

Expert Q&A

A one-on-one discussion with Per Falk, Vice President of Clinical Development, Medical & Regulatory Affairs for Novo Nordisk, on the history, research and development, and innovation of insulin.

Why Not Pen Devices?

A look at the benefits and advantages of insulin pen devices and their adoption rates in the U.S.

Government Update

An overview on Novo Nordisk's advocacy efforts in increasing federal diabetes funding and resources.

Insulin: The New Generation

A commentary on insulin drug development and ongoing advancements in research and technology in the discovery of new insulins.

INNOVATION IN CARE

Innovation, technology and drug discovery are crucial to enhancing the health and quality of life for the millions of people throughout the world with diabetes.

This second issue of the Novo Nordisk BlueSheet examines how insulin has evolved over the last 90 years, how it is developed today, the use of insulin devices in the U.S., and the outlook for new generations of insulins.

Letter from Per Falk

Welcome to the second issue of the Novo Nordisk BlueSheet, the industry's definitive resource for information on diabetes. Novo Nordisk is a healthcare company and world leader with an 87-year history of innovation and achievement in diabetes care. Each quarter, we will highlight key issues in diabetes prevention, detection, treatment and care and related topics such as legislative updates, innovation in patient care and public education.

From the development of insulin analogs to the launch of the first insulin pen device in 1985, the science of insulin continues to evolve and improve the quality of life for those living with diabetes. We need to remain ambitious in driving the development of innovative and effective new treatments that will benefit the millions of people living with diabetes. As an industry, we must also continue to educate health care practitioners, diabetes educators and patients on safe and efficacious insulins and insulin delivery methods that best meet individual lifestyle needs.

Over the past few years, the need for safety has risen as a paramount theme in the diabetes community. The recent release of the American Diabetes Association and American Cancer Society's consensus paper on diabetes and cancer and the ADA's 70th Scientific Sessions continued that momentum.

This growing dialogue and call for establishing even more confidence in diabetes therapies validated, for us, our own pursuit of innovation: that diligent research into new therapies cannot proceed without efficacy, safety and vigilant monitoring once products are marketed. In this issue, we provide insights into our philosophy for developing the safest possible and most effective products for people with diabetes.

For more than 80 years, Novo Nordisk has combined drug discovery with technology to turn science into solutions for people with diabetes. We are committed to doing so until diabetes is defeated and a cure is found.



Per Falk

*Vice President of Clinical Development,
Medical & Regulatory Affairs*



EXPERT Q&A

Not Your Grandmother's Insulin

Many call it a medical marvel. At nearly 90 years old, insulin remains one of the most significant discoveries in the field of medicine. Since its discovery in 1922 by Frederick Banting and Charles Best, this drug has evolved at the hands of researchers and scientists who continuously look for new ways to improve the safety, efficacy and effectiveness of the insulin molecule.

In its initial form, insulin was lifesaving, but those first insulin preparations were not user-friendly and had major side effects. Through innovation and advanced technology, substantial improvements in insulin therapy have been achieved to make it safe, effective and predictable for the millions of people who live with diabetes.

Novo Nordisk has led the way for insulin innovation over the past nine decades. Per Falk, Vice President of Clinical Development, Medical & Regulatory Affairs for Novo Nordisk discusses the science of insulin and the necessity for continuous innovation in the treatment and care of diabetes today.

Q How has the science of insulin evolved since its discovery?

A In the early days, insulin was purified from the pancreas of pigs. The first efforts to improve insulin focused on devising insulin preparations that more easily met the needs of patients. Purified animal-sourced insulin was the only type of insulin available to patients until the 1950s when scientists successfully decoded the structure of the insulin molecule. Through this breakthrough, scientists were able to convert pork insulin to human insulin. This brought us into the modern age of insulin development. The milestone was followed quickly by the advances in gene technology that allowed scientists to do two important things: 1) they were able to make human insulin in large scale; and 2) they were able to more easily manipulate the structure of the insulin molecule to engineer insulins with desired properties.

By 2000, researchers had created the first insulin analogs, which are human insulin molecules that have changes in the insulin structure that affect the insulin's rate and consistency of absorption.

Q What challenges has Novo Nordisk met through the course of insulin innovation over the years?

A In nearly nine decades of researching the insulin molecule, Novo Nordisk has had many successes along with our share of setbacks. But through these challenges, we have learned some invaluable lessons. That is the process of innovation. We learn from the development of every single product – even those that do not succeed.

