

**Testimony for the Record
Submitted to the United States Senate
Special Committee on Aging
for Hearings on Insulin Access and Affordability: The Rising Cost of Treatment**

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Chairman Collins and Ranking Member Casey, thank you for the opportunity to submit testimony on this vital matter. The affordability of lifesaving medicines has been a subject of central concern in my own career, both as a historian of the pharmaceutical industry^{1 2 3} and an internist in a busy inner-city community health center in East Baltimore. No single issue exposes the tragedy and absurdity of our inability to provide 20th century cures to patients in the 21st century as does the increasing unaffordability of insulin for Americans living with diabetes today.^{4 5}

As you know, diabetes mellitus is a disease that now affects more than 9% of the U.S., population, an estimated 30.3 million Americans as of 2015.⁶ For the 1.25 million of Americans with I diabetes, insulin is an absolute requirement for survival. Their bodies no longer produce this vital hormone, and without access to a pharmaceutical version they die, typically from diabetic ketoacidosis. Of the larger population of Americans living with type II diabetes, whose bodies are no longer responsive to the insulin they do produce, some can manage their illness with lifestyle measures such as dietary change, exercise, and weight loss. Most, however, require treatment with one or more oral medications in order to bring their escalating blood sugar levels under control, and prevent the many serious long-term complications that type II diabetes brings: loss of vision, loss of sensation, stroke, heart disease, kidney failure, loss of limbs, coma,

¹ Jeremy A. Greene, *Generic: The Unbranding of Modern Medicine*. Baltimore: Johns Hopkins University Press, 2014.

² Jeremy A. Greene, "Drug bust: For 30 years, generic medications helped make health care cheaper. Why is their cost surging?" *Slate*. Nov 20, 2014.
http://www.slate.com/articles/business/moneybox/2014/11/generic_drug_prices_why_their_prices_are_suddenly_surging.html

³ Jeremy A. Greene, "When old drugs are made new again," *Forbes*. April 23, 2015.
<http://www.forbes.com/sites/matthewherper/2015/04/23/when-old-drugs-are-made-new-again/>

⁴ Jeremy A. Greene and Kevin Riggs, "Why is there no generic insulin? Historical origins of a modern problem," *New England Journal of Medicine* 2015; 372:1171-5

⁵ Jeremy A. Greene, "Cornering the market on essential drugs" *Slate* September 23, 2015.
http://www.slate.com/articles/health_and_science/medical_examiner/2015/09/generic_drug_price_gouging_how_shkreli_and_other_monopolists_cornered_the.html

⁶ <http://www.diabetes.org/diabetes-basics/statistics/>

and death. For many of these patients, even those who observe dietary change, exercise, and oral medications, the combination simply is not enough control their disease. Between 20 and 30% of patients with type II diabetes require insulin to achieve control of their blood sugars: for these millions of Americans, this drug is a necessary tool to avoid preventable loss of life and limb.^{7 8}

I work as an internist in the East Baltimore Medical Center, a busy urban community health center associated with Johns Hopkins University School of Medicine that functions as a safety net for residents in the broader Baltimore area. Every week in my clinic I see patients with type II diabetes who require insulin to manage their disease and whose blood sugar is not controlled. Controlling diabetes with insulin is not easy, and there are a number of social, biological, economic, psychological, biological, and structural factors through which even the best-behaved patient can face challenges in using their medicines correctly to control this chronic disease. This is especially for many of the patients in my clinic. Factors including language barriers, health literacy, physical side effects, comorbid depression, homelessness, unstable work, and lack of access to regular medical care have all been documented to influence the ability of individual patients to make appropriate use of this lifesaving medicine.⁹ These factors are also known to exacerbate disparities in diabetes outcomes by race, ethnicity, social geography, education level, and income.^{10 11 12} Yet until recently, the cost of insulin itself was not understood to be part of the problem. Insulin was an old drug, an off-patent drug, first patented in 1923—how could the price of this drug meaningfully affect the delivery of care?

