The Business of Insulin: A Relationship Between Innovation and Economics

Steven B. Leichter, MD, FACP, FACE

Insulin, as a commercial product, is undergoing a substantial metamorphosis from a commodity item to a potential growth vehicle for its manufacturers. This trend has accelerated during the past 5 years with the introduction of a growing number of insulin analogs and novel insulin injection devices.

Although this innovation has, of course, been presented as improved medical therapy, the business aspects of the insulin market suggest that the economic rewards are important drivers of these developments. The trends in economic data prophesize that business considerations may enhance the pace of innovation and may lead to the elimination of traditional insulin products in favor of more profitable analogs.

Whether the clinical benefits of these trends justify the economic costs should be analyzed. Therefore, a consideration of the trends in the insulin market is clearly in order.

Innovations in Insulin Since 1980
From the clinical discovery and widespread application of insulin in the early 1920s, insulin products did not undergo major changes until 1980. Before then, insulin was partially purified from pig or cow pancreases. Much of the commercial insulin sold in the United States had relatively large levels of impurities.

Therefore, patients on insulin therapy often developed antibodies to the impurities in the product and to the animal insulin itself. In most instances, these antibodies functioned as “blocking antibodies,” which inactivated part of the administered doses and caused reduced glycemic control. In some cases, true allergic reactions occurred from the antigenic process.

As the 1980s dawned, two related trends improved the purity and reliability of commercial insulin. The impending release of purified, genetically engineered, biosynthetic human insulin by Eli Lilly and Co. caused the introduction of highly purified pork insulin products by Novo Nordisk Pharmaceuticals, Inc. Novo recognized that its human insulin product would be introduced later than that of Lilly, so it attempted to retain market presence with its purified pork insulins. Pork insulin was much less antigenic than beef insulin, and highly purified insulin preparations were much less antigenic than the products that had been sold to that point. The resulting market emphasis on purified pork or human insulins caused a fairly rapid reduction in the use of impure insulins and beef insulins.

In June 1982, Lilly marketed the first biosynthetic human insulin. The first patient to be treated with this product illustrated its potential therapeutic benefits. He was an 18-year-old college student with type 1 diabetes, who had poor glycemic control despite a progressive increase in daily insulin dose from 50 to 110 units. Anti-insulin antibody titers in this young man were extremely high, explaining the apparent ineffectiveness of his insulin therapy. Two days after he was started on human insulin, his daily insulin dosage had to be reduced to 65 units, suggesting that he was no longer generating the same titers of anti-insulin antibodies.

Although growth of human insulin sales was initially modest, this product line became the predominant insulin group by the mid-1990s. By 2000, both major manufacturers discontinued widespread sales of animal insulins.

Innovations in Insulin Therapy
Starting in the mid-1990s, specifically modified insulins, again made through biosynthetic technology, were introduced. These insulin analogs are “designer insulins,” with protein structures modified to achieve specific therapeutic goals (Table 1). The first to be introduced, insulin lispro (Humalog) appeared in 1996. It has been advocated as a product that mimics the postprandial action of endogenous, human insulin better than standard, biosynthetic human regular insulin.

Another vehicle for growth in the insulin marketplace has been the introduction of new injection devices for

<table>
<thead>
<tr>
<th>Table 1. Insulin Analogs</th>
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<tbody>
<tr>
<td>Insulin lispro (Eli Lilly and Co.)</td>
</tr>
<tr>
<td>Insulin aspart (Novo Nordisk Pharmaceuticals, Inc.)</td>
</tr>
<tr>
<td>Insulin glargine (Aventis)</td>
</tr>
<tr>
<td>Insulin detemir (Novo Nordisk Pharmaceuticals, Inc.)</td>
</tr>
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</table>
insulin. In the late 1990s, Novo introduced pen devices for insulin injection in the United States. Lilly introduced a pen device for the administration of lispro and, eventually, its other insulin products with the exception of regular insulin. In the past year, Novo has introduced several additional pen injection devices.

**Documentation of Efficacy**

The justification for the cost of these newer insulin products, based on their demonstrated clinical efficacy, remains to be completely confirmed. In each case, whether for insulin analog or the pen-injection device, there are no large-scale multicenter studies documenting that the new products yield clinically meaningful improvements in hemoglobin A1c (A1C) compared to standard, comparable products.  

For example, detailed kinetic studies of insulin glargine (Lantus) versus NPH or ultralente insulin have demonstrated a less variable pattern of insulin action over time. However, no study yet available has shown clearly that glargine reduces A1C results more than does NPH or ultralente insulin. Similarly, the rapid-acting insulin analogs lispro and insulin aspart (Novalog) have been shown to have positive effects in acute studies on patterns of postprandial glucose fluctuations. However, A1C reductions greater than those from regular insulin have not been routinely demonstrated. Still, the literature does provide fairly convincing evidence that these insulin analogs are associated with a moderately lower risk of hypoglycemia, particularly nocturnal hypoglycemia, than are equivalent human insulins.

Substantiation of the notion that pen injection of insulin leads to improved glycemic control is also unavailable. Pen-injection may be helpful in certain clinical circumstances, such as with patients who follow hectic daily schedules. Studies have not been carried out on the features of pen-injection that could be beneficial, such as its potential for reducing the time required to initiate insulin therapy or the numbers of patient errors in insulin administration.

