

Could “Generic” Insulin Soon Hit the U.S. Market?

By Scott Strumello

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Wal-Mart's and Target's September 2006 announcement that the giant retailers would sell nearly 300 generic drugs for \$4 per prescription, whether or not the consumer has insurance, was promoted as a big savings opportunity for all Americans. But diabetes patients who require insulin, including all of the 1.1 million Americans with type 1 diabetes, will not be sharing in the savings.

It's no secret generic pharmaceuticals usually cost significantly less than the branded versions of drugs, and the cost savings to patients and their healthcare providers has been enormous. According to figures released by the U.S. Food and Drug Administration (FDA), once a second generic version of a drug hits the market, the cost of a drug usually sells for about half the original's price and multiple copies often cost 80% less. Express Scripts Inc., the No. 3 U.S. pharmacy benefit manager, estimated that the potential savings from generics in 2006 alone would total nearly \$24.7 billion. While a number of type 2 diabetes medicines have money-saving generics available, in spite of patents that expired years ago, patients who require insulin have been forced to pay full price for brand-name products because no generic insulin formulations are sold. While frustrating, the reason no generics exist is even more troubling.

Hatch-Waxman

Generic drugs were first made possible to U.S. consumers back in 1984, when Congress passed the Drug Price Competition and Patent Term Restoration Act (better known as the “Hatch-Waxman” Act). Since that time, generic drug makers have had a cheap and easy way to bring generic drugs to market after the patent protections on the original drugs expire. The Hatch-Waxman Act enables generic manufacturers to avoid repeating the extensive (and expensive) 3 phases of clinical trials that are normally required to prove the safety and efficacy of brand new drugs.

But Hatch-Waxman did not address biotechnology medicines. The manufacturing of biologic medicines usually depends on living organisms (such as bacteria or yeast) and requires maintenance of precise conditions in order to grow. But even more critical is the fact that it's much more difficult to determine how comparable the generic biologic is or its manufacturing methods are to the original because they aren't simple chemical compounds, they're more complex proteins or antibodies, therefore its more difficult to prove a generic is the same.

The FDA has repeatedly stated that the law bars it from permitting biotech imitations and that Congress must pass laws to allow the Agency to approve generic biotech medicines. This is not entirely true. While vaccines and most biotech drugs are governed under the Public Health Services Act, which would indeed have to be amended to allow for generics, because insulin and HGH were already on the market Hatch-Waxman was signed into law, the law considers them “drugs” which are governed by the Federal Food, Drug & Cosmetic Act, therefore generics are legally permitted. Furthermore, the patents for Eli Lilly & Company's Humulin insulin products expired in 2001, and Novo Nordisk's Novolin insulin products expired in 2002, so patent protection is not at issue.

The fact that generic versions of insulin are not available seems to be due largely to the tremendous confusion about the regulatory environment and exactly how generic manufacturers can obtain approval from the FDA for generic versions of these medicines.

According to ThinkEquity Partners analyst Andrew McDonald, “There's no way to make a generic out of a protein-based drug. There's no regulatory path [with the FDA to do so.] Even if it goes off patent, there's no way to make a generic.”

The biopharmaceutical industry argues and has so far been successful in convincing FDA regulators that the human response that biologic medicines create in patients aren't always very well understood processes and it and be difficult to determine bioequivalency via simple blood assays, therefore the FDA should not allow any

copycat biotech medicines. They also maintain that biotech medicines do not lend themselves to generic production because living cell cultures yield considerable variation among batches.

According to the Washington, D.C.-based Biotechnology Industry Organization (BIO), which represents more than 1,000 biotechnology companies and related organizations including Eli Lilly & Company, Novo Nordisk, and Sanofi-Aventis; the safety and effectiveness of a chemical drug can be established by the specification of its active ingredient, but the safety and effectiveness of a biotech product is determined by the manner in which it is made. BIO claims that because generic (“follow-on” protein is the FDA’s preferred term) manufacturers can never duplicate the innovator’s process, generic biotech medicines are technologically impossible. But while biologic medicines are more difficult to copy than chemically engineered drugs because they require highly precise conditions in order to grow, it doesn’t mean that highly similar versions cannot be manufactured.



