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HISTORY

RESEARCH ARTICLE

The impact of biotechnology on the global insulin market

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Abstract

Biotechnology has had a dramatic impact on how insulin is manufactured, and how much it costs to produce it. This paper examines the political, economic and social impact of biotechnology on the global insulin market. It provides an assessment of claims made by manufacturers since the early 1980s that insulin produced using recombinant DNA technology would enhance affordability, safety, effectiveness, and access to this vital medicine. This study utilises primary and secondary sources, historical and current, over the period 1921 to 2024 including academic and medical journals, archival databases, legal opinions, government reports, newspaper and magazine articles and books, and personal files.

The study finds that biotechnology has failed on each of the counts claimed by the manufacturers, ie, affordability, safety, effectiveness, and access. Instead, it has transformed the global insulin market, leading to a collapse of domestic manufacturing in many countries and the emergence of a powerful oligopoly composed of three corporations: Novo Nordisk, Eli Lilly, and Sanofi. This has jeopardised the welfare of those who need secure access to safe and affordable insulin, particularly — but not only — those in low- and middle-income countries. A growing movement of diabetes activists around the globe is demanding changes to the global insulin market and to government policies.

Keywords: *insulin, biotechnology, access, recombinant DNA technology, genetic engineering*

Introduction

Since 1921, when it was discovered, the goal of insulin therapy has been to lighten the burden of diabetes and improve the quality of life for those who have the disease. However, these objectives have often clashed with those of corporate investors who are focused on profits and monopoly control of the insulin market. This study assesses the claims made by manufacturers since the early 1980s that biotechnology would improve safety and effectiveness for insulin users, and increase access and affordability.

This study utilises primary and secondary sources, historical and current, over the period 1921 to 2024, including academic and medical journals, archival databases, legal opinions, government reports, newspaper and magazine articles and books, and personal files. The sources were chosen both for their critical and noncritical perspectives on the subject of insulin and biotechnology, as well as for their accuracy, objectivity, authority, and respect for the experiences and voices of those — patients, researchers, physicians and others — who have sought fairness and justice in the global insulin market.

The dawn of insulin therapy

The discovery of insulin in 1921, extracted first from canine, and then cattle and pig pancreas glands, had a dramatic impact across the world, especially among those with Type 1 diabetes, for whom a diagnosis was followed by certain death. Since the 1980s, some conservative historians have described this scientific achievement as a good example of the "cooperation between a profit-making business [Eli Lilly] and an educational institution [the University of Toronto]," [1] where the discovery took place. In this narrative, the company and the university worked together for the greater good, in contrast to the "bitter personal rivalries" and "[p]hysical and verbal confrontations" [2] among the co-discoverers, Frederick Banting, Charles Best, JB Collip, and JJR Macleod.

While differences existed among these university collaborators, they were all aligned on the important political and ethical issues associated with patents and profits. The co-discoverers, like many others during the period, were opposed in principle to patents, described by Quebec's pharmacy association as "a curse to the physician, the pharmacist and the public" [3]. The University of Toronto, however, argued that patenting was necessary to protect patient safety and the integrity of the new miracle drug. Consequently, the reluctant patentees agreed to assign their rights to the University of Toronto for $1 each.[1] As Macleod explained in 1924, the sole purpose of the patent was to "[prevent] any other person from taking out a similar patent which might restrict the preparation of Insulin."[4] The overriding objective of the university's newly established Insulin Committee, Macleod said, was to ensure that "the best Insulin is supplied at the lowest cost" to countries around the world. The patentees insisted that the university widely publish the rationale behind the patent so that their reputations would not be sullied [5].

While Eli Lilly did not contribute to the discovery of insulin, an agreement was reached between the Canadian university and the American company to boost production, thereby expanding access to a safe supply. In exchange for its contribution to increasing production capacity and developing purification techniques to enhance safety, the university granted Eli Lilly a 13-month exclusive licence, in

effect a period of monopoly control [6]. However, tensions emerged between the Insulin Committee and the US company when Eli Lilly pushed to make this a permanent arrangement and indicated it intended to profit off the sale of insulin [7]. "At the risk of being considered to a degree selfish…", JK Lilly, the head of the company, argued the company should be the sole manufacturer in the United States. He claimed this would help lower the cost of insulin, as "competition… would require large expenditures in advertising and selling. Rivalry would be rife and expensive." [8]

This unfortunate licensing arrangement enabled the company to establish what would become a 60-year virtual monopoly in the United States. It stood in stark contrast to the arrangements made by the University of Toronto with most other countries. For example, it issued a licence to the United Kingdom's Medical Research Council which granted production rights to five companies from the United Kingdom (UK), free of royalties. By 1952, Britain was producing 3000 million international units of insulin per year, enough for up to 700,000 people, some of which it supplied to countries around the world, including Pakistan, India, Iceland, Peru, and Sri Lanka (then Ceylon). Like the University of Toronto, the Medical Research Council granted insulin licences to firms in other countries without royalty charges [9].

The University of Toronto focused much of its energy on assisting countries to set up domestic production capacity — a process described by Christopher Rutty, the University of Toronto's expert on the early history of insulin manufacturing, as "a slow and uneven process". Its licensing policies reflected this process [10]. The licences also gave the Insulin Committee the right to oversee the quality of the insulin the companies produced and to ensure there were enough producers to meet the growing demand, discourage monopoly control, and support access at low prices [11].

The principle articulated by JJR Macleod — "the best Insulin… at the lowest cost" — guided the work of the university's Insulin Committee, which administered the patent attached to the discovery to "set the standards of the new drug, control the quality of its industrial production, and regulate the conditions of its marketing."[11] It also helped influence an international regulatory framework designed to support the safety, effectiveness, and affordability of insulin that would survive until the dawn of the biotech era.

Access

From the moment of its discovery, access to insulin became a priority for countries worldwide. However, there were also rising concerns about barriers to access, especially during and after the Second World War. A 1949 review of the global insulin supply by the World Health Organization (WHO) noted that while demand for insulin had increased significantly during the war, producers had experienced problems obtaining pancreas glands due to rationing and declining international trade [12]. By 1942, the United States and other exporting nations refused to supply finished insulin to many countries due to wartime conditions, while British supply boats were often infrequent, interrupted, or damaged [13]. However, the report noted that since most insulin-producing countries were set to increase production in the post-war future, supplies would be more than adequate to meet the requirements of persons with diabetes.

During the debate on the report that followed at the World Health Assembly, delegates from South Asia, led by WG Wickremesinghe (Sri Lanka), KCKE Raja (India), and MK Afridi (Pakistan), disagreed. They argued that WHO should dedicate its efforts to "insulin self-sufficiency". One of the report's proposals was particularly controversial. It suggested that "countries lacking the necessary processing facilities" should supply pancreas glands to manufacturing countries, which, in return, would supply them with finished insulin. Wickremesinghe argued that such an approach would be "radically incorrect" and expensive, resulting in "undeveloped countries being forced to be dependent on external sources of supply". These delegates stressed that WHO's policy "should be to encourage local production". After some debate, the Assembly passed a resolution directing the WHO "to advise Governments, upon request, concerning the means of obtaining the necessary requirements for insulin." [12]

In the years that followed, many countries explored alternatives to import of insulin, including using more readily accessible local resources for domestic production. Other strategies focused on import duties to protect and support local producers and public manufacturing. Some studied the use of whale and fish pancreas glands, which had already been used in a few countries [13], including Japan, where whales were the source of insulin from 1944 to 1960 [14]. In New Zealand, researchers investigated the use of sheep, a key part of the agricultural sector, to determine whether this would be a safe source with adequate yields of the needed glands, and economically preferable to importing insulin. India, too, began to focus on pharmaceutical manufacturing after Independence in 1947. With support from the Soviet Union in the early 1960s, it introduced policies that encouraged self-reliance in producing affordable medicines [15].

The early post-war years also saw an emerging focus among researchers, scientists, and manufacturers on increasing the range of insulin options at a lower cost to patients. In a speech to the Industrial Research Institute in Pennsylvania in 1962, Thomas Carney, who was then Vice President of Research and Development at Eli Lilly, boasted that the price of its insulin had been reduced 13 times since 1923 while it had been increased just once in 38 years. According to him, during the same period, six new insulin products were introduced, which reduced the amount of insulin required for most diabetics from several daily doses to only one [16]. Fifteen years later, Connaught Labs in Canada published an inventory of its entire insulin portfolio, which included six

standard types of insulin in both beef and pork varieties and in two concentrations. In addition, the report described "more than a dozen speciality insulins vital to a small number of Canadian diabetics but amounting to less than ½% of production by volume."[17] By this time, producers had markedly improved the purity of insulin through advances in manufacturing, making allergic reactions a relatively rare experience [18].