And yet in the past decade, when I asked my patients why it was that they were having a difficult time adhering with the insulin regimens that I was prescribing for them, I increasingly heard that the cost of the medicine itself had become prohibitive. I thought that perhaps the problem was that these patients were mistakenly given one of the newer, more expensive versions of insulin, or a patented delivery device such as an injection pen, when what they really needed in order to make insulin a practical part of their lives was older, but more affordable, generic vial of regular and NPH insulin. So I called a series of pharmacies in Baltimore to ask how to make sure that my patients received affordable generic insulin, and was surprised to learn that this thing, “generic insulin”, simply did not exist. Indeed, all insulin for sale in the United States in 2015 came from one of three brand-name manufacturers: Eli Lilly, Sanofi-Aventis, and Novo

⁷ IDF: International Diabetes Federation Diabetes Atlas 8th Edition. Brussels, International Diabetes Federation, 2017.

⁸ Health Action International. *Access to Insulin: Current Challenges and Constraints*. March 23, 2017. <http://haiweb.org/publication/access-study-report-access-insulin-current-challenges-constraints/>

⁹ K Capoccia, PS Odegard, N Letassy. Medication adherence with diabetes medication: A systematic review of the literature. *Diabetes Education* 2016; 42(1):34-71.

¹⁰ A Fernandez, J Quan, MM Parker, D Schillinger, AJ Karter. Adherence to newly prescribed diabetes medications among insured Latino and White patients with diabetes. *JAMA Internal Medicine* 2017; 177(3):371-9

¹¹ I Lerman, JP Diaz, ME Ibarguengoitia, FH Perez, AR Villa, ML Velasco, RG Cruz, JA Rodrigo. Nonadherence to insulin therapy in low-income, type 2 diabetic patients. *Endocrinology Practice* 2009; 15(1):41-6.

¹² JR Canedo, ST Miller, D Schlundt, MK Fadden, M Sanderson. Racial/ethnic disparities in diabetes quality of care: the role of healthcare access and socioeconomic status. *Journal of Racial and Ethnic Healthcare Disparities* 2018; 5(1):7-14.

Nordisk. These three brand-name firms dominated the nearly \$27 billion dollar global insulin market, controlling 99% of the market by volume.¹³

We know from a number of studies the off-patent pharmaceutical marketplace that robust price competition does not occur in the pharmaceutical marketplace until four or more manufacturers compete in a given drug market.^{14 15} But in the case of the insulin market, prices have been rising dramatically over the past decade, with no clear indication of why.¹⁶ Eli Lilly's Humalog cost \$21 a vial when it was first introduced in 1996. At the time, that price was substantially more expensive than existing insulin products, but innovative products are expected to cost more when they are first introduced, and then gradually decrease in price once patents expire and competition emerges. By 2017, however, the now off-patent Humalog cost \$275 for a month's supply.¹⁷ All told, the price of insulin products have increased more than 270% in the past decade. These dramatic increases have real consequences in the lives of Americans living with diabetes, who face increasingly untenable choices between insulin and other necessary expenses of daily life.¹⁸

An survey of people living with type I diabetes found that more than one out of four had rationed insulin at least once due to cost in the past year, and more than half of them had rationed insulin monthly, weekly, or daily due to cost.¹⁹ This is not only true for type I diabetes: after a colleague of mine, who runs a busy diabetes clinic including both type I and type II patients began systematically asking her patients whether they ever rationed or withheld insulin due to costs, the same proportion—one in four—of her patients said that they did. Patients who rationed or withheld insulin due to cost were more likely to come from lower income levels, have variable insurance coverage, and were more likely to present with uncontrolled blood sugar levels (and therefore be at higher risk of complications). The most common cause of death worldwide for children with diabetes is lack of access to insulin, and not only in poorer countries.²⁰ Independent studies indicate that more than 25% of life-threatening hospitalizations for diabetes in U.S. inner-city minority patients could be attributed to inability to afford a regular

¹³ Health Action International. *Access to Insulin: Current Challenges and Constraints*. March 23, 2017. <http://haiweb.org/publication/acciss-study-report-access-insulin-current-challenges-constraints/>

¹⁴ Berndt ER, Mortimer R, Bhattacharjya A, Parece A, Tuttle E. Authorized generic drugs, price competition, and consumers' welfare. *Health Affairs* 2007;26(3):790-799.

¹⁵ Jonathan Alpern, William M. Stauffer, Aaron Kesselheim. High cost generic drugs: implications for patients and policymakers. *New England Journal of Medicine* 2014; 371:1859-62.

