

MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

Why Is There No Generic Insulin? Historical Origins of a Modern Problem

Jeremy A. Greene, M.D., Ph.D., and Kevin R. Riggs, M.D., M.P.H.

Although the exact development costs of any particular drug are never disclosed, economists estimate the average investment for an innovative drug that is brought to market at more than \$1 billion and rising.^{1,2} These high costs of pharmaceutical research and development are often invoked to justify the high price tags of new medications. Although the price point of effective new drugs — from hepatitis cures to new agents for heart failure — may initially be out of reach for many patients, market laws predict that drugs with strong demand should become more accessible after market exclusivity ends and generic competition begins. Since 1984, when the Drug Price Competition and Patent Term Restoration Act was passed, pharmaceutical innovation and access have been balanced on that premise: innovative drugs are rewarded with high prices during their window of patent protection, and generic competition reduces prices thereafter.^{3,4}

What happens when this expectation is not met for a drug that is essential for managing a disease with enormous public health significance? When insulin was discovered in 1921, it was hailed as one of the first “wonder drugs” of the 20th century, capable of transforming a fatal affliction into a manageable chronic condition.⁵ Today, there are 21 million people living with diabetes in the United States alone, 6 million of whom take insulin.⁶ And yet insulin is available only in brand-name forms — out-of-pocket costs for uninsured patients range from \$120 to \$400 per month. Whereas many other essential medications are available as \$4 generics, no similarly low-priced versions of insulin are available. For many patients — especially those without insurance — the price of insulin is still too high to pay, and the consequences are disastrous for individual and systemic management of diabetes.⁷

The conundrum of why a medication discov-

ered almost 100 years ago is still not available as a low-priced generic agent has historical origins — and implications for contemporary policy and practice.

THE ORIGINS OF INSULIN

In a widely celebrated tale of biomedical serendipity, insulin was discovered in 1921 by an unlikely scientific team at the University of Toronto, led by a young orthopedic surgeon without laboratory training, Frederick Banting, and a medical student, Charles Best. After improving their technique of extracting the active insulin (initially termed isletin) from whole animal pancreas, they produced enough to treat the first patient, Leonard Thompson, in 1922. A patent was not filed until later, however, in part because academic medicine viewed the patenting of biomedical research products with some distaste. When the team applied for a U.S. patent in January 1923 (which they later sold to the university for \$1), they stated that their goal was not profit, but ensuring the speedy and safe availability of their discovery to the public.⁸ The patent, they wrote to their university’s president, was a form of publication: “When the details of the method of preparation are published anyone would be free to prepare the extract, but no one could secure a profitable monopoly.”⁹

Patenting insulin also provided a means to control the quality of a product by controlling who could manufacture it.¹⁰ After attempting to manufacture insulin in a production facility on the university campus, the researchers realized they lacked the expertise needed to produce enough drug for North American markets. In 1923, they teamed up with Eli Lilly, an established pharmaceutical company with experience producing glandular extracts.⁹ Lilly was allowed to take out U.S. patents for any manufacturing-

process improvements, but the university would receive the patent rights for the rest of the world.⁹ The Toronto team licensed the rights to produce insulin to numerous other companies in various countries. One of those companies, Denmark's Nordisk Insulinlaboratorium (which later merged with Novo Terapeutisk Laboratorium to form Novo Nordisk), would soon become a major innovator in insulin products.

IMPROVING THE PRODUCT

Insulin was immediately perceived as a lifesaving drug of vast clinical and public health significance. And yet the initial animal extracts had limitations.

First, their short duration of action necessitated frequent injections. In the early 1930s, Hans Christian Hagedorn and his colleagues at Nordisk discovered that adding protamine to insulin altered its absorption and prolonged its action.¹¹ These first protamine insulins represented an important innovation, but their physical form did not allow mixing with crystalline fast-acting (regular) insulin. A subsequent innovation, the addition of small amounts of zinc to form the crystalline protamine-isophane insulin, now known as neutral protamine Hagedorn (NPH),¹² was patented in 1946. This advance made it possible to combine long-acting and short-acting insulin, allowing many people with diabetes to be treated with a single daily injection. Soon afterward, a method was discovered for prolonging the action of insulin without adding protamine, which led to the introduction of the lente ("slow") insulins in the mid-1950s.¹³ These discoveries offered more options for dose adjustment of insulin but extended the reach of insulin patents into the 1970s.

Second, these initial beef and pork insulins were plagued with problems inherent to animal-tissue extracts. Impurities could cause local reactions, and immunologic reactions to nonhuman proteins could reduce the efficacy of insulin and precipitate allergic responses. A series of innovations in the insulin manufacturing process in the early 1970s helped to improve purity and reduce these side effects. In short succession, Novo introduced "monocomponent" insulins and Lilly introduced "single-peak" insulins. These safety improvements extended insulin patents into the late 1980s.