Despite the strong support for local production expressed by delegates to the World Health Assembly 30 years earlier, and the ethical framework established by the co-discoverers in 1922, secure access to safe and affordable supplies of insulin has remained a problem for many people across the world. Several factors, including sanctions, regional wars, privatisation, the collapse of domestic manufacturing, deregulation, and patents, have negatively impacted access [19]. Health Action International [20] and others [21] have extensively documented these and other factors affecting people who need insulin, half of whom are unable to access it, particularly in low- and middle-income countries (LMICs).

Many of these factors also supported the development of an oligopoly composed of three dominant manufacturers — Eli Lilly, Novo Nordisk, and Sanofi. This development also adversely affected access to insulin, particularly since the mid-1980s when Eli Lilly and Novo Nordisk began to aggressively expand their presence in higher-income markets — Novo into the United States and Lilly into Europe. Although Eli Lilly claimed a 50% share of the world market, it was concentrated almost entirely in the United States, where it had a near monopoly [22]. Novo, with roughly 30% of the global market, was present mainly in Europe and Japan [23]. Nordisk, the third largest insulin producer, had no significant presence outside Germany (16%) and Denmark (75%) [24]. In 1989, Novo merged with its Danish competitor, Nordisk [25] to boost its plans to expand globally.

Together, Eli Lilly, Novo Nordisk, and Sanofi currently control 99% of the global market by value and 96% by volume [26]. Several developments contributed to this high level of corporate concentration, but perhaps none were as decisive as the emergence of recombinant DNA (rDNA) technology in the late 1970s and early 1980s, a development in which insulin played an important role.

The very short road to recombinant human insulin

In August 1978, Genentech, a young start-up based in South San Francisco, announced it had succeeded in cloning the insulin gene. It beat two other research centres — Harvard University and the University of California at San Francisco (UCSF) — all racing to cross the finish line first [27]. In stark contrast to the ethical qualms felt among insulin's co-discoverers nearly 60 years earlier, the very next day, Genentech filed a patent application and signed an exclusive licensing agreement with Eli Lilly, which had been funding the Genentech and UCSF research teams [28]. However, Genentech was not the only group filing for patents on the insulin gene. By 1997, six lawsuits involving Lilly, Genentech, and UCSF had been filed in the US Supreme Court contesting ownership of the product and process, costing $30 million, and establishing legal precedents in patenting processes and DNA sequences in the United States [29].

Gene splicing was a controversial field in the mid-1970s when Eli Lilly began courting molecular biologists, most of whom worked in US universities. It sparked debates about whether the financial incentives offered by private investors overshadowed ethical considerations in developing rDNA technology [30]. Irving Johnson, who led Eli Lilly's collaboration efforts, recounted that the public and scientists were deeply divided on whether rDNA research was harmful or beneficial. Many demanded to know when Eli Lilly was "going to quit lobbying against legislation to regulate and control rDNA research?" — an activity that Johnson preferred to portray as an effort to educate legislators and the public about the benefits of the technology [31].

The demands for regulatory framework governing rDNA research were widespread. They sparked one of the largest lobbying efforts in US history, which, according to one report, "helped to persuade legislators that the scientific and commercial benefits of genetic engineering outweighed its potential risks."[32] In the 1980s, 16 bills that aimed to restrict research died before Congress. The US Supreme Court reversed the established norm, which held that life was not patentable, and instead ruled that live, human-made micro-organisms could be patented [33].

Eli Lilly maintained that its decision to invest heavily in biotechnology was triggered by its own prediction that pancreatic glands for the production of animal insulin "could likely be in very short supply" in the future [34]. However, a study by the US Department of Health, Education and Welfare contradicted these dire warnings, concluding that it was "clear that no shortage of insulin [was] anticipated."[35] Nonetheless, Eli Lilly insisted, and the media dutifully reported that the main reason the company had chosen the "genetic engineering route…was a growing fear of a future shortage of pig and cattle pancreases."[36] However, Robert Swanson, co-founder of Genentech, gave a different and more plausible explanation. In 1984, he told *Esquire* magazine that "the first product [of biotechnology] should have an existing market" which would reduce the cost of marketing. "And the economics of production," he said, "would have to compare favorably to the way it is produced currently."[37] It was that simple.

Very few people needed to be persuaded that insulin was essential in treating diabetes. Eli Lilly asserted that biotechnology could guarantee uninterrupted, limitless supplies of "human" insulin, a vital medicine. In many ways, insulin represented the perfect product to launch biotechnology into a world that was wary of the science, and concerned about patenting human genetic material.

In December 1980, Eli Lilly commenced clinical trials on Humulin insulin [38, 39] and, within 18 months, was applying to regulators in the United Kingdom, the Netherlands, West Germany, and Canada for market authorisation. In the US and many other countries, Humulin received approval five months after the company submitted its application to the US Food and Drug Administration (FDA) [40] although the median regulatory review times during the period ranged between 28 and 34 months [41].

Meanwhile, on the other side of the Atlantic, Novo announced that it had chemically transformed the porcine insulin molecule into human insulin and was prepared to begin clinical trials, first in the United Kingdom and then internationally [42]. In 1982, it launched its version of human insulin in Malta, where, at the time, new drug products did not require regulatory approval [43].

Enough insulin for the world

Genetic engineering promised what was described by the FDA in 1982 as a "virtually limitless supply of…insulin" [44]. Manufacturers claimed that the age of biotechnology would "ensure a readily available and less expensive supply for diabetics around the world."[45] Unfortunately, the shift to gene splicing guaranteed neither lower-priced insulin nor secure access. It did, however, support the efforts of Novo Nordisk and Eli Lilly to restructure the global insulin market, valued at $400 million when the first recombinant human insulins (RHIs) were approved [36].

Both Novo and Lilly invested heavily in the development of factories that would significantly reduce the cost of production and increase production capacity. In 1980, Eli Lilly announced it was spending $40 million to build two new manufacturing plants [46], a cost that would jump to $60 million when it finally completed the construction. Initially, Novo employed a chemical process rather than rDNA to produce its own version of human insulin, enabling it to expand its existing facilities. Subsequently, it adopted the same rDNA technology as Eli Lilly.

The increased production capacity of both companies made it imperative that they expand their markets, both in terms of geography and populations living in higher income countries. Eli Lilly's first foray across the Atlantic was Britain, home to seven insulin manufacturers [47]. At the same time, Novo pursued strategic partnerships with several companies, including ER Squibb in the United States, Canada's publicly-owned Connaught Labs, and Commonwealth Serum Laboratories, owned by the Australian government. Lilly and Novo faced competition from each other and from domestic manufacturers who were well-established in the countries whose markets they were targeting, some of which were also interested in biotechnology.

Even before Eli Lilly set up its biotech production facilities, according to the *Financial Times of London,* the company had, in 1982, "the capacity to produce enough [insulin] for all of America's needs." [36] Three years later, it was producing 30 billion units per year of bovine insulin alone, some of which came from its subsidiary in Argentina [48]. Competition on its home turf from Novo, which had increased its share of the US market to 20%, was unwelcome [49]. In contrast, Lilly's own progress in Europe was painfully slow, with its share of the insulin market stalled at 4% [50]. Furthermore, it was also facing sceptical physicians in the US who were reluctant to prescribe a new insulin that was as safe and effective as older animal insulins but cost two to three times more [51].

Argentina, which had been producing insulin since the early 1930s, was probably the first country to feel the impact of Lilly's over-capacity problems. It relied on a robust domestic stockbreeding industry to supply the raw materials until the 1960s when Eli Lilly purchased the only production facility [52]. Some 20 years later, amid an economic crisis with inflation rates above 800%, Argentina imposed price controls on all products, including medicines. Eli Lilly, which exported 85% of production from its Argentinian plant, most of it to the United States, demanded an exemption so it could increase prices by up to 72%. The government refused, and Lilly closed the plant, leaving 73,500 people with diabetes without access to insulin [48].

Argentina recovered from Eli Lilly's abrupt withdrawal by implementing a regulatory regime to ensure long-term stability in the insulin market and support local production. In 1987, a national producer, Laboratorios Beta, began producing both beef and pork insulin. Beta continued to produce insulin, introducing a biosynthetic option as early as 1990. However, it was unable to compete with Novo Nordisk's aggressive expansion into Latin America, which began in 2001, when the Danish company entered negotiations to acquire Biobras, based in neighbouring Brazil [53]. Biobras, Brazil's only domestic producer of animal and human insulin products, was the world's fourth largest insulin producer and an increasingly important supplier of low-cost human, bovine, and porcine insulins to the Mercosur member states, Eastern Europe, India, China, and South Korea [54].