¹⁶ Luo J, Avorn J, Kesselheim AS: Trends in Medicaid Reimbursements for Insulin From 1991 Through 2014. *JAMA*

¹⁷ Paul Barret and Robert Langreth. The crazy math behind drug prices. *Bloomberg Businessweek* June 29, 2017. <https://www.bloomberg.com/news/articles/2017-06-29/the-crazy-math-behind-drug-prices>

¹⁸ Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND: Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. *JAMA* 2014;311:2331-2333

¹⁹ T1 International. *Access to Insulin and Supplies Survey*. 2016. <https://www.t1international.com/insulin-and-supply-survey/>

²⁰ Gale EA: Dying of diabetes. *Lancet* 2006;368:1626-1628

supply of insulin.²¹ Yet uninsured or under-insured Americans face a particular burden, as the price of insulins are higher here in the United States than anywhere else in the world.

Why is there no generic insulin?²²

Until recently, most national debates over the high prices of prescription drugs have centered on the price of newer, on-patent medications, with the assumption that the prices of older, off-patent medications become negligible once they are subject to generic competition. Much of present-day American pharmaceutical policy takes it as a given that the historical relationship between on-patent brand name and off-patent generic drugs serves to balance pharmaceutical innovation and pharmaceutical access. The story goes something like this: in the first (patent-protected) phase of its life, a new drug is given a patent-monopoly to reimburse its developers for the substantial costs of pharmaceutical innovation. In the second (off-patent) phase of its life, competition brings prices down so that a supply of effective but affordable medications are widely available. So far so good. But as the Senate Aging Committee carefully documented in your investigative work leading to the 2016 report on *Sudden Price Spikes in Off-Patent Prescription Drugs*,²³ we are finding that drugs enter a third, uncharted phase, where dwindling competition creates new monopolies and the accelerated series of drug shortages and price hikes now affecting millions of Americans. In spite of recent efforts by the U.S. Food and Drug Administration to create a “fast track” for approvals for generic versions of off-patent pharmaceutical products with little or no competition, and recent actions by several state governments to provide greater transparency into pharmaceutical pricing and eliminate price-gouging of off-patent drugs,²⁴ recent evidence suggests these practices continue.^{25 26 27}

The unaffordability of old drugs is particularly tragic in the case of insulin. Why is a medication discovered almost 100 years ago still not available as a low-priced generic agent? To understanding the problem of access to insulin, it is essential to trace the historical origins of this modern conundrum, and its implications for contemporary policy and practice.

²¹ L. Randall, J. Begovic, M. Hudson, D. Smiley, L. Peng, N. Pitre, D. Umpierrez. Recurrent diabetic ketoacidosis in inner city minority patients: behavioral, socioeconomic, and psychosocial factors. *Diabetes Care* 2011; 34(9):1891-6.

²² Parts of this and subsequent sections of this testimony are excerpted, with updated references, from Jeremy A. Greene and Kevin Riggs, “Why is there no generic insulin? Historical origins of a modern problem,” *New England Journal of Medicine* 2015; 372:1171-5

²³ Special Committee on Aging, United States Senate. *Sudden Price Spikes in Off-Patent Prescription Drugs: The Monopoly Business Model that Harms Patients, Taxpayers, and the U.S. Health Care System*. Washington, D.C.: Government Printing Office, December 2016.

²⁴ Jeremy A. Greene, “Targeting unconscionable prescription-drug prices: Maryland’s anti-price-gouging law.” *New England Journal of Medicine* 2017; 377:101-103. <http://www.nejm.org/doi/full/10.1056/NEJMp1704907>

²⁵ Rachel B. Doyle, “The limits of charity from a drug company” *New Yorker* February 28, 2017. <https://www.newyorker.com/business/currency/the-limits-of-charity-from-a-drug-company>

²⁶ Peter Loftus, “Drug prices soar without generics” *Wall Street Journal* December 26, 2017.

<https://www.wsj.com/articles/cancer-drug-price-rises-1400-with-no-generic-to-challenge-it-1514203201>

²⁷ R Gupta, A Henkel, HP Forman, JS Ross. The impact of off-patent drug acquisitions on prices. *Journal of General Internal Medicine* 2018.