For example, in the 1980s we were on the frontline of insulin analog development. We tested many molecules for their safety and clinical effects. During this time we discovered a molecule that showed potential clinical improvements over human insulin, but it showed it could induce cell division via binding to growth factor receptors -- a potential safety concern -- as it could lead to potentially cancerous growths. The discovery of this safety issue halted our research and forced us to go back and identify the cause of this effect. Although we lost many years of development, we also learned about the features we should look for in an insulin



Frederick Banting and Charles Best, 1921.

molecule including low growth factor receptor affinity, fast dissociation from the insulin receptor and a balance of growth factor receptor to insulin receptor affinity equal to or lower than human insulin. These traits have become protocol and integrated into our screening of candidates. Ultimately, we believe this leads to developing safer drugs that are clinically effective.

These experiences in insulin research have created a wealth of knowledge and shaped our beliefs in how safe, efficacious and user-friendly insulin therapy should look. These are the values we employ when striving to improve treatment and it is why we know the insulin molecule better than anyone in the world.

Q Can you describe the research and development process for insulin today?

A Today, insulin is produced by recombinant technology. Since insulin is a protein it is coded by a gene. The insulin gene is introduced into bacteria or yeast that produce and secrete the human insulin molecule because these “factories” have been programmed to now make human insulin or insulin analogs. Novo Nordisk insulins are produced by yeast cells. The insulin molecules must then go through a number of purification steps and tests to verify authenticity and to make sure the product behaves as insulin should. Once we know the insulin has the profile and safety features we are looking for, it must then undergo a thorough testing process in the lab before moving on to human testing and development.

Since scientists have the ability to modify the coding signals for insulin, they can design specific changes to the insulin molecule to produce insulins that have the best possible characteristics for absorption and action. These insulin molecules are designed to fulfill two major criteria. The insulin first needs to be absorbed from the skin in a stable, predictable way to achieve good glucose control and a low risk of hypoglycemia. Then the insulin needs to act on the cells in the same way that normal human insulin behaves – without unexpected effects.

Q How long will the research and development of insulin continue?

A Scientists, bioengineers and clinicians continuously work on improving the profiles of insulin molecules to develop better and more effective treatments for diabetes. Currently, Novo Nordisk is working on a second generation of analogs that are designed to meet the individual needs of people with diabetes even better than currently available insulins.

Q What differentiates Novo Nordisk when it comes to the innovation in the R&D process?

A No other company in the diabetes therapy area has the combination of commitment to continuous innovation or history in diabetes that Novo Nordisk has. For more than 87 years, we have strived to find new ways to defeat diabetes at all stages of its progression. We believe there is more value to be achieved in insulin use and we’ve been successful in the early adoption of new technologies that allow us to realize this goal.

Globally, thousands of people work to realize our goal of defeating diabetes through better methods of prevention, detection and treatment. The biotech expertise that is a trademark of Novo Nordisk’s research and development units is evidenced by the biopharmaceuticals that have been discovered and developed.



Insulin Novo in sterile liquid solution, 1925.



The Novo syringe, 1925. Marketed by Novo Therapeutisk Laboratorium.

WHY NOT PEN DEVICES?

Insulin was discovered nearly 90 years ago and since that time it has evolved significantly because of innovative research and advancements in technology. Yet, such progress begs an important question. Why are the majority of people with diabetes in the U.S. still using the syringe – the same delivery device from 1922 – to take insulin?

Since 1985, the insulin pen — first in a durable, refillable version to the more recent development of a pre-filled, disposable insulin device — has offered people with diabetes a convenient and easy-to-use option in the taking of insulin. But, the adoption rates for these devices among physicians and patients in the U.S. are still relatively low – particularly in comparison to device usage in Europe and Asia today. In fact, according to a September 2009 study – “Insulin Delivery Systems Market Analysis (2008-2012)” by RNCOS, a leading market research and information analysis company, only 17% of insulin units are delivered in the U.S. through insulin pens compared to 95% and 88% in Japan and Europe, respectively. So what are the barriers to insulin device adoption in the U.S.?