By the late 1970s, however, further purity improvements were sidelined when it became possible to produce human insulin through recombinant technology. Biotechnology investors saw insulin as an ideal product for the new industry after Genentech scientists produced the first recombinant DNA human insulin in 1978 by inserting the cloned insulin gene into *Escherichia coli* bacteria.¹⁴ This technology allowed Lilly to bring the first recombinant human insulins — Humulin R (rapid) and N (NPH) — to the U.S. market in 1982. Around the same time, Novo and Nordisk developed methods for chemically converting bovine insulin into human insulin, which allowed them to compete in the human insulin market. Novo Nordisk eventually brought its first recombinant insulin to market in 1988. A new web of insulin patents, held by Lilly, Novo Nordisk, and Genentech, promised to stretch into the 21st century.

Once recombinant technology opened the door to using the genetic code to make insulin, scientists quickly began modifying the structure of insulin, attempting to improve its physiological effects. In the late 1980s, it was shown that single amino acid substitutions could result in substantially faster insulin absorption,¹⁵ theoretically allowing injected insulin to more closely mimic prandial insulin release by the pancreas. In 1996, lispro became the first short-acting insulin analogue to be approved; aspart followed in 2000, and glulisine in 2004.

The same concept that allowed for fast-acting analogues also permitted engineering of long-acting analogues. Because NPH has an unpredictable peak and a duration of action of less than 24 hours,¹⁶ long-acting synthetic insulins could theoretically reduce hypoglycemia and improve glycemic control. Glargine became the first long-acting analogue insulin in 2000, followed by detemir in 2005; the first patents on these products expired in June 2014.

COPYING LARGER MOLECULES

Why, then, is a drug originally patented in 1923 not available in generic form in 2015? It's true that large-molecule biologic drugs are more complex and harder to copy than the small-molecule drugs on which the generic-drug industry was built, but the widely anticipated entry of bio-similar insulins may promise more competitive

pricing, now that the most recent insulin patents have expired. Last summer, Lilly and Boehringer Ingelheim announced that the Food and Drug Administration (FDA) had granted tentative approval to a biosimilar version of insulin glargine.¹⁷ Other companies have also announced plans to produce biosimilar analogue insulins in the United States. The European Medicines Agency (EMA) recently granted approval to the first biosimilar glargine on the European market,¹⁸ and unregulated biosimilar insulins have already popped up in countries with less-stringent regulatory bodies, including China, India, Mexico, and Peru.¹⁹

New biologic drugs are orders of magnitude larger than small-molecule drugs, and it's often impossible to know on an atom-by-atom basis whether one large-molecule drug is the same as another. Subsequent versions of off-patent biotech drugs are therefore called biosimilar rather than generic. Differences in the tissue systems that produce them can lead to differences in protein folding and glycosylation, which could theoretically result in efficacy or safety differences. But the FDA, the EMA, and the generic-drug industry hope these issues can be addressed by new regulatory sciences of biosimilarity.²⁰

Although regulatory pathways for biosimilar insulin are being finalized in the United States and Europe, economists warn that the introduction of biosimilars may not lead to price reductions equivalent to those seen with typical generic medicines. Even an abbreviated approval process for biosimilars will require substantially more original data than the typical abbreviated new drug application required for small-molecule generics and will necessitate immunogenicity and other safety studies in humans.²¹ Price reductions for biosimilar insulins in the United States are predicted to be about 20 to 40% — much less than the reductions of 80% or greater for most small-molecule generics.²² Europe, which has already approved numerous noninsulin biosimilars, has seen similarly disappointing price reductions in biosimilar products.²¹

THE PARADOX OF INCREMENTAL INNOVATION

Reducing the problem of generic insulin to the contemporary debate over biosimilarity ignores the historical reason why we have always lacked

generic insulin: incremental innovation has repeatedly precluded the formation of a generic-insulin industry in North America when earlier patents expired. The history of insulin hasn't followed the standard chronology of pharmaceutical innovation, in which patent monopolies predictably give way to generic competition.

Viewed in historical perspective, insulin is not a single entity but a family of related products that has evolved through incremental improvements. Subsequent iterations of insulin represented actual innovations, each one being safer, more effective, or more convenient than its predecessor. And yet after generations of incremental innovation, insulin may be no more affordable than it was when the original patent holders sold their stake for \$1 to ensure access to this essential medicine.

Pharmaceutical-industry analysts have described a repatenting tactic called evergreening, in which a series of related patents — often on metabolites or optical isomers — extend the life of a product after initial patent expiration.²³ Evergreening can shift market share within a family of products: for example, after Pfizer lost patent exclusivity on the antiepileptic agent gabapentin (Neurontin) in 2004, it retained a healthy share of the market through patents on a metabolic cognate, pregabalin (Lyrica). Critics of evergreening often claim that the incremental innovations leading from a given drug to a “me-too” drug are trivial: pregabalin, for example, is not clearly safer or more efficacious than gabapentin.