When insulin was discovered in 1921, it was hailed as one of the first “wonder drugs,” capable of transforming a fatal affliction into a manageable chronic condition.²⁸ And yet today—with the exception of two recently-approved “follow on” versions, insulin is only available in more expensive brand-name forms. 99% of the global insulin market by volume is supplied by three firms: Eli Lilly, Novo Nordisk, and Sanofi-Aventis. While many other common medications are available as \$4 generics, there are no similarly low-priced versions of insulin available, particularly for those without insurance (with the exception of ReliOn, a version of Novo Nordisk’s Novolin insulin which Wal-Mart exclusively sells for \$25). For many with insurance—and many more without it—the price of insulin is still too high to pay, with disastrous consequences for individual and systemic management of this most prevalent of chronic diseases.^{29 30}

In a widely celebrated tale of biomedical serendipity, insulin was discovered by an unlikely scientific team at the University of Toronto in 1921, 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 were able to produce enough insulin to treat the first patient, Leonard Thompson, in 1922. A patent was not filed for the discovery until later, in part because academic medicine viewed the patenting of biomedical research in the early 20th century with some distaste. When the Toronto team applied for an American patent on insulin in January of 1923, they were careful to state their goal was not profit, but ensuring the speedy and safe availability of their discovery to the general public. The patent, as they wrote in a letter to the president of the University of Toronto that year, 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.”³¹

Patenting insulin also allowed those at the University of Toronto to ensure high quality control by controlling *who* could manufacture insulin.³² After attempting to manufacture insulin in a production facility on the campus at the University of Toronto, the original researchers realized that they needed help, as they did not have the pharmaceutical manufacturing expertise needed to produce enough drug for North American markets. In 1923, they teamed up with the Eli Lilly Company, an established pharmaceutical company with experience in glandular extracts. Lilly was allowed to take out American patents to any improvements to manufacturing process, but Toronto would receive the patent rights for rest of world. Throughout that year, the team at Toronto licensed the rights to produce insulin to numerous other companies in different

²⁸ Feudtner JC. *Bittersweet: Diabetes, Insulin, and the Transformation of Illness*. Chapel Hill: University of North Carolina Press, 2003.

²⁹ Piette JD, Heisler M, Wagner TH. Problems paying out-of-pocket medication costs among older adults with diabetes. *Diabetes Care* 2004;27:384-91.

³⁰ Lipska KJ, Ross JS, Van Houten HK, Beran D, Yudkin JS, Shah ND: Use and out-of-pocket costs of insulin for type 2 diabetes mellitus from 2000 through 2010. *JAMA* 2014;311:2331-2333.

³¹ Bliss M. *The Discovery of Insulin*. Chicago: University of Chicago Press; 2013.

³² Cassier M, Sinding C. ‘Patenting in the public interest’: administration of insulin patents by the University of Toronto. *History and Technology* 2008;24:153-71.

countries. One of those companies, Nordisk Insulinlaboratorium (which later merged with Novo Terapeutisk Laboratorium to form Novo Nordisk) in Denmark, would become a major innovator of brand-name insulin products in its own right.

The public health impact of insulin was visible almost immediately after the first demonstration of its efficacy in a Toronto patient named Leonard Thompson in 1922. By October of that year, newspapers in Ontario announced that for the first time in the history of the city of London, Ontario, three months had passed with no deaths due to diabetes. Before the introduction of insulin, the life expectancy for a patient with type I diabetes diagnosed at age 10 was only 1-3 years. By the end of the 1920s, life expectancy had jumped to 32 years; by the onset of WWII it had jumped further to 45 years, while the person diagnosed with type I diabetes in the year 2011 could expect an average life expectancy of 75 years.³³

Modifying insulin: safety, efficacy, and palatability

Insulin was immediately perceived to be a lifesaving drug of vast clinical and public health significance. And yet the initial animal extracts produced by Lilly and others had limitations. First, the short duration of action necessitated frequent injections. In the early 1930s, Hans Christian Hagedorn and colleagues at Nordisk discovered that adding protamine to insulin altered the absorption and prolonged the action.³⁴ These first protamine insulins represented a significant innovation, but their amorphous 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, or NPH,³⁵ was patented in 1946. This advance made it possible to combine long-acting and short-acting insulin, allowing many with diabetes to be treated with a single daily injection. Soon afterwards, a method for prolonging the action of insulin without the addition of protamine was discovered, which led to the introduction of the lente insulins in the mid-1950s.³⁶ These discoveries offered more options in titrating insulin regimens, but extended the reach of insulin patents into the 1970s.