But supporters of clearing a path for generics note that the FDA has allowed biotech companies to change their own manufacturing processes without conducting new clinical trials. Perhaps the most compelling argument in favor of generic biopharmaceuticals like insulin is the fact that the FDA has already established a precedent by approving insulin formulations created using entirely different manufacturing processes. So while the manufacturing process may affect the medicine, regulators should be focusing their efforts on methods to ensure consistency in the manufacturing process rather than by trying to prevent new manufacturers from entering the market. But confusion about the regulatory environment has left potential suppliers with many questions on how to proceed, but has provided few answers.

Dr. Jayaram (“Jay”) Chigurupati, the New Jersey-based Chairman and Managing Director of Zenotech Laboratories, a generic biopharmaceutical company that is officially headquartered in Hyderabad, India claims that the technology is now available to bring copies of biotech medicine products to market, but the biggest problem seems to be with U.S. regulators, whose rulemaking simply hasn’t kept up. He told *NJBIZ* that while the biopharmaceutical industry “would like you to believe otherwise, it is not impossible anymore.”

FDA About Face



Back in 2001, the FDA announced that it was working on guidelines for pharmaceutical companies to produce generic versions of insulin and HGH. The Agency had long had suggested the guidelines were forthcoming, but in April 2006, the FDA suddenly announced it would not be releasing the long-delayed guidelines for the production of generic versions of insulin and HGH as anticipated. In a March 17, 2006 letter obtained by the *Associated Press*, which was written in response to a Feb. 10, 2006 letter from Sen. Orrin Hatch (R-UT), and

Rep. Henry Waxman (D-CA), the FDA associate commissioner for legislation Patrick Ronan said that the FDA instead intended to publish broader guidelines that applied to ALL generic versions of protein-based drugs, also known as follow-on protein products, therefore the FDA would not be outlining specific guidelines for insulin or HGH. In response, Rep. Waxman said in a statement that the Agency’s action was “a misguided step that will only result in further delay” of rules for low-cost generics. The regulatory hiatus regarding generic versions has effectively extended the patents for the past few years at the expense of consumers and their healthcare providers.

Bruce Downey, chief executive of Barr Pharmaceuticals Inc. and chairman of the Generic Pharmaceutical Association board, said, “We want to eliminate the perpetual nature of the monopoly. As it stands now, patents aren’t the impediment. The impediment is the regulatory impasse.”

Last year, Sen. Hatch admitted as much, saying that the absence of a comparable route for biotechnology drugs, “essentially acts as a second patent to keep off-patent biological products off the market.”

According to Datamonitor, in the U.S., branded opposition to biogenerics have had a much greater influence at slowing regulatory reform enabling generics than in other countries. Datamonitor’s pharmaceutical markets analyst, David Evans, says that Congress has yet to create legislation for biogenerics and the FDA has been unwilling to use “the controversial 505(b)(2) pathway to approve generic versions of growth hormone and insulin.”

But under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, a “generic” doesn’t have to be an exact duplicate of the brand-name original in order to be approved by the FDA.

Cost Implications

The Generic Pharmaceutical Association (GPA) based in Arlington, VA, says that sales of biotech drugs in the U.S. have already reached \$30 billion and that figure is expected to double by 2010. Many of these medicines have either already lost, or will soon lose their right to patent protection. According to analysts, approximately \$11.5 billion worth of biologic drug patents supposedly expired by the end of 2006. An estimated \$3.5 billion is spent on the insulin and HGH alone each year; and the introduction of lower-cost generic versions could reduce that total by hundreds of millions of dollars. But so far, the FDA has yet to outline a process to determine whether biogeneric medicines will have the same therapeutic effect as the name brand biologic medicines do.

Lawmakers may force the FDA to move soon. Healthcare spending already accounts for more than 15% of gross domestic product, up from 10% in 1985 and 13% in 2000, and this figure is expected to grow rapidly as the baby boom retires. Growth in healthcare spending could soon start to wreak fiscal havoc, especially with the recently implemented Medicare Drug bill. The Medicare drug benefit took effect in January 2006 and offers prescription-drug coverage to some 38 million Americans with Medicare, according to the Centers for Medicare and Medicaid Services. The Bush administration’s price estimate for the new Medicare drug benefit was revised from \$400 billion over the next decade to \$720 billion.

At a March 2006 gathering of generic drug manufacturers, Rep. Waxman said, “With the rapid spread of biologics and the meteoric rise in the price of these products, I believe that it is simply no longer possible for Congress to stand by and do nothing.”