But the cascading generations of insulin products can hardly be dismissed as simply “me-too” medicines. Protamine insulin offered a distinct advantage over regular insulin, NPH insulin offered a distinct advantage over protamine insulin, and so on. On the whole, insulin today is demonstrably safer and more convenient to use than products available in 1923. But whether each incremental innovation is worth the price we pay, in a world where insulin remains unaffordable to many patients with diabetes, is less certain. When lente insulin was introduced in the 1950s, some observers questioned whether its minimal theoretical advantages over NPH warranted the complexity introduced by adding another insulin formulation to the market.²⁴ The theoretical advantages offered by the monocomponent extract insulins may sometimes have been outweighed by the inconvenience and risk



He's four years old.
And already he's living in the past.

In 1982 a new form of insulin was launched on the U.K. market. Humulin. It's outstandingly pure.¹ And it's a less immunogenic form of insulin than that which comes from the pancreas of pigs and cattle.² Hence it produces fewer antibodies.² Basically, Humulin uses genetic engineering and the techniques of recombinant DNA technology as the method of manufacture. Which means it can be produced economically and in large quantities for years to come.

In spite of this, however, many young diabetics like Matthew are still being prescribed purified pork insulin. Why? We don't really know. But what we do know is that the future is likely to see all patients on human insulin. So why shouldn't they be prescribed it now? After all, it's available in a variety of formulations to suit differing needs.

Humulin
Human Insulin (crb)
THE HUMAN WAY TO TREAT DIABETES

Figure 1. 1984 U.K. Advertisement for Humulin.
Humulin, from Eli Lilly, was the first recombinant human insulin on the U.S. market. In the original ad, the instructions for use appeared on the next page.

caused by transitioning patients to an insulin of different potency.²⁵ Although recombinant insulin was heavily advertised as a clinically superior agent in the 1980s (Fig. 1), almost no evidence was provided to demonstrate its superiority to the best available animal-extract insulins.²⁶ Although long-acting analogues cause less hypoglycemia than NPH does,²⁷ it has yet to be shown that analogues lead to better long-term outcomes than standard recombinant human insulin does.²⁸

No doubt for many patients, these incremental innovations were worth the added price.

What's surprising is that the trailing edge of old insulin products did not generate a market for generic competition but rather became a set of obsolete products that were promptly removed from the U.S. market. Pork and beef insulins are not merely underutilized, they are unavailable for human use in the United States. Even when practitioners prescribe NPH and R insulin in place of insulin glargine and insulin aspart, these cheaper prescriptions are filled with newer recombinant products sold under brand names. And yet on the whole, it's hard to say that contemporary patients who cannot afford their insulin (let alone the patent-protected glucometers and test strips required to adjust the dose) are well served by having as their only option an agent that is marginally more effective than those that could have been generically available 50 or 30 or 10 years ago, had generics manufacturers introduced cheaper versions when patents expired.

Generic-drug companies have evidently not considered it worthwhile to invest in the additional good manufacturing practices needed to produce a version of insulin that may already be obsolete, when off-patent small-molecule drugs represented lower-hanging fruit. Only recently, with insulin-analogue patents expiring and no next-generation products on the horizon, have prominent generics manufacturers shown serious interest in the insulin market.

It is hard to overstate the economic and public health impact of generic drugs in improving access to safe, effective, inexpensive medications in the United States. In the early 1960s, fewer than 1 in 10 medicines dispensed in pharmacies were generic, and most prescription drugs were effectively monopolies. Today, more than 80% of prescriptions are filled with generics, which saves the health care system billions of dollars each year.^{29,30} These savings are critical both for payers that are squeezed by rising health care costs and for patients, because lower medication costs are associated with better adherence³¹ and better outcomes.³²

But the case of insulin demonstrates that the generics market is like other markets — not an automatic phase in the life cycle of a drug. As the increasing waves of generic-drug shortages in the past decade also remind us, the drugs that ultimately see extensive generic competition differ from those that attract few, if any, manu-

facturers. The history of insulin highlights the limits of generic competition as a public health framework. Nearly a century after its discovery, there is still no inexpensive supply of insulin for people living with diabetes in North America, and Americans are paying a steep price for the continued rejuvenation of this oldest of modern medicines.

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From the Division of General Internal Medicine (J.A.G., K.R.R.), the Department of the History of Medicine (J.A.G.), and the Berman Institute of Bioethics (K.R.R.), Johns Hopkins University School of Medicine, Baltimore.

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