Second, these initial beef and pork insulins also were plagued with the problems inherent to extracts of animal tissue. Impurities in the medication could cause local site reactions, and immunological reactions to non-human proteins could decrease efficacy and precipitate allergic responses. A series of innovations in the manufacturing process of insulin 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 improvements in product safety extended insulin patents into the late 1980s.

³³ Gale EA: Dying of diabetes. *Lancet* 2006;368:1626-1628

³⁴ Hagedorn HC, Jensen BN, Krarup NB, Wodstrup I. Protamine insulinate. *JAMA* 1936;106:177-80.

³⁵ Heller S, Kozlovski P, Kurtzhals P. Insulin's 85th anniversary--An enduring medical miracle. *Diabetes Res Clin Pract* 2007;78:149-58.

³⁶ Lawrence RD, Oakley W. A new long-acting insulin; a preliminary trial of lente Novo insulin. *Br Med J* 1953;1:242-4.

By the late 1970s, however, further improvements to the purity of animal extracts were sidelined when it became possible to produce human insulin through recombinant technology. Investors in the field of biotech saw insulin as an ideal product for the new industry after Genentech scientists succeeded in producing the first recombinant DNA human insulin in 1978 by inserting the cloned insulin gene into the bacteria *Escherichia coli*.³⁷ This technology led to Lilly bringing the first recombinant human insulins to the US market in 1982, Humulin R (rapid) and N (NPH). Around the same time, Novo and Nordisk developed methods for chemically converting bovine to human insulin, allowing them to compete in the initial market of human insulin. Novo Nordisk eventually brought their first recombinant insulin to market in 1988. A new web of insulin patents, held by the 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 very structure of insulin in attempt to improve its physiologic effects. In the late 1980s, it was shown that single amino-acid substitutions could result in significantly more rapid absorption of insulin.³⁸ Theoretically, more rapid absorption allowed injected insulin to more closely mimic the prandial insulin release by the pancreas. Lispro was the first short-acting insulin analog approved in 1996 followed by aspart in 2000 and glulisine in 2004. The same concept that allowed for fast-acting analogues also allowed for engineering long-acting analogues. Since NPH has an unpredictable peak and duration of action less than 24 hours,³⁹ 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 insulin in 2005; the first patents on these products expired in June 2014.

Are larger molecules just harder to copy?

Why, then, is a drug originally patented in 1923 not available in generic form in 2014? Some have argued that biological drugs are larger, more complex, and harder to copy than the small molecules on which the generic drug industry was initially built in the second half of the 20th century. Many have hoped that a new era of “biosimilar” insulins would lead to competitive pricing and more affordable insulin products now that the latest crop of insulin patents have expired. Biological drugs developed by biotech firms in recent decades are larger than small-molecule drugs by orders of magnitude, and it is often impossible to know on an atom-by-atom basis whether the molecule is the same. Off-patent biotech drugs are therefore called biosimilar or follow-on rather than generic.⁴⁰

³⁷ Goeddel DV, Kleid DG, Bolivar F, et al. Expression in *Escherichia coli* of chemically synthesized genes for human insulin. *Proc Natl Acad Sci U S A* 1979;76:106-10.

³⁸ Brange J, Ribel U, Hansen JF, et al. Monomeric insulins obtained by protein engineering and their medical implications. *Nature* 1988;333:679-82.

³⁹ Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000;23:644-9.

⁴⁰ Perrin C, Ewen M, Beran D: The role of biosimilar manufacturers in improving access to

Yet economists warn that the introduction of biosimilars are unlikely to lead to equivalent price reductions compared to those seen with typical generic medicines. Even an abbreviated approval process for biosimilar approval requires significantly more original data than the typical abbreviated new drug application required for small-molecule generic approval, and can require other forms of data on immunogenicity and other safety studies in humans.⁴¹ It was predicted that price reductions for biosimilar insulins in the US will be in the range of 20–40%, much less than the 80% or greater price reduction for most small molecule generics.⁴² So far, follow-on or biosimilar insulin products have lived up to these diminished expectations. In December 2015, the FDA approved Basaglar, Eli Lilly’s follow-on version of Sanofi’s long-acting analog insulin glargine (Lantus). Priced at \$234 for a carton instead of \$278,⁴³ Basaglar is technically cheaper than Lantus, but the difference can be a moot point for those for whom paying more than \$200 per month for a single medication is not tenable. More recently, in December 2017 the FDA approved Admelog, Sanofi’s follow-on version of Eli Lilly’s short-acting analog insulin lispro (Humalog); while Sanofi promises significant savings to consumers it is unlikely that the savings will be substantial. As this trading of follow-on products also documents, the promise of biosimilar competition has not yet expanded the network of insulin producers outside of the original trio of brand-name companies.