According to his staff, Rep. Waxman was reportedly considering introducing an amendment to the Public Health Services Act last summer to address the issue of generic biotech medicines. Although that did not happen, free-market forces may soon force the FDA to do something about this issue.

Jim Greenwood, president of BIO, sooner or later expects Rep. Waxman to propose legislation on this issue. Last summer, he told the *Pittsburgh Post Gazette* that he was anticipating Rep. Waxman to “drop a bill before this Congress is over. One way or another, we are a month, or two months, or six months away from this being a real issue in Congress.” To address those concerns, Greenwood has been working to convince lawmakers that generics are a bad idea. The former Pennsylvania Congressman has been busy visiting members of Congress trying to explain the complexities of biotech drugs compared to traditional small-molecule (chemical) pharmaceuticals.

But not everyone is convinced by BIO’s position on the issue. In August 2006, four state governors, looking to ease drug costs under state programs, petitioned the FDA to provide guidelines for generic versions of insulin and somatropin/human growth hormone (HGH). In their petition, the governors joined other critics in accusing the Agency of dragging its feet.

“The FDA’s delay in informing manufacturers of the requirements for obtaining approval of therapeutically equivalent versions of insulin and HGH has cost the states and other health-care providers hundreds of millions of dollars,” the petition said. Democratic Governors Kathleen Sebelius of Kansas and Jim Doyle of Wisconsin joined Republicans Tim Pawlenty of Minnesota and James Douglas of Vermont in signing the petition. Since then, the governors of New Mexico, Virginia and West Virginia have also signed the petition.

“We have been informed that there are no scientific reasons for delaying the issuance of the guidance documents FDA already has drafted,” the bipartisan group of governors wrote the FDA. “There is no legal or regulatory obstacle to the immediate issuance of these guidance documents,” they added.

The governors said that insulin and human growth hormone are a breed apart from other biotech medicines and should therefore be considered distinct from other biotech drugs. Insulin and human growth hormone both have relatively simple structures and a long history of safe use, they said.

Omnitrope

In July 2003, the Sandoz unit responsible for generics of pharmaceutical giant Novartis filed, and the FDA accepted, an Abbreviated New Drug Application for a “follow-on” version of Pfizer’s brand-name human growth hormone named Genotropin that that Sandoz called Omnitrope using the 505(b)(2) pathway. Sandoz was already selling Omnitrope in Australia, and the application was submitted following lengthy discussions with the FDA and contained preclinical, clinical, and comparability data, as well as literature references to the FDA’s original decision on Pfizer’s Genotropin.

But on September 2, 2004, the FDA told Sandoz that the Agency was unable to reach a decision on whether to approve the company’s application for Omnitrope. Sandoz provided far more than generic pill manufacturers are required to, yet the FDA refused to take action, first by delaying the decision, then by claiming that Congress needed tell the FDA how it should proceed with regulation on generic proteins, enzymes and antibodies. After two years of regulatory inaction and finger pointing, Sandoz grew frustrated with the FDA’s failure to give them a decision on Omnitrope, so they sued the FDA in U.S. District Court in Washington, D.C., citing a statutory requirement that the FDA is required by law to act on drug applications within 180 days. On May 30, 2006, Judge Ricardo Urbina ruled in favor of Sandoz on the Omnitrope case in a very strongly worded opinion, calling the FDA’s repeated delays “egregious” noting there was absolutely no excuse for a delay that was nearing 1,000 days, and effectively ordered the FDA to give the company a response.

Following the lawsuit, the FDA approved Omnitrope. In approving the Sandoz drug, the FDA said that it found that the active ingredients in Omnitrope and Genotropin were “highly similar,” therefore the Agency could rely on its previous findings that the Pfizer product was safe and effective in addition to Sandoz’s own studies. But the FDA also noted that its approval did not rest exclusively on proprietary information from the original Genotropin application as it does with ordinary chemical drugs. Sandoz told the press that it had submitted an “abbreviated” version of the typical clinical trials (the abbreviated trials were done on just 51 people vs. thousands normally required to prove the efficacy of a brand new medicine), as well as safety studies and a detailed document outlining how the company planned to manufacture Omnitrope to ensure its quality. Finally, the FDA stated that the law governing generics permits approvals like Omnitrope’s because they aren’t technically forbidden, “as long as the current state of science allows the evaluation necessary to support approval,” the FDA wrote in its response to Pfizer’s petition against Omnitrope’s ANDA. The Generic Pharmaceutical Association (GPhA) President and CEO Kathleen Jaeger responded by saying “The FDA’s Omnitrope decision clearly demonstrates that sound science exists to support the approval of generic biopharmaceuticals despite assertions from special interests to the contrary.” Rep. Waxman’s staff also noted that by approving Omnitrope, the Congressman believes the FDA now has provided evidence that generic manufacturers can indeed make biotech copies as good as the original.