Novo's acquisition of Biobras raised international alarm bells, with doctors and patients expressing concerns that this move could jeopardise ongoing access to low-cost and, for a subset of people with diabetes, safer animal insulin. As noted in *BMJ,* the Brazilian company was "one of the few remaining producers of the insulin crystals used by other companies as source material for their own animal insulin." However, Novo's vice president, Lars Jorgensen, quoted in the same article, stated that they had "no plans for the discontinuation of production of animal insulin" and that they did not intend to stop the supply of the necessary raw materials required by other manufacturers [55].

One of the Brazilian partners in Biobras, explaining the decision to sell the company, told reporters that "we competed with high-tech firms that were at least 50 times larger than us… we either had to sell our stakes or passively

wait for the competition to break us."[56] The inability to compete in their home market was a pattern many insulin producers experienced. In 2013, Beta announced that it too had fallen victim to similar forces and was getting out of the insulin business altogether. Beta's vice president, Gregorio Zidar, told the online publication *PharmaBoardroom,* "Unfortunately, we had to discontinue our insulin business at the end of 2013. The competition was very aggressive. We couldn't compete any more with the technology from MNCs like Novo Nordisk or Sanofi." [57]

It was not too long before Novo Nordisk, exploiting its monopoly position in the Brazilian market, began to adjust its prices upwards and extend its reach into Argentina, Mexico, and other Latin American markets. When Novo acquired Brazil's skill and expertise in insulin manufacturing and associated technologies, the country's efforts to establish itself in the biotech production market for insulin were over. Three years after its acquisition, Novo Nordisk halted the production of animal insulin in Brazil and discontinued its supply of insulin crystals [58].

Growing the market

Harvard biology professor and ethicist Ruth Hubbard was an early critic of the rationale insulin producers employed to promote insulin use beyond the estimated 5-10% of diabetics with Type 1 diabetes (then termed juvenile-onset diabetes). In 1978, she wrote that insulin "does not improve the diabetes-associated vascular problems from which most diabetics die eventually," adding that the focus of therapy for the Type 2 population should be on diet and weight control [59]. While Hubbard was generally considered radical, she commanded great respect as a scientist and was far from alone in her concerns about the social consequences of rDNA research [60]. She challenged the claims that using biotechnology to increase production would benefit people with diabetes, commenting that "if we produce more insulin, more insulin will be used, whether diabetics need it or not." [61]

As Hubbard anticipated, biotechnology enabled Eli Lilly and Novo Nordisk to increase production capacity and expand their respective markets which viewed Type 2 diabetes not only as a chronic disease, but also as an investment opportunity. In 2005, Sanofi joined the exclusive club of insulin producers with its blockbuster insulin glargine (Lantus) priced at three times above the most expensive insulin on the market. While maintaining a picture of stiff competition, the three companies all devised similar strategies to increase the use of insulin among people with Type 2 diabetes, an issue that was the subject of intense study. Sanofi even began testing its insulin on people with "pre-diabetes," [62] a hotly debated condition [63], but one that also held a lot of potential for investors.

For people with Type 1 diabetes, neither alternative medicines nor diet and exercise are adequate replacements for insulin therapy. But today, approximately 80% of Americans who use insulin have Type 2 diabetes [64], despite ongoing and often tense debates about whether this population experiences more harm than benefit. In the United Kingdom, the percentage of people on insulin therapy increased six-fold between 1991 and 2010, according to Edwin Gale, former editor of *Diabetologia*. He describes the controversy over the evidence used to support this treatment strategy in his recent book, *Life in the Age of Insulin* [65].

Not only did the number of people with Type 2 diabetes who are prescribed insulin rise, but the amount they use on a per capita basis also increased, along with the financial burden they must bear. Xinyang Hua and colleagues estimated that between 2002–04 and 2011–12, the amount of insulin used per person with Type 2 diabetes annually in the United States went from 171mL to 206mL, an increase of over 20%. However, the increase in costs was even more stark, at 218% during the same period. The authors noted that "the mean price of insulin increased from $4.34 per mL in 2002 to $12.92 in 2013" and along with increased treatment intensity, the per capita expenditure on insulin among people with Type 2 diabetes was "greater than all other antihyperglycemic medications combined."[66] They concluded that these factors "suggest a need to reassess the effectiveness and cost-effectiveness of alternative antihyperglycemic therapies." [66]

The fight for animal insulin

Novo Nordisk and Eli Lilly likely initiated their plans to phase out animal insulin from the global market soon after building their new production facilities for RHI. The aim was to eliminate a competing product line they no longer wanted to maintain [67]. However, it also forced reluctant patients to switch from low-cost animal insulins with a well-known track record to a more expensive and unproven alternative [68]. By 2006, manufacturers had withdrawn 33 insulin products of animal origin, not a single one for reasons of safety or effectiveness [64]. On the contrary, the narrowing of options for insulin users occurred despite both clinical and anecdotal evidence that a subset of people experienced poorer control and the loss of hypoglycaemic warning signals when using recombinant human and analogue insulins [69]. Additionally, the withdrawal also removed more affordable and equally safe and effective alternatives to human and analogue insulins.

For people with Type 1 diabetes, insulin is not only a life-sustaining medicine, but it also serves as a lifelong companion from the moment of diagnosis, providing a significant degree of independence and autonomy that would otherwise not be possible. Those who use insulin must regulate their blood glucose levels to ensure they are neither too high (hyperglycaemia) nor too low (hypoglycaemia). When the latter occurs, they experience an "insulin reaction" or "hypo", characterised by shakiness, hunger, and sweating. Each type of insulin has a specific profile of action and duration, which the diabetic must align,

as closely as possible, with their diet and activities to avoid both high and low blood sugar levels. Once they have identified a type of insulin that works well for them, most people prefer not to switch to something different.

But that wasn't Eli Lilly's and Novo Nordisk's plan. Both companies initiated an aggressive marketing campaign designed to shift reluctant diabetics from animal insulin (which worked well for most) to human insulin (which was no better yet cost twice as much) [69]. Novo boasted it had spent as much on promoting its new insulin as it had on research [70]. This concerted push by the two companies was needed to overcome the slow uptake of their human insulin products which could only claim 5% of the total insulin market three years after they were released [71]. Unless individuals faced allergies or other complications using animal insulin, they and their doctors were reluctant to switch to human insulin.

There were also mounting complaints from patients, starting in the UK, who reported that when they switched to human insulin, their diabetes went out of control, and they lost their early warning signals of hypoglycaemia. The British Diabetes Association (now Diabetes UK) also identified other problems associated with the use of human insulin, including joint pains, memory loss, confusion, depression, and lethargy [72].

By the end of the 1980s, RHI's share of the total insulin market had increased to an astonishing 80% in Europe, North America, and other regions. Nevertheless, debates regarding the safety and effectiveness of RHI persisted and emerged in medical literature. The first English-language paper to describe a relationship between RHI and "hypoglycaemia unawareness" was authored by two Swiss diabetologists, Arthur Teuscher and Willy Berger, and published in *The Lancet* in 1987. The authors reported that 36% of patients interviewed stated that the familiar symptoms of hypoglycaemia (sweating, tremors, hunger) had changed (light-headedness, anxiety, fear) or were entirely absent [73].

Britain's *Drug & Therapeutics Bulletin,* distributed among physicians and doctors, was also monitoring these developments. In 1989, its editor, Alex Herxheimer, advised that the "Clinical advantages of human over existing animal insulins have not become apparent over the last 6 years. Prescribers should not change the type of species of insulin without good reason… A general change-over to human insulin is inappropriate." In addition, the bulletin expressed concern about persistent and widespread reports that patients lost the vital warning signs that alerted them to low blood sugar after switching to human insulin [74].