The paradox of incremental innovation

Reducing the problem of generic insulin to the contemporary debate over biosimilarity also fails to address the underlying historical problem of why there was no generic insulin in the 2000s, or the 1990s, or the 1980s, or earlier: that incremental innovation itself has repeatedly precluded the formation of a generic insulin industry in North America when earlier patents expired. Simply put, the history of insulin does not follow the standard chronology of pharmaceutical innovation in which patent monopolies naturally 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 a series of incremental improvements. Subsequent iterations of insulin represented actual innovations, each one safer, more effective, or more convenient than the product that came before. And yet at the end of these generations of incremental innovation, insulin is not necessarily any more affordable to the general public than it was when the original patent holders sold their stake for \$1 to insure access to this essential medicine.

Several pharmaceutical industry analysts have described a repatenting tactic called evergreening, in which a nest of subsequent patents—often metabolites or optical isomers—iteratively help to

insulin globally. *The Lancet Diabetes & Endocrinology* 2017

⁴¹ Engelberg AB, Kesselheim AS, Avorn J. Balancing innovation, access, and profits—market exclusivity for biologics. *N Engl J Med* 2009;361:1917-9.

⁴² Heinemann L. Biosimilar insulins: how will this story evolve? *Diabetes Technol Ther* 2012;14:986-8.

⁴³ <https://www.goodrx.com/lantus/>; <https://www.goodrx.com/basaglar/>

extend the life of a product after initial patent expiry.⁴⁴ Evergreening can shift market share within a related family of products: for example, after Pfizer lost patent exclusivity on the antiepileptic gabapentin (Neurontin) in 2004, the firm managed to retain a healthy share of the market through patents on a metabolic cognate, pregabalin (Lyrica). Critics of evergreening often claim that the incremental innovations from one drug to another “me-too” drug are trivial: pregabalin, for example, is not clearly safer or more efficacious than gabapentin. But the cascading generations of insulin products described in this article can hardly be dismissed as simply “me-too” medicines. Protamine insulin offered a distinct advantage over regular; NPH insulin offered a distinct advantage over protamine, and so on.

On the whole, today’s insulin 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 diabetics, is a more difficult question to answer. When lente insulin was introduced in the 1950s, some questioned whether the minimal theoretical advantages it offered over NPH warranted the additional complexity introduced by adding another insulin formulation to the market.⁴⁵ The theoretical advantages offered by the monocomponent extract insulins may have been outweighed in some cases by the inconvenience and risk caused by transitioning patients to a form of insulin with different potency.⁴⁶ Although recombinant insulin was heavily advertised as a clinically superior agent in the 1980s, almost no evidence was provided at the time to demonstrate clinical superiority to the best available animal extract insulins.⁴⁷ Although long-acting analogues cause less hypoglycemia than NPH,²⁷ significantly better long-term outcomes have yet to be demonstrated with analogues compared to recombinant human insulin.²⁸ Serial evidence-based reviews conducted by the World Health Organization in 2011 and 2017, and by the Cochrane Collaboration in 2005, 2006, 2007, and 2017 have failed to find substantial evidentiary basis for the widespread utilization of analog insulins over recombinant human insulins. In 2011, the World Health Organization Expert Committee on the Selection and Use of Essential Medicines “concluded that insulin analogues currently offer no significant clinical advantage over recombinant human insulin and there is still concern about possible long-term adverse effects.”⁴⁸ The 2017 WHO report likewise did not recommend widespread use of analog insulins, “noting the small magnitude of benefit and current high price compared to human insulin.”⁴⁹

It is possible that the field of value-based pricing may offer some tools for understanding how to manage future incremental innovations in the field of diabetes care. Value-based pricing systems promise to set the price of a new drug according to its relative value (for example, the degree of

⁴⁴ Hitchings AW, Baker EH, Khong TK. Making medicines evergreen. *BMJ* 2012;345:e7941.