The GPhA said at the time that the Omnitrope approval was a first step to opening the industry to competition from generics. But according to the governors who sued the FDA in August, while the Omnitrope approval helped, FDA guidelines are still needed to help expedite the process. A spokesman named Brian McClung speaking on behalf of Minnesota Gov. Tim Pawlenty said that before generic insulin products could be released, the FDA must create manufacturing standards, which they have not done. “It’s been 22 years,” McClung said. “There is no scientific reason for the FDA not to do this, especially when American patients spend \$1.5 billion a year on insulin.”

Economics of Generic Insulin



According to Datamonitor, of the global biopharmaceutical market, \$20.2 billion in sales is derived from six key product classes that are at immediate risk from biogenerics, and insulin is included on this list. But if the Minnesota governor is correct, then insulin accounts for only 7% of that figure, and most of that small slice can be attributed to the emergence of more costly insulin analogs, which still enjoy patent protection. The bigger question is whether margins on insulin are sufficient to attract the interest of generic manufacturers.

It's not unusual for many biopharmaceuticals to cost \$100 per dose, said Jake Hansen, vice president of government affairs for Barr Laboratories, which is a specialty pharmaceutical company that develops, manufactures and markets both generic and proprietary prescription pharmaceuticals. By comparison, the retail price for an entire vial of the most expensive insulin analog still costs less than a single dose of the higher-margin products.

Dr. Keith Campbell, associate dean and professor of pharmacy practice at Washington State University College of Pharmacy and a CDE who himself has type 1 diabetes told diabetes writer David Mendosa that "Most pharmacies now charge general public about what they pay for insulin. Insulin is a loss leader. The markup on chronic disease drugs is pretty low."

Datamonitor says that market size and patent expiry are not the only two considerations, as proven by the minimal interest among manufacturers in making generic insulin. They indicate that medicines other than insulin are expected to account for the majority of the forecast sales of biogeneric medicines by 2010.

According to The Pharmaceutical Business Review, for various reasons, insulin will likely be minimally affected by generics, at least initially, and it's not simply a matter of low margins. One hugely important factor they cite is the emergence of 'second-generation' branded products such as insulin analogs. These will rapidly diminish the market for first-generation biogenerics. However, insulin analogs themselves could become the target for generics in the not-too-distant future. Martin Soeters, the U.S. president of Novo Nordisk, which recently surpassed Eli Lilly & Co. to become the U.S. market share leader in insulin, recently predicted that by 2009, human insulin would account for no more than about 15% of the market.

"At that point in time there is hardly a medical need anymore because the majority of patients will be switched to the insulin analogs, which clearly show superiority in different criteria," Soeters said.

Not surprisingly, rival Eli Lilly & Company expressed a very similar view. In August 2006, Scott MacGregor, a spokesman for Eli Lilly & Company, told Chris Emery of the *Baltimore Sun*, "When you look at that kind of space-age technology [associated with insulin analogs] and compare it to an 80-year-old therapy, you can see why the market has changed."

But others don't see the situation as so definitive. Some believe that the major insulin manufacturers intend to completely stop selling all forms of human insulin. Jenny Hirst, the co-chair of the Insulin Dependent Diabetes Trust, a UK-based organization which supports the right for patients' to be able to choose which type of insulin is the most appropriate for their needs and to maintain their health and well-being, believes that the major manufacturers intend to phase out all forms of human insulin, leaving only the more costly analogs available. Hirst noted that the 2005 Cochrane Review of short-acting insulin analogs suggested only a minor benefit of rapid-acting insulin analogs in the majority of diabetic patients treated with insulin, and is troubled by treating insulin-dependent patients with analogs that are neither human nor insulin.

Novo Nordisk does not deny its intention to eliminate all forms of human insulin. In January 2006, Jesper Brandgaard, the chief financial officer of Novo Nordisk, told CNBC/Dow Jones Business Video "We are taking our portfolio from being generic product, human insulin, onto a patent-protected insulin analogue. So we are actually getting our portfolio on-patent, not off-patent."