The lack of early warning signs of low blood sugar — "hypoglycaemia unawareness" — was described early in the history of insulin therapy. But prior to the introduction of human insulin there were a few studies about the phenomenon, with instances of hypoglycaemia leading to coma described in the literature as "relatively rare" [75, 76]. The sudden surge in reports of severe, unexpected hypoglycaemia beginning in the 1980s ignited intense debates over the validity of claims linking them to human insulin [77]. In 1989, Dr Patrick Toseland, head of medical chemistry at Guy's Hospital in London, informed reporters of an alarming rise in diabetic deaths, particularly among patients under the age of 25. "I cannot explain it," he stated, "and I cannot say the insulin they have used is unsafe, but there is cause for concern."[78] Another report on unexpected deaths by Robert Tattersall and Geoff Gill described a "puzzling group" of 22 young patients who had "gone to bed in apparently good health and been found dead in the morning." [79] The authors concluded that hypoglycaemia or a hypoglycaemia-related event was responsible for the deaths. While there was nothing to implicate the type of insulin used, they noted, "all patients were taking human insulin at the time of death, but most had been changed from animal insulin between 6 months and 2 years earlier." [79]

Eli Lilly and Novo Nordisk rejected claims that RHI might be dangerous for some people. While Novo insisted there was "extensive scientific evidence" showing animal and human insulins were "almost identical" [80], Eli Lilly maintained that "Our product [Humulin] is equal to or better than the best porcine insulin in purity." [81]

Several years later, the *Cochrane Review,* a highly respected global network that publishes systematic reviews, evaluated the scientific evidence and were more circumspect about the quality of the evidence about human insulin. *Cochrane* found that, with few exceptions, the studies — 70% of which were sponsored by manufacturers — were of "poor methodological quality" and had failed to investigate essential endpoints such as mortality, morbidity, and health-related quality of life issues. The evidence did not show any therapeutic or clinical advantage of recombinant human compared with animal insulins, and only 40% of the studies reviewed provided information about adverse effects. *Cochrane* concluded that the introduction of RHI should serve as an example of "pharmaceutical and technological innovations that are not backed up by sufficient proof of their advantages and safety." [82]

An apparent disregard exhibited by the companies for patients' concerns over reported adverse effects and the clash between their actual experiences and the industry-sponsored evidence prompted demands for independent enquiries in several countries. The United Kingdom and Canada took steps to ensure ongoing access to animal insulin; however, most governments, including the United States, did as little as possible. Class action lawsuits alleging a range of harms linked to human insulin were attempted in at least three countries (Britain, Canada, and the United States). Although these never reached court, they sparked widespread interest among activists, media, and the broad "diabetes community" [83].

The withdrawal of animal insulin galvanised activists, including individuals with diabetes and their families, to

urge governments to intervene and ensure ongoing access. They succeeded in the UK, where the Department of Health acknowledged that "some people are better suited to animal insulin and that animal insulin should continue to be made available."[84] In Canada, the House of Commons Standing Committee on Health conducted two days of hearings on the issue of access, during which the federal regulator "recognised that there are some Canadians who need animal-sourced insulin not only to manage their diabetes, but in fact to maintain their lives."[85] Both countries took steps to accommodate this population, with Canada requesting the WHO to intervene [86].

These campaigns presented a sophisticated analysis of the role played by insulin manufacturers in the public policy arenas of each country, the influence they exercised within the medical profession, and the negative impact industry funding had on advocacy for diabetes patients [72]. Advocacy groups with financial ties to insulin manufacturers largely remained on the sidelines, resulting in the formation of independent organisations in many countries. For instance, in the UK, the InDependent Diabetes Trust (IDDT) continues as a vocal, non-industry–funded, international voice for patients and their families. Importantly, the activists drew heavily on the history of insulin and its co-discoverers at the University of Toronto who, they repeatedly emphasised, had foregone patent rights and "…refused financial gain in order to serve science, research and humankind – and to conquer diabetes."[69] This legacy, they argued, had been overshadowed by industry greed and callousness, and as a result the health and well-being of patients had been harmed.

The fight for lower prices

If the introduction of RHI was followed by an aggressive "switch campaign" to encourage or (if that failed) force people to abandon low-cost animal insulin, the launch of insulin analogues in 1995 was a repeat performance [67]. RHIs are structurally identical to the natural human insulin molecule, while analogues "have a modified molecular structure resulting in different pharmacokinetic profiles." That is, the duration and peak action of analogues are different from their human insulin predecessors. The *Cochrane Review's* analysis of the evidence on short-acting insulin analogues revealed that the "quality of the included studies was low or very low"; none of the studies were blinded, and the "risk of bias, especially for outcomes such as hypoglycaemic episodes, was present in all of the studies."[87] A 2009 meta-analysis found that "Rapid- and long-acting insulin analogues offer little benefit relative to conventional insulins in terms of glycemic control or reduced hypoglycemia."[88] However, despite the apparent lack of additional benefit, the per-unit cost of analogue insulin was 81% to 126% higher than that of human insulin alternatives in 2011 [89]. These results appeared to have had little impact on prescribing. Between 2004 and 2014, the percentage of insulin users in higher-income countries who were prescribed analogues rose from 32% to almost 80% [90].

While the market for insulin was expanding, production costs were declining and by 2018 ranged from $3.69 to $17.35 for a 10mL vial of analogue insulin and from $2.38 to $4.93 for human insulin [91]. The 7.4 million Americans who use insulin [92] pay the highest prices in the world, estimated at an average of $99 per vial [93]. Not surprisingly, the US is also the most lucrative and coveted market for the three big manufacturers. According to one study, North America (Canada, the United States, and Mexico) constitutes 51% of Novo Nordisk's global insulin sales, with the United States alone accounting for 97% of that [94]. In contrast, people in LMICs, where median insulin prices range from $9.36 to $29.39, often have very poor access to insulin [95]. Half of the world's population, most of them in LMICs, have no access to insulin [91]; their chances of living a healthy life are similar to those born before the discovery of insulin at the University of Toronto.

In 2006, Health Action International (HAI) began publishing damning evidence of the injustices within the insulin market, particularly concerning the practices of Eli Lilly, Novo Nordisk, and Sanofi. It documented the struggles of those in poorer countries to afford insulin that is grossly overpriced, a situation that is exacerbated by limited competition and inadequate distribution systems. [20]. The work of HAI provided activists in many countries with evidence showing the impact of an out-of-control market on the health and lives of millions of people.

In 2013, T1 International (T1-I), a global advocacy organisation founded by Elizabeth Pfeister, emerged as another significant voice challenging manufacturers on insulin prices. T1-I successfully tapped into evidence that had been previously unavailable to earlier advocates who confronted companies on issues of safety and choice and who, in effect, helped to validate patient experiences as crucial yet overlooked components of that evidence base. T1-I framed pricing and access as fundamental issues of social justice [96] and identified allies within the medical community, academics, and other researchers. Together, they campaigned for companies to provide insulin at affordable prices, not just to those in wealthy countries but to everyone who needed it [97]. Like the UK-based IDDT, T1-I also refuses funding from the pharmaceutical industry and has influenced legislators and leaders at WHO [98].

India: Safety, effectiveness, fair pricing, and domestic production

In 2003, Wockhardt, based in Mumbai, introduced the first domestically produced RHI to the Indian market. It was struggling to maintain its small share in an insulin market dominated primarily by Novo Nordisk. The Danish company had been supplying India since 1935, and in 1992, it established its first offices in Bengaluru. This move was

followed a year later by Eli Lilly and ten years later by Sanofi. All three companies have been aggressive actors in India, both in terms of acquisitions and market control [99].

Until the 1970s, India imported most of its drugs; Western multinationals dominated its pharmaceutical market, and the country had some of the highest drug prices in the world [100]. These conditions prompted a radical shift in policy beginning in 1970 to support self-sufficiency in the production of insulin and other drugs, reflecting India's stance at the World Health Assembly in 1949. Two changes — a 50% cap on foreign ownership in the pharmaceutical sector and the recognition of process rather than product patents — benefited small and medium-sized domestic producers. A number of Indian companies, most of them established in the early days of Independence, benefitted from the policy and began manufacturing insulin [101]. Today, in addition to Wockhardt, three other Indian companies compete with the three global corporations in the domestic insulin market [99].

When Wockhardt announced the launch of its own brand of RHI — described by the BBC as "vegetarian insulin" [102] — beef and pork insulin accounted for an estimated 50% of the market and sold for about $1.58 per vial, which was significantly cheaper than the heavily marketed human insulin priced at $4.38 [103]. With a new competitor entering the arena with a human insulin product priced at $2.65 per vial, the two foreign corporations had reason for concern.

The lower prices set by Wockhardt were not merely a tactic to strengthen the ability of indigenous manufacturers to compete with global corporations. In India, insulin is subject to a complex system of price controls, administered by the National Pharmaceutical Pricing Authority (NPPA). This system favours companies that import insulin since they are able to set prices based on production and other costs. Furthermore, the price caps that were introduced do not apply to insulin analogues [99]. According to a 2013 report, the NPPA asserted it was unable to determine the actual cost of production for insulin manufactured outside of the country. Consequently, it sets price caps "based on the costs declared by multinational companies," plus post-production (including marketing) expenses. The main beneficiaries of this policy have been Novo Nordisk, with a 58% share in the Indian market, and Eli Lilly and Sanofi, each holding 14% [104].