Adherence to an insulin regimen is crucial to managing diabetes; therefore, patients must choose an insulin delivery method that will enable compliance and work for their lifestyle. Using simple, adjustable dosing with shorter, finer needles, insulin pen devices may provide flexibility, convenience and discretion, but they can also serve a greater purpose. Newer versions of the device now come with a variety of features like color-coding and large type designed to improve dosing accuracy. This is particularly advantageous to certain patients according to “Insulin Pen — The “iPod” for Insulin Delivery - Why Pen Wins over Syringe” (Journal of Diabetes Science and Technology, March 2008). In this article, Dr. Ernest Asamoah highlights some of the advantages of the insulin pen vs. syringes¹:

- Some pen devices have been shown to be more accurate than syringes for the delivery of doses of insulin ≤ 5 units. ^{2,3}
- Older patients with diabetes who have comorbidities or disabilities (e.g., visual impairment, impaired motor skills) that may exacerbate the difficulties of self-injection and increase the risk of dosing errors may find solace in using a pen-injecting device.⁴

So why such low adoption rates in the U.S.? The low rate of insulin pen usage in the U.S. compared with European countries and the fact that many patients report that they are not offered the option of an insulin pen by their physician suggest that there is a need to increase patient and provider awareness of the currently available devices for insulin administration.⁵ According to Dr. Etie S. Moghissi who practices endocrinology and diabetes care in Marina Del Rey, California: “Low patient awareness and the lack of device education and training among physicians as well as perception of the higher cost are significant barriers to device adoption. Even 25 years after its entry to the market, a high percentage of primary care physicians are still unfamiliar and uncomfortable with the ‘new’ insulin pen device compared to the universally-accepted vial and syringe. As a result, physicians

are unable to confidently communicate the true value of devices to their patients, which is why the industry needs to do a better job of educating and training physicians and patients about the many benefits of insulin pen devices and the value in providing accurate and convenient dosing.”

Health insurance companies may also impact device usage. In a 2007 DOC News article (formerly published newsletter from the American Diabetes Association), Dr. James Chamberlain, an assistant professor of medicine, diabetes, and metabolism at Utah Diabetes Center in Salt Lake City, acknowledges that health insurers can serve as a barrier to the adoption of pen devices. Dr. Moghissi concurs, “Many perceive the device pen to be a premium beyond the benefit. In the past, there was more of a price differentiation between the syringe and pen device. This, combined with the lack of coverage consistency among insurance carriers, created added confusion around the value of new devices. The coverage of pen devices has improved significantly in recent years, but the misperception remains among many physicians and patients.”

But according to some studies, insulin devices may have a positive impact on both adherence and overall health care costs in treating diabetes. In October 2006, Clinical Therapeutics published a study on medication adherence and the associated health-economic impact among patients with Type 2 Diabetes. The study concluded, “Among these patients with type 2 diabetes treated in a managed care setting, a switch from administration of insulin therapy by vial/syringe to a prefilled insulin analogue pen device was associated with improved medication adherence, fewer claims for hypoglycemic events, reduced emergency department and physician visits, and lower annual treatment costs.”⁶

Per Falk, VP of Clinical Development, Medical & Regulatory Affairs for Novo Nordisk, agrees that the industry needs to create better awareness and educate health care practitioners, patients and payors on the value and benefits of today’s insulin devices. Falk notes, “Devices are an integrated part of diabetes treatment and the successful outcome of diabetes treatment today. We need to work harder in generating the information required to convince the diabetes community in the U.S. to adopt insulin pen devices.”

The journey from conventional syringe to device has been slow moving at times, but the adoption of insulin pens is starting to show promise. Since its debut, the insulin pen device has evolved significantly through advancements in research and technology. Today, there are approximately 10 insulin pens through varying companies on the market. With increased support from health care professionals, device manufacturers will continue to enhance awareness in the U.S. about the benefits of devices. Building on this, they will continue to innovate aiming to provide patients with better insulin delivery options that enable them to actively manage their own health and engage in a productive lifestyle.