⁴⁵ Slayton RE, Burrows RE, Marble A. Lente insulin in the treatment of diabetes. *N Engl J Med* 1955;253:722-5.

⁴⁶ Logie AW, Stowers JM. Hazards of monocomponent insulins. *Br Med J* 1976;1:879-80.

⁴⁷ Richter B, Neises G, Bergerhoff K. Human versus animal insulin in people with diabetes mellitus. A systematic review. *Endocrinol Metab Clin North Am* 2002;31:723-49.

⁴⁸ Report of the World Health Organization Expert Committee on the Selection and Use of Essential Medicines. Geneva: WHO: 2011.

⁴⁹ Report of the World Health Organization Expert Committee on the Selection and Use of Essential Medicines. Geneva: WHO: 2017

improved efficacy or safety over existing medications).⁵⁰⁵¹ One could imagine that application of such an approach during the introduction of recombinant and analog insulin products could have resulted in a clearer differentiation of how much benefit, and for whom, these newer insulin products afforded. But it is harder to understand how a value-based pricing model can help contain the rising costs of drugs, such as Humalog, whose prices have risen exponentially in the decades following introduction—not when they were new drugs, but when they were approaching the end of their patent life.

No doubt for many patients these incremental innovations were worth the added price. What is surprising in the case of insulin, however, is that the trailing edge of old insulin products did not become a market for generic competition, instead becoming a set of obsolete products that were promptly removed from the American 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 glargine and aspart insulin, these “cheaper” prescriptions are filled with newer recombinant products sold as brand name drugs. And yet on the whole, it is hard to say that the patient in 2018 who cannot afford their insulin (let alone the array of patent-protected glucometers and test strips required to titrate it) is better served by only having the option of the marginally more effective agent than the quite effective versions that could have been generically available as of 1968, or 1988, or 2008, had generic manufacturers companies 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 have already become obsolete, when other off-patent small-molecule drugs represented lower-hanging fruit. Only recently, with insulin analogue patents expiring and no other next-generation products on the horizon, have prominent follow-on manufacturers showed serious interest in the competitive insulin market. Indeed, at this point there are no remaining patents on human insulin products—but there are an increasing amount of patents on insulin delivery devices.⁵² ⁵³

It is hard to overstate the economic and public health impact that generic drugs have played in improving access to safe, effective, and inexpensive medications for the American public. In the early 1960s, less than one out of every ten medicines dispensed in a pharmacy were generic, and the majority of prescription drugs were effectively monopolies. Today, more than 80% of prescriptions are filled generically, which saves the health care system billions of dollars each year.⁵⁴ On a macro level, these cost savings are critical for governments and other payors who are squeezed by rising health care costs; on a micro level they are critical for patients, as lower

⁵⁰ Bach PB, Pearson SD. Payer and policy maker steps to support value-based pricing for drugs. *JAMA*. 2015;314(23):2503-2504.

⁵¹ Anna Kaltenboeck, Peter B. Bach. Value-based pricing for drugs: themes and variations. *JAMA* April 30, 2018. E-publication ahead of print, <https://jamanetwork.com/journals/jama/fullarticle/2680422>

⁵² Jing Luo, Aaron S. Kesselheim. Evolution of insulin patents and market exclusivities in the USA. *The Lancet Diabetes & Endocrinology* 2015;3:835-837.

⁵³ Kaplan W, Beall R: Insulin Patent Profile. Amsterdam, Health Action International, 2016

⁵⁴ Haas JS, Phillips KA, Gerstenberger EP, Seger AC. Potential savings from substituting generic drugs for brand-name drugs: medical expenditure panel survey, 1997-2000. *Ann Intern Med* 2005;142:891-7

medication costs are associated with better compliance⁵⁵ and better outcomes.⁵⁶ But the case of insulin demonstrates that the generic market is a market space like other market spaces—it is 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, there is a heterogeneity of *which* drugs become the subject of extensive generic competition after patent expiry, and which attract few if any manufacturers. The history of insulin highlights some of the limits of the 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 continue to pay a steep price for the continued rejuvenation of this oldest of modern medicines.

What can Congress do?

By directing national attention towards the problem of insulin access and affordability, the Senate Special Committee on Aging has already taken an important first step towards resolving this problem. But there are a further set of steps that Congress can take that will be essential to insuring that future patients do not suffer from the increasing inaccessibility of these essential medicines.