Despite the advantages they are granted in the Indian market, the three companies have acted to ensure that domestic competitors remain at a disadvantage. When Wockhardt, followed soon after by Biocon, entered the human insulin market, other companies such as Ranbaxy, Dr Reddy's, and Shantha Biotech also expressed interest. Assessing the threat posed by cheaper insulin to their hold on the market, and unable to influence Indian manufacturers to withdraw their animal insulins, Novo Nordisk and Eli Lilly cut prices by up to 35% in 2003. *The Economic Times* predicted that this move, which became a routine practice whenever the companies deemed it necessary, would "play a pivotal role in changing the market dynamics of [the] diabetic segment." [105]

That, of course, was the intended consequence, according to many critics of the price cuts, including Biocon's Kiran Mazumdar Shaw, who told reporters that the "MNCs are trying to create entry barriers" because a majority of domestic players had plans to compete in the human insulin market. Khalil Ahmed, executive director of Shantha Biotech, accused the companies of "slash[ing] the prices only because domestic biotech companies are gearing up to launch recombinant versions of human insulin."[106] Six years later, Shantha Biotech would be acquired by Sanofi, one of many multinationals "hunting for generic drug makers" to ease the impact of expiring patents and minimise any potential competition [107].

But others were worried about the impact the price war would have on those who required insulin, 60% of whom were poor and preferred beef insulin [108]. Dr NP Kochupillai, the internationally renowned head of India's Department of Endocrinology and Metabolism at the All-India Institute of Medical Sciences (AIIMS), was a key leader in the fight to retain access to low-cost animal insulin. In 2000, he co-authored one of the very few studies comparing the safety and efficacy of beef insulin and RHI [109], which found that the two insulins were equally effective. Kochupillai was joined by other experts who pointed out that none of the human insulin studies conducted by Eli Lilly and Novo Nordisk had assessed cost and socio-economic impacts [110]. India stands out as one of the very few jurisdictions where, each for their own reasons, physicians and domestic manufacturers (who were disappearing from most countries) publicly challenged the tactics of the large global corporations who were intent on reshaping the country's insulin market and overseeing price increases.

There continues to be a struggle over the price control mechanisms employed by the Indian regulator, with domestic companies continuing to push for a level playing field. The price war initiated by Eli Lilly and Novo Nordisk in 2003 was short-lived, and two years later insulin prices began a sharp upward climb. Today the cost of a monthly supply is estimated at INR 10,000–12,000 ($120–$144) [111]. Two decades ago, most Indians requiring insulin relied on low-cost beef insulin. However, the market now has shifted; in 2017, 58.96% of insulin users relied on RHI, while 35.7% used insulin analogues [112]. Most (84.4%) of the human insulin produced in India is manufactured for foreign companies located overseas, while all insulin analogues are imported [99].

India, once a supplier of low-cost insulin to countries worldwide, is now an emerging destination for insulin exported from Denmark, Germany, France, and the United States, which dominate the global retail trade [113]. The country is almost unique in the world today as it has several domestic manufacturers in the insulin market. Several of

these — Wockhardt and Biocon — are focused on biosimilar insulin products that raise hopes for lower prices and increased access for Indian patients with diabetes. Unlike generic drugs, which are interchangeable with their reference products, biosimilars closely resemble but are not identical to reference brand biologics. They face challenges in the insulin market due to patent monopolies, prescribing and payer bias, and the complexity of replicating insulin's protein structure, among other reasons [114]. Nonetheless, Indian manufacturers, whose share of the domestic insulin market is 14% and diminishing, appear to be interested in expanding their business to a global platform where there is a higher potential for revenue and profits. There also is more opportunity to form partnerships with global corporations that have greater market reach and more experience navigating complex regulatory systems in other countries. Biocon, for example, partnered with Mylan, based in Pennsylvania, to develop and launch Semglee, the first biosimilar insulin to receive market authorization in the US [115].

Like most countries, India is vulnerable to the decisions made at the corporate headquarters of Novo Nordisk, Eli Lilly, and Sanofi. The country's hopes for "insulin self-sufficiency" expressed in 1949 have been undermined by a system of manufacturing geared towards mass production and maximising profits rather than the supply of safe, affordable and effective insulin to those who need it. India is dominated by the insulin oligopoly and, tragically, its role as a supplier of low-cost and generic drugs to the world has been weakened. As Abhishek Sharma and Warren Kaplan point out, the "limited market competition has implications for suppliers' incentives to meet patients' need and for insulin prices and usage in lower income countries." [99]

Conclusion

Today, very few countries, including wealthier ones, can claim to have effective control over the kind of insulin that is available to their own people, its cost, and whether the types of insulin being manufactured meet the needs of the very diverse populations who require this drug to maintain their health and quality of life. Almost all countries voluntarily relinquished their control just as industries ranging from pharmaceuticals to agriculture to fossil fuels began embracing biotechnology. In 1978, while researchers were still working to clone the molecule, the production of human insulin was considered the Holy Grail of genetic engineering, one that, if successful, "would go far towards convincing the public of the benefits of rDNA research."[116] A mere four years later, insulin became the first product of the new biotech era to make its way to the marketplace.

Although expectations were high that biosimilars would lower costs, most biosimilar insulins are now expected to reduce insulin prices by only 15%. By comparison, generic drugs have traditionally lowered prices by up to 90% [117]. Although some contend that the lack of competition in the biosimilar insulin market is hindering price reductions [118], there are also valid questions about whether more competitors in the domestic private sector would be as effective as a public or quasi-public manufacturer. Perhaps the answer to that question will come from the state of California, which, in response to high prices in the US market, is partnering with a nonprofit manufacturer to produce biosimilar insulin products [119].

So, how should we address the issue of insulin access and affordability? Charitable donations from global manufacturers fall far short of a long-term solution and often serve merely as opportunistic publicity exercises [120]. There are legitimate questions about whether biotechnology aligns with the goals articulated by many countries since the end of the Second World War, including insulin self-sufficiency, or if smaller-scale methods and public ownership might better support this objective and meet the needs of insulin users. Increased competition in the private sector may not be as practical as a public or quasi-public manufacturer, a situation that existed in many countries before the rise of austerity and privatisation in the 1980s.

What is clear is that biotechnology's contribution to the goals articulated in 1921 by the co-discoverers of insulin to ensure access to safe, effective, and affordable insulin has been limited at best and negative at worst. While the technology may provide manufacturers with the capacity to meet the needs of all those who require insulin, it has instead met the objectives of those who designed it specifically as an engine of massive profiteering and monopolisation. Those regions of the world that have been historically excluded from the pharmaceutical technology landscape [121] have suffered the most. Nevertheless, all countries have lost or forfeited the ability to exercise control over the quality, range, and price of insulin products available in their own markets. Worse still, most have signed away their ability to limit the monopoly control exerted mainly by three powerful global corporations.

International movements have emerged to demand changes in how the insulin market operates. This has included pressure to expand the range of options (animal, recombinant human, and analogue insulins) that people can access, along with calls for prices to be significantly reduced to reflect the actual cost of production. People with diabetes and their families have urged governments to take a more proactive role in ensuring the insulin market meets the needs of their citizens instead of patent holders. These efforts have achieved some success thus far — for example, ongoing access to animal insulin in the UK, Canada, and elsewhere, as well as proposals in the United States to legislate lower insulin prices.

However, even these modest success stories are threatened by a global market beyond the control of national governments and currently experiencing dramatic shifts,

including Novo Nordisk's withdrawal of certain lines of insulin and the supply of insulin cartridges in India and other countries [122]. And while some changes have been important, too many people continue to face barriers to accessing the insulin they need. For this to improve, more diverse options will have to be available for insulin users. The principles articulated in 1921 by the co-discoverers (access to safe, effective, and affordable insulin) must be prioritised over profits and corporate control — an effort that biotechnology has, to date, undermined.

[1]***Note:*** *All dollars in US currency.*

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Conflict of Interest: From 2001-2007, Colleen Fuller led a successful national campaign in Canada in support of a public enquiry into the withdrawal of animal insulin. She was a member of the Expert Advisory Panel on Insulin, Health Canada, in 2008. In addition to the Panel, she has acted in an advisory capacity to Health Canada on the issue of access to animal insulin.