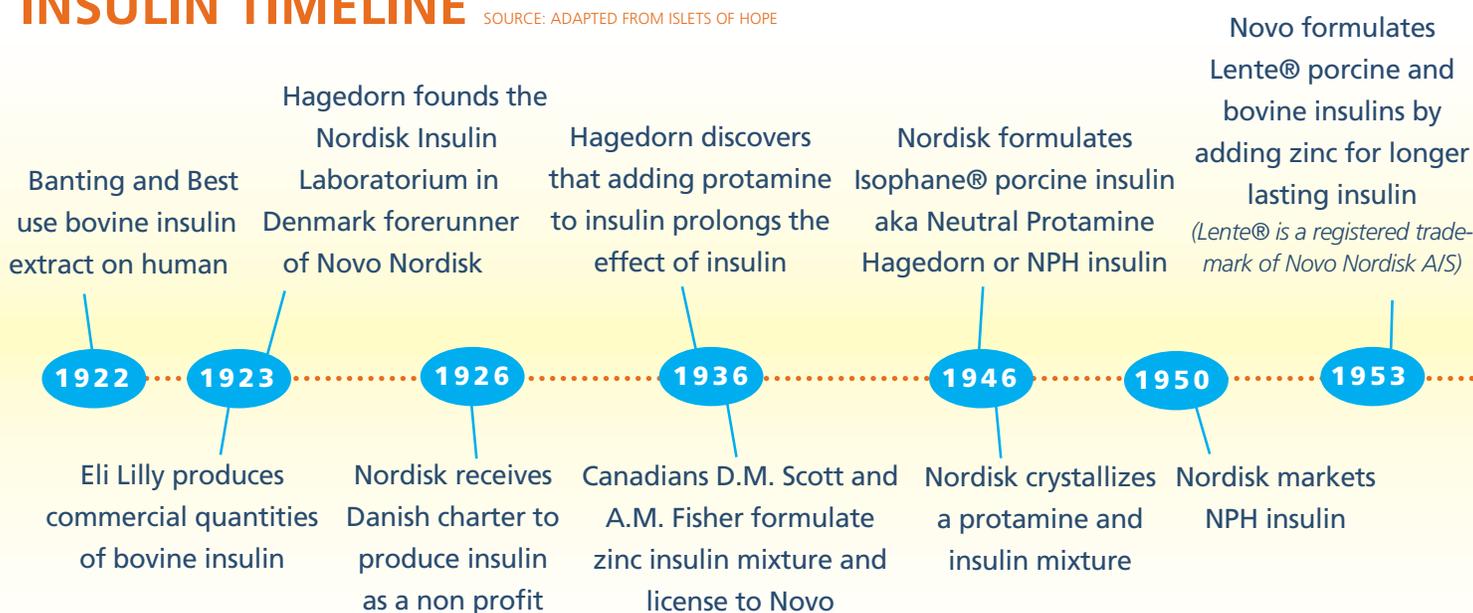
FOOTNOTES

- 1,4 Asamoah, Ernest, M.D., FACP, FACE, FRCP. Insulin Pen – The ‘iPod’ for Insulin Delivery (Why Pen Wins Over Syringe. *Diabetes Technology Society*. March 2008.
- 2 Gnanalingham MG, Newland P, Smith CP. Accuracy and reproducibility of low dose insulin administration using pen-injectors and syringes. *Arch Dis Child*. 1998;79:59–62. PubMed.
- 3 Gnanalingham MG, Newland P, Smith CP. An evaluation of NovoPen, BD-Pen, and syringe devices at small doses of insulin [abstract no. P118]. *British Diabetic Association’s Medical and Scientific Section Spring Meeting*; 1998 Mar 25-27. Edinburgh: Heriot Watt University; 1998. p. S49.
- 5 Selam, Jean-Louis. Evolution of Diabetes Insulin Delivery Devices. 2010 May. *Journal of Diabetes Science and Technology*. Volume 4, Issue 3. p. 505-513
- 6 PhD Won Chan Lee, PhD, MBA Sanjeev Balu, MSc, MPH David Cobden, MS, PhD Ashish V. Joshi and PhD Chris L. Pashos. Medication Adherence and the Associated Health-Economic Impact Among Patients with Type 2 Diabetes Mellitus Converting to Insulin Pen Therapy: An Analysis of Third-Party Managed Care Claims Data. *Clinical Therapeutics*. Volume 28, Issue 10. October 2006. Pages 1712-1725.

GOVERNMENT UPDATE

Recently, Novo Nordisk Government Affairs helped form a broad coalition of health care professional membership and patient advocacy organizations committed to changing how the nation perceives and approaches the diabetes epidemic. The coalition currently includes nine organizations: the American Association of Clinical Endocrinologists, American Association of Diabetes Educators, American Clinical Laboratory Association, American Diabetes Association, American Optometric Association, the Endocrine Society, Medicare Diabetes Screening Project, Novo Nordisk, and Vision Service Plan.