A niche opportunity might exist for generic manufacturers to resurrect recently discontinued human insulin varieties, most notably Humulin L (Lente) and Humulin U (Ultralente) and sell them for full price provided they

could move quickly enough. But it's unclear how big the opportunity might be since Lilly discontinued those products due to declining sales.

Forecasts and predictions are fine; but competition may nevertheless emerge from big generics manufacturers, including the Sandoz generics unit of Novartis and Israel-based Teva Pharmaceutical Industries Ltd., two of the largest generic manufacturers in the U.S. According to Atlantic Information Services, Inc., a publishing and information company that has served the health care industry for nearly 20 years, Teva has already filed for a follow-on version of insulin in the U.S. This claim is impossible to verify because applications that are still under review by the FDA are inaccessible to the general public and Teva did not respond to any of my inquiries.

Meanwhile, Sandoz believes generic biotechnology drugs in the U.S. will be a key growth driver. Sandoz chief executive Andreas told *The Wall Street Journal* that with Omintrope's approval, "Sandoz believes there is a viable pathway for getting a limited number of follow-on biotech drugs approved in the U.S., and it is currently developing five others. The company said it can file for approval for some of the drugs via the same route used for Omnitrope."

Insulin could potentially be one of the five biotech medicines Sandoz is pursuing. Internet sources indicate that in addition to HGH, generic versions of insulin and a few other biotech medicines which are grandfathered under the Federal Food, Drug & Cosmetic Act are reportedly already in development. Although a spokesperson for Sandoz did respond to my inquiry about what other biopharmaceutical medicines the company might be pursuing, the spokeswoman said only "Sandoz does not comment on what products may or may not be under development. As noted, Dr. Andreas Rummelt has stated publicly that Sandoz has five additional follow-on protein products in its pipeline, but beyond that, the company won't comment."

If You Can't Beat Them, Join Them

In fact, Novo Nordisk's Martin Soeters fully expects to see inexpensive generic human insulin on the market by 2008 or 2009, but he told *Reuters* in early June 2006 that the world's largest insulin supplier was not concerned.

"The new generation of insulins are so clearly superior and there is such a change in doctor and patient attitude toward it that they will not go back," Soeters said.

Soeters also said that Novo Nordisk was prepared to provide human insulin to certain larger clients, such as the U.S. Department of Veterans Affairs, at prices "that cannot be met by generic human insulin producers."

"In places where it will still be used, we are offering extremely low prices," according to Soeters.

Novo Nordisk is following a growing trend among brand-name pharmaceutical manufacturers to drastically reduce the prices on its medicines when patents expire to in order retain market share rather than ceding sales to generic competitors.

For example, in late June 2006, the FDA approved the first generic versions of Merck's popular cholesterol pill Zocor (simvastatin), and Merck made the unusual decision to slash the price of Zocor so that with some health plans, it would actually be cheaper than the generic. United Healthcare, for example, will reportedly offer brand-name Zocor for a \$10 a month co-pay, while the generic version will cost \$50.

Novo Nordisk has several years of patent protection left on its newer insulin analogs. It's Novolog rapid-acting insulin analog has patent protection until 2014; while it's slightly newer long-acting insulin analog Levemir has patents that run through 2017 before being challenged by biogenerics. By then, Martin Soeters told *Reuters* confidently, that Novo would already have its next generation insulin products on the market.

Patients with diabetes are irritated by what they see as the big pharmaceutical company's arrogance and greediness and the FDA's failure to assist in bringing generic competition to market. For example, if human insulin formulations are such a small part of its overall business, it's certainly not profits that is keeping Novo Nordisk from reducing its prices now.

While so-called “second-generation” products like insulin analogs may limit the initial impact that generics may have on the market today, until the FDA outlines procedures for generic manufacturers to apply for and obtain approvals, patients who require insulin are being denied a significant money-saving opportunity being offered to patients who are able to treat their condition with pills largely due to bureaucratic red tape. But the new Congress will be forced to legislate a procedure for generic biopharmaceuticals soon. Failure to move may result in taxpayers being forced to pick up the cost via the funds it must allocate to the recently implemented Medicare drug benefit, a cost that is expected to grow rapidly as the baby boom retires and becomes eligible for benefits.

For many years, the insulin market has been an oligopoly. American consumers have benefited tremendously by the destruction of oligopolies, ranging from AT&T’s complete control of the telecommunications industry, to airline deregulation, to foreign automakers entering the U.S. market.