Preserving access to insulin is not a Democratic or a Republican issue. This essential medicine, first patented 95 years ago, represents a vital infrastructure of our biomedical and public health system made increasingly precarious through price increases. These soaring prices occurs in a unique market space containing only three manufacturers, which is no longer exhibiting the pricing behavior one would expect of a truly competitive system. Solutions to this problem can be readily proposed from both sides of the aisle. But I repeat that all of these answers are premature if we do not understand how insulin prices are actually determined, if real prices are never visible, and if their impact on supply and demand cannot be understood. My colleagues who work in the field of pharmacoeconomics themselves have no means of studying true drug prices because the listed prices for pharmaceutical products in the United States of America—the AWP, or “average wholesale price”—bears almost no relation to the actual price negotiated between buyers and sellers through undisclosed bundling and discounting agreements.

The promise of generic competition in reducing costs is based in part on the assumption that the therapeutic marketplace allows direct interaction between the supply from competing producers and the demands of health care consumers. But in the decades since the passage of Hatch–Waxman Act of 1984, a host of mediating bodies have proliferated between drug manufacturers and those who directly consume their products. Beyond prescribing doctors and dispensing pharmacists there are now pharmacy and therapeutics (P&T) committees of hospitals or insurance plans, which determine which drugs are covered and which are not. There are also pharmacy benefit managers (PBMs) and group purchasing organizations (GPOs), two relatively

⁵⁵ Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol* 2014;32:306-11.

⁵⁶ Tamblyn R, Laprise R, Hanley JA, et al. Adverse events associated with prescription drug cost-sharing among poor and elderly persons. *JAMA* 2001;285:421-9.

obscure and thinly regulated parts of the health care sector that determine which manufacturers obtain contracts to supply most hospital and pharmacy chains in the United States. What we first imagine as a free market for price competition turns out, on closer examination, to be a space crowded by different forms of middlemen, whose roles in influencing supply and demand in the generic drug sector are poorly understood. In recent years, the General Accounting Office has investigated the pricing structures of GPOs and the U.S. Senate has held hearings on the competitiveness of the PBM industry. But independently these efforts have been insufficient to piece together all the steps between producer and consumer in which the true price of insulin is set.

While existing state pharmaceutical pricing transparency laws are an important start to addressing the rising cost of off-patent prescription drugs,⁵⁷ none of these measures has yet been able to fully capture the real costs of drugs moving through interstate commerce, which are still protected as trade secrets. More action is clearly needed, at the federal level, in order to achieve a meaningful knowledge of insulin price increases and forge rational policies to respond appropriately and effectively. I urge you to consider the recommendations of the recent National Academies of Science, Engineering, and Medicine Consensus Study Report, *Making Medicines Affordable*, which call on Congress to require quarterly disclosure of information on a drug-by-drug basis from insurance plans (regarding the net prices paid for drugs, including patient cost sharing) and biopharmaceutical companies (about the average net volume of and prices for drugs, including discounts provided to pharmacy benefit managers and insurance plans), as well as annual public reports stating list prices, rebates, and the average net price of each drug sold in the United States, with a requirement for the U.S. Department of Health and Human Services to inform relevant Congressional committees of all net drug price increases that exceed the growth in the consumer price index for the previous year.⁵⁸

Congress alone holds the power to illuminate how the hidden pieces in the puzzle of drug pricing actually fit together. Only Congress has the power to follow the molecule through all the steps from production to consumption and understand where, exactly, the market is being distorted and help provide evidence that will allow us to reach a true and lasting solution. As this Special Committee did just a few years ago when confronted with the problem of rising prices of off-patent drugs, I urge you to find continued space for bipartisan investigation into this issue affecting millions of Americans.

⁵⁷ Nevada Senate Passes Insulin-Price Bill Tough on Drugmakers. *U.S. News and World Reports*, May 19, 2017. <https://www.usnews.com/news/best-states/nevada/articles/2017-05-19/nevada-senate-passes-insulin-price-bill-tough-on-drugmakers>

⁵⁸ Norman R. Augustine, Guru Madhavan, and Sharyl J. Nass, *Making Medicines Affordable: A National Imperative*. Washington, DC: National Academies of Science, Engineering, and Medicine, 2018.