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References

1. Bliss M. Resurrections in Toronto: fact and myth in the discovery of insulin. *Bulletin of the American Academy of Arts and Sciences.* 1984 [cited 2025 Mar 18];38(3):15–36. Available from: https://www.jstor.org/ stable/20171755
2. Bliss M. The history of insulin. *Diabetes Care.* 1993 Dec;16 Suppl 3:4–7. https://doi.org/10.2337/diacare.16.3.4
3. Malleck D. *When good drugs go bad: opium, medicine, and the origins of Canada's drug laws.* Vancouver: UBC Press; 2015.
4. Macleod JJR. Statement read by JJR Macleod at the Insulin Committee meeting regarding patents and royalties 28/04/1924. 1924 Apr 28 [cited 2025 Mar 18]. Available from: https://collections.library.utoronto.ca/view/insulin:W10029
5. Banting FG. Letter to Sir Robert Falconer regarding Banting's views on patents 27/01/1923. 1923 Jan 27[cited 2025 Mar 18]. Located at: University of Toronto Archives; A1982-0001, Box 62, Folder 1. Available from: https://collections.library.utoronto.ca/view/insulin:L10256
6. Eli Lilly Company. Indenture between the Governors of the University of Toronto and the Eli Lilly Company. 1922 May 30[cited 2025 Mar 18]. Located at: Thomas Fisher Rare Book Library Digital Collections; MS. COLL. 269 (Collip), Box 37, Folder 5. Available from: https://collections.library.utoronto.ca/view/insulin:Q10014
7. Lilly JK. Letter to Dr. Clowes. 1923 Jan 3[cited 2025 Mar 18]. Located at: University of Toronto Archives; A1982–0001, Box 12. Available from: https://insulin.library.utoronto.ca/islandora/object insulin%3AL10241#page/1/mode/1up/search/Eli%20Lilly
8. Clowes GHA. Letter to Dr. JJR Macleod 7/03/1923, 1923 Mar 7 [cited 2025 Mar 18]. University of Toronto Archives; A1982–0001, Box 12. Available from: https://collections.library.utoronto.ca/view/insulin:L10242
9. Medical News. Helping the world's diabetic sufferers: how British laboratories developed insulin. *Ind Med Gaz.* 1952 Dec;87(12):579–92. PMID: 29015035.
10. Rutty C. "It works! now what?": insulin development, production, and distribution at Connaught Laboratories, University of Toronto, 1922–24. *Canadian Journal of Health History.* 2022;39(2):419-450. https://doi.org/10.3138/cjhh.2022-573-032022
11. Cassier M, Sinding C. Patenting in the public interest: administration of insulin patents by the University of Toronto. *History and Technology.* 2008;24(2):153–71. https://doi.org/10.1080/07341510701810948
12. Decisions and resolutions. Official Records of the World Health Organization, No. 21: Second World Health Assembly, Rome, 1949 Jun 13 to Jul 2[cited 2025 Mar 18]: 212–13. Available from: https://iris.who.int/handle/10665/85600
13. Harper C. Towards self-sufficiency: public health responses to diabetes in New Zealand c.1920–2000 [dissertation]. Auckland [New Zealand]: University of Auckland; 2015. Chapter 2, 'The common purpose should be to assist diabetics to help themselves': diabetic societies, c.1942–1984; p. 86.
14. Nagasawa K. Use of fish and whale insulin as drugs in Japan. *J AOAC Int.* 1968;51(2):326–329. https://doi.org/10.1093/jaoac/51.2.326
15. Smith SE. Opening up to the world: India's pharmaceutical companies prepare for 2005. Asia-Pacific Research Centre, Institute for International Studies, Stanford University (US). 2000 [cited 2025 Mar 18]. Available from: https://fsi9-prod.s3.us-west-1.amazonaws.com/s3fs-public/Smith.pdf
16. Carney TP. Research and patents in the drug industry. *Research Management.* 1962;5(3): 193–208.
17. Saipe A. Insulin inventories at CLL: a case study in assessing inventory levels, *INFOR.* 1977;15(2):148–59. https://doi.org/10.1080/03155986.1977.11731662
18. Home PD, Alberti KG. The new insulins. Their characteristics and clinical indications. *Drugs.* 1982 Nov;24(5):401–13. https://doi.org/10.2165/00003495-198224050-00003
19. Beran D, Lazo-Porras M, Mba CM, Mbanya JC. A global perspective on the issue of access to insulin. *Diabetologia.* 2021 May;64(5):954–62. https://doi.org/10.1007/s00125-020-05375-2
20. Beran D, Ewen M, Laing, R. Constraints and challenges in access to insulin: a global perspective. *Lancet Diabetes Endocrinol.* 2016; 4:275-285. https://doi.org/10.1016/S2213-8587(15)00521-5
21. Haji MHAA. Enhancing insulin supply chain resilience: a critical importance for diabetes management. *Glob J Obes Diabetes Metab Syndr.* 2023;10(2):9–13. https://doi.org/10.17352/2455-8583.000063
22. Lilly splices its growth to a new type of insulin. *Business Week,* 1980 Aug 4.
23. Cane A. Novo takes fight to Lilly. *Financial Times (London),* 1982 Mar 16.
24. Barnes H. Flotation by insulin producer. *Financial Times (London),* 1986 Sep 2.
25. A market face-off for two insulin pioneers. *Business Week,* 1982 Nov 1.
26. Beran D, Laing RO, Kaplan W, Knox R, Sharma A, Wirtz VJ, Frye J, Ewen M. A perspective on global access to insulin: a descriptive study of the market, trade flows and prices. *Diabet Med.* 2019 Jun;36(6):726–33. https://doi.org/10.1111/dme.13947
27. Hall SS. *Invisible frontiers: The race to synthesize a human gene.* Redmond, WA: Tempus Press. 1987.
28. Gans JS, Stern S. The product market and the market for "ideas": commercialization strategies for technology entrepreneurs, *Research Policy.* 2003;32(2): 333–50. https://doi.org/10.1016/S0048-7333(02)00103-8
29. Cook-Deegan R, Heaney C. Patents in genomics and human genetics. *Annu Rev Genomics Hum Genet.* 2010;11:383–425. https://doi.org/10.1146/annurev-genom-082509-141811
30. King J, Stabinsky D. Biotechnology under globalisation: the corporate expropriation of plant, animal and microbial species. *Race and Class.* 1999;40(2/3):73–89.
31. Johnson IS. The trials and tribulations of producing the first genetically engineered drug. *Nat Rev Drug Discov.* 2003 Sep;2(9):747–51. https://doi.org/10.1038/nrd1179
32. Hughes SS. Making dollars out of DNA. The first major patent in biotechnology and the commercialization of molecular biology, 1974-1980. *Isis.* 2001 Sep;92(3):541–75. https://doi.org/10.1086/385281
33. Wright S, Wallace DA. Varieties of secrets and secret varieties: the case of biotechnology. *Politics and the Life Sciences.* 2000;19:45–57. https://doi.org/10.1017/s0730938400008893
34. Eli Lilly. (no title) [News Release]. *PR Newswire.* 1980 Jul 21. No longer available online but is available with the author of this article.