**The Pricing of Insulin**

Innovation has come with increasing cost. The retail prices of analog or pen-injected insulins are significantly higher than those of conventional insulin preparations (Table 2). In most cases, the cost of equivalent amounts of insulin, in terms of units of insulin, is at least 50% higher and more often more than 200% higher for the new insulin products and devices than for conventional preparations in vials.

The Innolet disposable pen devices recently marketed by Novo have the smallest price differential versus human insulin in vials, but they only deliver traditional human insulin products. At least for now, the long-acting insulin analogs are sold at a lower premium than the short-acting insulin analogs. The highest cost for these new insulin products applies to disposable pen injectors of insulin analogs.

**Growth of the Insulin Market**

The market for insulin in the United States is currently growing at more than 10% per year. Between May 2000 and May 2001, it grew at 11% to $1.4 billion. Growth is projected to continue at that rate or more at least until 2020, when insulin sales are projected to exceed $7.5 billion. Much of this growth will be fueled by the introduction of more and more insulin analogs. The data do not account for the potential impact of inhaled insulin, if and when it is released for commercial use.

Insulin is also an important part of the product portfolio for its established manufacturers. During the last fiscal year, insulin and other diabetes-related products represented the second-largest product line for Lilly ($1.2 billion in annual worldwide sales) and the largest product group for Novo ($1.9 billion in

### Table 2. Retail price comparison of different forms of injected insulin

<table>
<thead>
<tr>
<th>Product</th>
<th>Size (ml)</th>
<th>Concentration</th>
<th>Container</th>
<th>Units</th>
<th>Online Pharmacy 1</th>
<th>Online Pharmacy 2</th>
<th>Local Pharmacy (Georgia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analog, long-acting</td>
<td>10</td>
<td>U100</td>
<td>Vial</td>
<td>1,000</td>
<td>$43.95</td>
<td>$0.044</td>
<td>$50.00</td>
</tr>
<tr>
<td>Analog, rapid-acting</td>
<td>5 × 1.5</td>
<td>U100</td>
<td>Cartridge</td>
<td>750</td>
<td>$41.54</td>
<td>$0.055</td>
<td>$42.50</td>
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<tr>
<td>Analog, rapid-acting</td>
<td>5 × 3</td>
<td>U100</td>
<td>Cartridge</td>
<td>1,500</td>
<td>$89.92</td>
<td>$0.060</td>
<td>$65.00</td>
</tr>
<tr>
<td>Analog, rapid-acting</td>
<td>5 × 3</td>
<td>U100</td>
<td>Pen</td>
<td>1,500</td>
<td>$94.53</td>
<td>$0.063</td>
<td>$72.00</td>
</tr>
<tr>
<td>Analog, rapid-acting</td>
<td>10</td>
<td>U100</td>
<td>Vial</td>
<td>1,000</td>
<td>$48.40</td>
<td>$0.048</td>
<td>$65.00</td>
</tr>
<tr>
<td>Human</td>
<td>5 × 3</td>
<td>U100</td>
<td>Cartridge</td>
<td>1,500</td>
<td>$67.25</td>
<td>$0.045</td>
<td>$72.00</td>
</tr>
<tr>
<td>Human</td>
<td>5 × 1.5</td>
<td>U100</td>
<td>Cartridge</td>
<td>750</td>
<td>$34.00</td>
<td>$0.045</td>
<td>$65.00</td>
</tr>
<tr>
<td>Human</td>
<td>5 × 1.5</td>
<td>U100</td>
<td>Pen</td>
<td>750</td>
<td>$35.40</td>
<td>$0.047</td>
<td>$65.00</td>
</tr>
<tr>
<td>Human</td>
<td>5 × 3</td>
<td>U100</td>
<td>Pen</td>
<td>1,500</td>
<td>$136.85</td>
<td>$0.091</td>
<td>$60.00</td>
</tr>
<tr>
<td>Human</td>
<td>5 × 3</td>
<td>U100</td>
<td>Innolet</td>
<td>1,500</td>
<td>$60.00</td>
<td>$0.040</td>
<td>$60.00</td>
</tr>
<tr>
<td>Human</td>
<td>20</td>
<td>U500</td>
<td>Vial</td>
<td>10,000</td>
<td>$160.58</td>
<td>$0.016</td>
<td>$200.00</td>
</tr>
<tr>
<td>Human</td>
<td>10</td>
<td>U100</td>
<td>Vial</td>
<td>1,000</td>
<td>$25.00</td>
<td>$0.025</td>
<td>$29.00</td>
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</table>
annual worldwide sales). In addition, worldwide sales of insulin for Aventis exceeded $250 million during 2001, more than 10% of the total sales of the company. Thus, total worldwide insulin sales for the three largest manufacturers exceeded $3.3 billion in the last fiscal year.

Clinical and Economic Decisions About Insulin Therapy

Business or economic considerations will not and should never be the sole or even the prime basis for decision-making in the selection of insulin therapy. On the other hand, cost should be one criterion in treatment design. Certainly, a theoretical relationship between cost and clinical efficacy constitutes one valid basis for the selection of treatment.

The current climate in the insulin market involves strong marketing and clinical advocacy in favor of newer products. As discussed, there are possible specific advantages of these newer products. However, clinicians should consider price differentials as well in their selection of insulin products with their patients. Novel pharmacokinetic properties of insulin analogs and the ease of use of injection devices may enhance patient acceptance of insulin therapy and reduce hypoglycemia.

REFERENCES

8. Trautmann ME: Effect of the insulin analog ([LYS(B28),PRO(B29)]) on blood glucose control. Horm Metab Res 26:588–590, 1994

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