According to microeconomic theory, free market competition forces companies to develop new products and services, giving consumers greater selection and better products. This usually results in lower prices compared to what the price would be if there was little competition as there is today.

Ultimately, the cost of regulatory inaction is borne by patients with diabetes. Approximately 45 million people in the U.S. – 17% of the working-age population – are not covered by health care insurance. Given that roughly 6% of people in the U.S. have diabetes, of the approximately 45 million people with no healthcare cover, we can conservatively estimate that approximately 3 million people with diabetes in the U.S. lack healthcare insurance, and their prognosis isn’t good. Analysis of a study done in 2002 revealed that when compared to people who had health insurance, people without any form of health insurance received fewer preventive diabetes care interventions and showed generally less-desirable diabetes outcomes. Specifically, a higher percentage of uninsured people had HbA1c levels of 9% or higher; fewer had an annual blood lipid test and/or annual foot exam. It’s hard to imagine, but on average, fully one-fourth (25%) of people with diabetes go without a checkup for two years if they have been without health insurance for a year or more vs. only 5% of diabetes patients *with* insurance. Obviously, the cost of prescription medicines, including insulin, is especially difficult for this segment of the population to pay out-of-pocket. For example, based on IMS Health data, excluding the effect of rebates, the typical cash customer pays nearly 15% more for the same medicines than do customers with third-party coverage. For a quarter of the most common drugs, the price difference between cash and third parties is even higher – over 20%. The real question, regardless of which type of insulin we use personally, is why we continue to tolerate regulatory inaction on such an important matter? All patients with diabetes should consider this a priority, and urge their legislators to support legislation that removes barriers to price competition in the insulin market.

AUTHOR POSTSCRIPT (APRIL 2007):

In February 2007, Senator Hillary Rodham Clinton and Representative Henry Waxman introduced legislation (H.R. 1038, the "Access to Life-Saving Medicine Act of 2007") that would give the FDA the legal authority to approve cheaper, generic versions of biotech drugs known as biologics or follow-on protein products. Waxman, a California Democrat who is now chairman of the House Oversight and Government Reform Committee, introduced similar legislation in 2006, but his bill was never voted on. The new bill, if approved and signed into law, would change U.S. patent laws under the 1946 Public Health Services Act that now prevents the FDA from approving some generic versions of biotech drugs and require the FDA to outline procedures to get these medicines approved. The bill would give the FDA the express legal authority to approve generic biotech drugs, and in many cases, remove the need for expensive and time-consuming repetition of clinical trials. The FDA would also be given the authority to decide on a case-by-case basis what additional clinical information is required before approval will be granted. Also, in an effort to avoid the various legal loopholes that now delays FDA approval of many generic chemical drugs, this legislation also calls for timely resolution of patent disputes.

According to a study undertaken by pharmacy benefits manager Express Scripts Inc., some estimates of the potential savings generated by the pending bill now in Congress on prescription expenditures have been forecast, including specific estimates for generic insulin. That study estimates that the cost savings for generic insulin would be noteworthy \$797 million in the first year, and would total more than \$16 billion over 10 years. Express Scripts conducted its study by assuming a 25% discount off brand-name medicines in the 4 classes of drugs that would already have generic competition because of patent expirations if copycat biologics were allowed. Express Scripts decided on that discount because it said that the generic version of human growth hormone sells at a 25% discount to its brand name counterparts in Europe. They also assume that just 25% of patients on insulin would ultimately switch to generics, which seems to be a conservative yet realistic estimate, and is significantly smaller than the estimates that generics will capture for the other major biotech drug classes evaluated. Although human insulin (basically, everything but insulin analogs) still has a large share (more than 50%) of total insulin sales, growth for human insulin formulations has essentially ground to a halt since the introduction of analogs, and the share of human insulin is expected to show little if any growth for the foreseeable future. For that reason, the estimate of 25% seems reasonable.

As might be expected, the Biotechnology Industry Organization (BIO), which represents companies including Novo Nordisk, Eli Lilly and Company and Sanofi Aventis immediately disputed the Express Scripts estimates, adding that they doubted the validity of the study. But a closer look at the "flaws" BIO cites indicates that its claims are no more convincing than the Express Scripts study's estimates, suggesting that the entire debate is really about arguments being made by a trade group who is trying hard to prevent any competitors from entering their lucrative market than about the best interests of patients.