35. US Department of Health Education and Welfare. *A study of insulin supply and demand. Bethesda,* Maryland (US): National Institute of Health ; 1978 [cited 2025 Mar 18]. 68p. Publication No. (NIH) 78–1588. Available from: https://babel.hathitrust.org/cgi/pt?id=ien.35558000598041&seq=1
36. Snoddy R, Cane A. Lilly replies to Novo's drug shot. *Financial Times* (London). 1982 Jun 15.
37. Rothenberg R. Robert A. Swanson, Chief Genetic Officer. *Esquire.* 1984 Dec: 366–74.
38. Eli Lilly. Clinical evaluation of biosynthetic human insulin in diabetic patients [News Release]. *PR Newswire.* 1981 Feb 12.
39. Whitehouse F. Future of human insulin. *JAMA* (Letters). 1983 Aug 26; 250(8):1027–28. https://doi.org/10.1001/jama.1983.03340080017016.
40. Junod, SW. Celebrating a milestone: FDA's approval of first genetically engineered product. Food and Drug Law Institute. Update Sep–Oct 2007 [cited 2025 Mar 18]. Available from: https://fda.report/media/110447/Celebrating-a-Milestone--FDA%27s-Approval-of-the-First-Genetircally-Engineered-Product.pdf
41. Spivey RN, Lasagna L, Trimble AG. New drug applications: how long to gain approval? Clin. *Pharmac. Ther.* 1985;3:361–66. https://doi.org/10.1038/clpt.1985.54
42. Lilly's insulin process has a rival. *Chemical Week* (New York). 1980 Sep 10.
43. Cane A. Novo takes fight to Lilly. *Financial Times* (London). 1982 Mar 16.
44. Russell C. FDA approves insulin made by splicing genes. Washington Post (Washington DC). 1982 Oct 30.
45. Scientists develop synthetic insulin. *Globe and Mail* (Toronto). 1983 Dec 21.
46. Tests begin on insulin synthesized from bacteria through gene-splicing. *New York Times.* 1980 Jul 24[Cited 2025 May 6]. Available from: https://www.nytimes.com/1980/07/24/archives/tests-begin-on-insulin-synthesized-from-bacteria-through.html
47. A market face-off for two insulin pioneers. *Business Week.* 1982 Nov 1.
48. Bisang R, Cogliati C, Groisman S, Katz J. Insulina y economía política: el difícil arte de la política pública. *Desarrollo Económíco.* 1986;26(103): 1–25.
49. Barnes H. An injection of co-operative spirit. *Financial Post* (London). 1989 Jan 19.
50. Yanchinski S. First big breakthrough for genetic engineering. *Financial Times* (London), 1985 Apr 22.
51. Chase M. Genentech's insulin excites doctors less than it did brokers. *Wall Street Journal.* 1982 Nov 2.
52. Campins M, Pfeiffer A. Business strategies, abilities and paths of two Argentinian family laboratories. Paper presented at XIV International Economic History Congress; August 21-25, 2006. Helsinki. Session number 40: Innovation and Networks in Entrepreneurship.
53. Novo Nordisk A/S. Novo Nordisk expands activities in Latin America - acquires the voting majority of Biobras. *GlobeNewswire.* 2001 Dec 13. [cited 2025 April 21]. Available from: https://www.globenewswire.com/news-release/2001/12/13/1732566/0/en/Novo-Nordisk-expands-activities-in-Latin-America-acquires-the-voting-majority-of-Biobrás.html
54. Biobras challenges world insulin monopoly. *Gazeta Mercantil Inc.* 1996 July 1.
55. Hunter, M. Doctors worried about threat to supplies of animal insulin. *BMJ.* 2002 Jan 19; 324:130. https://doi.org/10.1136/bmj.324.7330.130a
56. Cassiolato J, Zucoloto G, Rapini M, Antunes S. The recent evolution of the biotech local innovation system of Minas Gerais: university, local firms and transnational corporations. In: B Göransson, C Pålsson, editors. *Biotechnology and innovation systems. the role of public policy.* Cheltenham (UK): Edward Elgar Publishing; 2011. p. 13–57.
57. Laboratorios Beta: Gregoria Zidar, Vice President–Argentina [Interview]. *Pharma Boardroom.* 2104 Aug 25 [cited 2025 Mar 18]. Available from: https://pharmaboardroom.com/interviews/laboratorios-beta-gregorio-zidar-vice-president-argentina/
58. Parliament. House of Commons. Health Animal-based Insulin. 2006 Jul 17 [cited 2025 Mar 18]. Column 244W. Available from: https://publications.parliament.uk/pa/cm200506/cmhansrd/vo060717/text/60717w1784.htm
59. Hubbard R. Hubbard on DNA. *The Harvard Crimson* . 1978 Nov 20 [cited 2025 Mar 18]. Available from: https://www.thecrimson.com/article/1978/11/20/hubbard-on-dna-pto-the-editors/
60. Botelho A. The insights of radical science in the CRISPR gene-editing era: a history of science for the people and the Cambridge recombinant DNA controversy. *Sci Cult* (Lond). 2021; 30(1): 74–103. https://doi.org/10.1080/09505431.2019.1623190
61. Comstock GL. *Vexing Nature? On the Ethical Case Against Agricultural Biotechnology.* Chapter 2, Against Herbicide Resistance (1990). Boston, MA: Kluwer Academic Publishers. 2000, p. 139 (fn. 20).
62. Sanofi. Lantus in prediabetes: assessment of safety and tolerability of Lantus® (insulin glargine) in subjects with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) [Clinical trial]. US National Library of Medicine. 2006 Jul 6 [cited 2025 Mar 19]. ClinicalTrials.gov ID: NCT00348972. Available from: https://clinicaltrials.gov/study/NCT00348972?tab=table
63. Blond MB, Færch K, Herder C, Ziegler D, Stehouwer CDA. The prediabetes conundrum: striking the balance between risk and resources. *Diabetologia.* 2023 Jun;66(6):1016–23. https://doi.org/10.1007/s00125-023-05890-y
64. Feldman R. Leading with the trailing edge: facilitating patient choice for insulin products. *J Law Biosci.* 2023 Dec 12;10(2):lsad033. https://doi.org/10.1093/jlb/lsad033
65. Gale EAM. *Life in the age of insulin: a brief history.* Switzerland: Copernicus Books, Springer Nature; 2023.
66. Hua X, Carvalho N, Tew M, Huang ES, Herman WH, Clarke P. Expenditures and prices of antihyperglycemic medications in the United States: 2002–2013. *JAMA.* 2016 Apr 5;315(13):1400–2. https://doi.org/10.1001/jama.2016.0126
67. Holleman F, Gale EAM. Nice insulins, pity about the evidence. *Diabetologia.* 2007 Sep;50(9):1783–90. https://doi.org/10.1007/s00125-007-0763-4
68. Mitka M. Switch to human insulin worries some diabetics. *JAMA.* 1999;281(2):121–122. https://doi.org/10.1001/jama.281.2.121-JMN0113-2-1
69. Teuscher A. Hazards of 'Human' Insulin Hypoglycemia. In: *Insulin: a voice for choice.* Basel: Karger; 2007. p 25–43.
70. Rapport C. Human insulin fights for market share. *Financial Times* (London). 1983 Apr 28.
71. Alexander WD. Human insulin: lessons from the UK? *The Medical Journal of Australia.* 1993; 159:75–76.
72. Hirst J. Consumer involvement, a dream or a reality? *CERES Newsletter.* Consumers for Ethics in Research (Great Britain). Winter 97/98; No. 23.
73. Teuscher A, Berger WG. Hypoglycaemia unawareness in diabetics transferred from beef/porcine insulin to human insulin. *Lancet.* 1987;ii:382–85. https://doi.org/10.1016/s0140-6736(87)92394-4
74. Herxheimer A. Humans insulin: an update. *Drug and Therapeutics Bulletin.* 1989; 27:21–24.
75. Nabarro, JDN. Diabetic and insulin coma. *Br Med J.* 1955 Apr 9;1(4918):902–04. https://doi.org/10.1136/bmj.1.4918.902
76. Maddock RK, Krall LP. Insulin reactions: manifestations and need for recognition of long-acting insulin reactions, *AMA Arch Intern Med.* 1953 Jun;91(6):695–703. https://doi.org/10.1001/archinte.1953.00240180004001
77. Campbell I. Dead in bed syndrome: a new manifestation of nocturnal hypoglycaemia? *Diabet Med.* 1991 Jan;8(1):3-4. https://doi.org/10.1111/j.1464-5491.1991.tb01507.x
78. Prentice T. Warning after diabetics die: human insulin alert. *The Times of London*. 1989 Oct 12.
79. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. *Diabet Med.* 1991; 8:49–58. https://doi.org/10.1111/j.1464-5491.1991.tb01516.x
80. Letters: Change from porcine to human insulin, *Br Med J.* 1986 Oct 25; 293(6554): 1099–1100. https://doi.org/10.1136/bmj.293.6554.1099-c. KR Hunter's letter and manufacturer's response from MW Edwards, Novo Laboratories.
81. Donovan GB. The Development of Human Insulin. In: *The Human Insulin Debate: A case study of contested innovation in medical technology.* Goldsmiths, University of London. [Doctoral thesis]. 2000 [cited 2025 April 25]. Available from: https://research.gold.ac.uk/id/eprint/28909/#:~:text=However%2C%20as%20human%20insulin%20began,'%20and%20'scientific'%20sources. p 97
82. Richter B, Neises G. 'Human' insulin versus animal insulin in people with diabetes mellitus. *Cochrane Database Syst Rev.* 2005 Jan 25; 2005(1): CD003816. https://doi.org/10.1002/14651858.CD003816.pub2
83. Insulin. Marketplace, Canadian Broadcasting Corporation. 2001 Feb 13.
84. Elkins L. Threat to diabetics as drug giant goes over to GM insulin. *Daily Mail* (London). 2006 Feb 14.
85. Hill, Julia (Acting Director General, Biologics and Genetic Therapies Directorate, Health Canada). Letter to: Karen Butler (Chair, National Advocacy Council, Canadian Diabetes Association). Society for Diabetic Rights. 2003 Feb 11. Available from: https://

