 2003;26:S83-S86. 8. National Heart, Lung, and Blood Institute. *Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)*. Bethesda, Md: National Institutes of Health; 2002. NIH Publication 02-5215. 9. Davidson MH. Reducing residual risk for patients on statin therapy: the potential role of combination therapy. *Am J Cardiol.* 2005;96(suppl):3K-13K. 10. Mosca L, Appel LJ, Benjamin EJ, et al. AHA Guidelines. Evidence-based guidelines for cardiovascular disease prevention in women. *Circulation.* 2004;109:672-693. 11. American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care.* 2006;29(suppl 1):S4-S42. 12. Mosca L, Ferris A, Fabunmi R, Robertson RM. Tracking women's awareness of heart disease: an American Heart Association national study. *Circulation.* 2004;109:573-579.