members.tripod.com/diabetics_world/SDR-BPI.htm
86. Griffiths E (Acting Director General, Biologics and Genetic Therapies Directorate, Health Canada) Letter to: Dr Lembit Rägo (Coordinator, Quality Assurance and Safety: Medicines, Dept of Medicines Policy and Standards, World Health Organization, Geneva) 2007 Dec 12.
87. Fullerton B, Siebenhofer A, Jeitler K, Horvath K, Semlitsch T, Berghold A, Plank J, Pieber TR, Gerlach FM. Short-acting insulin analogues versus regular human insulin for adults with type 1 diabetes mellitus. *Cochrane Database Syst Rev.* 2016 Jun 30;2016(6): CD012161. https://doi.org/10.1002/14651858.CD012161
88. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennett H. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ*. 2009 Feb 17;180(4):385–97. https://doi.org/10.1503/cmaj.081041
89. Mayer BD. Insulin analogs – is there a compelling case to use them? *No! Diabetes Care.* 2014 Jun 1; 37 (6): 1771–74. https://doi.org/10.2337/dc13-2915
90. Wirtz VJ, Knox R, Cao C, Mehrtash H, Posner NW. Insulin Market Profile. Health Action International. 2016 Apr [cited 2025 Mar 19]. Available from: https://haiweb.org/wp-content/uploads/2016/04/ACCISS_Insulin-Market-Profile_FINAL.pdf
91. Gotham D, Barber MJ, Hill A. Production costs and potential prices for biosimilars of human insulin and insulin analogues. *BMJ Glob Health*. 2018 Sep 1;3(5):e000850. https://doi.org/10.1136/bmjgh-2018-000850
92. Cefalu WT, Dawes DE, Gavlak G, Goldman D, Herman WH, Van Nuys K, Powers AC, Taylor SI, Yatvin AL. Insulin Access and Affordability Working Group: conclusions and recommendations. *Diabetes Care.* 2018 Jun 1; 41 (6): 1299–1311. https://doi.org/10.2337/dci18-0019
93. Beran D, Gale EAM, Yudkin JS. The insulin market reaches 100. *Diabetologia.* 2022 Jun;65(6):931–35. https://doi.org/10.1007/s00125-022-05680-y
94. Collington R. Profits, innovation and financialization in the insulin industry. Institute for New Economic Thinking Working Paper. 2020; 120:1–36. https://doi.org/10.36687/inetwp120
95. Lepeska M, Beran D, Even M. Access to insulin: a comparison between low- and middle-income countries and the United Kingdom. *Pract Diabetes.* 2021;38(4):13–16. https://doi.org/10.1002/pdi.2345
96. History. United States: T1 International. [cited 2025 Mar 19]. Available from: https://www.t1international.com/history/
97. Pfiester, E. How I fought big pharma on insulin prices – and won. *StatNews.* 2024 Sep 20 [cited 2025 Mar 19]. Available from: https://www.statnews.com/2024/09/20/patient-advocacy-big-pharma-t1international-diabetes-insulin-price/
98. Our impact in 2022. Annual report. United States: T1 International. [cited 2025 Mar 19]. Available from: https://www.t1international.com/media/assets/file/T1International_2022_Impact_Report.pdf.
99. Sharma A, Kaplan WA. Challenges constraining access to insulin in the private-sector market of Delhi, India. *BMJ Glob Health.* 2016 Oct 12;1(3):e000112. https://doi.org/10.1136/bmjgh-2016-000112
100. Greene WL. The emergence of India's pharmaceutical industry and implications for the US generic drug market. US International Trade Commission Office of Economics Working Paper. 2007 [cited 2025 Mar 19]; No. 2007-05-A. Available from: https://www.usitc.gov/publications/332/EC200705A.pdf
101. Bhattacharjea A, Sindhwani F. Competition issues in the Indian pharmaceuticals sector. New Delhi: Centre for Development Economics, Delhi School of Economics. 2014 [cited 2025 Mar 19]. Available from: https://cuts-ccier.org/pdf/Report-Pharmaceutical_Sector_Study.pdf
102. Wockhardt launches first locally produced "human" insulin. *IDDT Newsletter.* 2003 October. [cited 2025 April 22]. Available from: https://www.iddt.org/wp-content/uploads/2009/10/IDDT-Newsletter-October-2001.pdf?x68589
103. Stapp K. On World Diabetes Day, many still can't afford insulin. *InterPress Service,* 2001 Nov 14.
104. Dey S. The bitter-sweet policy on insulin pricing. *Business Standard* (India). 2013 Feb 8.
105. Senthil Kumar KP. Price cut to hasten growth of human insulin market. *The Economic Times of India.* 2003 Jan 10.
106. Anand MS. Insulin price cuts may hinder local cos' entry. *The Economic Times of India.* 2003 Feb 26.
107. Mehta N, Alexander GS. Sanofi-Aventis scans India for acquisitions. *The Economic Times of India.* 2009 Sep 26.
108. Miglani S, Goswami R, Tandon N, Dudha A, Kochupillai N. Glycaemic control and microvascular complication among patients with youth onset diabetes in India using differing types of insulin and methods of glucose monitoring. *Diabetes Res Clin Pract.* 2004 Aug ; 65(2):183-5. https://doi.org/10.1016/j.diabres.2004.01.005
109. Goswami R, Jaleel A, Kochupillai NP. Insulin antibody response to bovine insulin therapy: functional significance among insulin requiring young diabetics in India. *Diabetes Res Clin Pract.* 2000 Jul; 49(1):7–15. https://doi.org/10.1016/s0168-8227(00)00130-3
110. Mohan V. Which insulin to use? Human or animal? *Current Science.* 2002[Cited 2025 May 6]; 83(12): 1544–47. Available from: https://www.currentscience.ac.in/Volumes/83/12/1544.pdf
111. Rajagopal D. WHO calls for end to insulin monopoly. *Mint.* 2021 Nove 16 [cited 2025 Mar 18]. Available from: https://www.livemint.com/news/india/who-calls-for-end-to-insulin-monopoly-11637004733237.html
112. Baruah MP, Kalra S, Bose S, Deka J. An audit of insulin usage and insulin injection practices in a large Indian cohort. *Indian J Endocrinol Metab.* 2017 May–Jun;21(3):443–52. https://doi.org/10.4103/ijem.IJEM_548_16
113. Kaplan WA, Sharma A, Kolacyzk E, Shappell H. *Insulin trade profile.* Amsterdam: Health Action International. 2016. [cited 2025 April 21]. Available from: https://www.academia.edu/25595232/INSULIN_TRADE_PROFILE
114. Luo J, Kesselheim AS, Sarpatwari A. Insulin access and affordability in the USA: anticipating the first interchangeable insulin product. *Lancet Diabetes Endocrinol.* 2020 May;8(5):360-62. https://doi.org/10.1016/S2213-8587(20)30105-4
115. Mylan and Biocon Biologics Announce Launch of Semglee™ (insulin glargine injection) in the U.S. to Expand Access for Patients Living with Diabetes [News Release]. 2020 August 31. [cited 2025 April 23]. Available from: https://investor.mylan.com/news-releases/news-release-details/mylan-and-biocon-biologics-announce-launch-semgleetm-insulin#:~:text=About%20the%20Mylan%20and%20Biocon,the%20rest%20of%20the%20world
116. Gil D. A scientific race: recombining DNA. *The Harvard Crimson.* 1978 Nov 14 [cited 2025 Mar 18]. [cited 2025 April 21]. Available from: https://www.thecrimson.com/article/1978/11/14/a-scientific-race-recombining-dna-pion/
117. Greener M. Why isn't the NHS making the most of biosimilar insulin? *Prescriber.* 2019; 30(8): 21–24. https://doi.org/10.1002/psb.1781
118. Kumar PKM, Chowdhury S, Bantwal G, Unnikrishnan AG, Kalra S, Aggarwal S, Singh AK, Pandit K, Shukla R, Vishwanathan V, Khobragade K, Sarda PS. Insulin access enhancement in India: expert views on integrating interchangeable biosimilar insulin glargine. *Cureus.* 2024 May 24;16(5):e60983. https://doi.org/10.7759/cureus.60983
119. California governor vetoes bill that would have set a $35 cap for insulin. *The Guardian.* 2023 Oct 8 [cited 2025 Mar 18]. Available from: https://www.theguardian.com/us-news/2023/oct/08/gavin-newsom-california-insulin-bill-35-dollar-cap
120. Das S, Ungoed-Thoomas J, Godier M. Revealed: pharma giants pour millions of pounds into NHS to boost drug sales. *The Guardian* (London. 2003 Jul 8 [cited 2025 Mar 18]. Available from: https://www.theguardian.com/business/2023/jul/08/revealed-pharma-giants-pour-millions-of-pounds-into-nhs-to-boost-drug-sales
121. Technology transfer has been the subject of international efforts for decades. See: A draft proposal for an international code on pharmaceuticals – Health Action International discussion document (1982). *World Development.* 1983;11(3); 317–28.
122. Times of India. Novo Nordisk to continue India's largest insulin brand Mixtard supply in vials. 2025 Apr 25 [cited 2025 Apr 26]. Available from: https://timesofindia.indiatimes.com/business/india-business/novo-nordisk-to-continue-largest-insulin-brand-mixtard-supply-in-vials-amid-penfill-device-phase-out/articleshow/120605410.cms