INSULIN TIMELINE SOURCE: ADAPTED FROM ISLETS OF HOPE



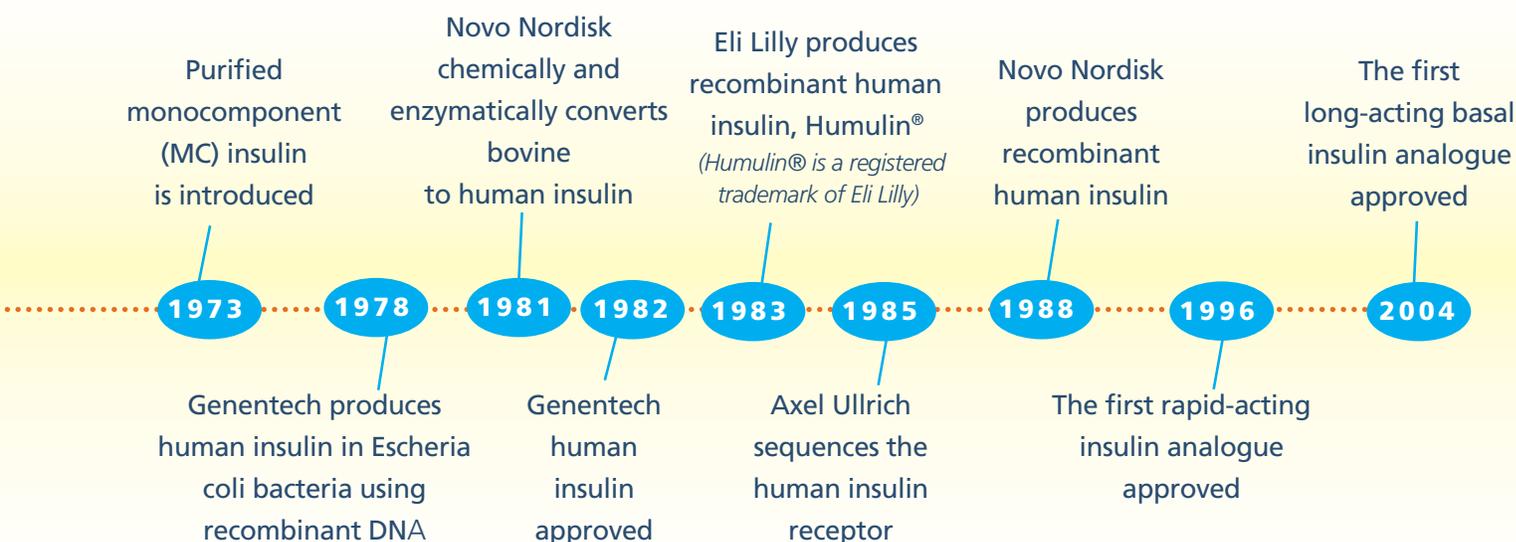
To date, the coalition has sent a letter to Secretary of Health and Human Services Kathleen Sebelius signed by 21 organizations advocating for \$5 billion in funding for diabetes from the Prevention and Public Health fund created under health care reform; met with Congresswoman Diana DeGette and the House and Senate Appropriations Committees to advocate for increased diabetes funding; and met with the Assistant Secretary for Health, Howard Koh, to discuss the need for a targeted diabetes testing objective in Healthy People 2020.

The coalition plans to grow its membership to include likeminded organizations and corporations committed to the prevention and improvement of care for individuals with diabetes. Diabetes is dramatically underfunded at the federal level, although it is the sixth leading cause of death in the U.S.; affects almost 24 million Americans; and costs the nation \$218 billion each year (in 2007 dollars) in medical expenses and lost productivity.

The Novo Nordisk Government Affairs team works constantly at the federal and state levels to increase awareness about diabetes and educate policy makers about the need to increase funding for diabetes prevention, detection, treatment and care.

INSULIN: THE NEW GENERATION

Insulin drug development is paving the way for new forms of insulin delivery options to patients today. While much advancement has been made to diabetes injections, scientists and clinicians are always preparing for the new generation of insulin, which may set a new standard for future insulin therapy. The purpose of this research is to develop safe and efficacious treatment solutions that may more closely resemble the way insulin works in individuals that do not have diabetes. Together, sophisticated technologies and field research are enabling progress for the new generation of insulin at a faster pace than ever before.



Currently, Novo Nordisk is in the process of developing new versions of insulins that will further improve user convenience for insulin users. The diabetes development pipeline at Novo Nordisk includes insulin analogs that target different aspects of diabetes therapy. Over the past year, we've seen significant progress both in our diabetes research platform and across the range of our available therapies. Committed to innovation, Novo Nordisk continues to invest in research covering the breadth of our therapeutic portfolio, especially insulin.



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INSULIN *continued...*

Diabetes will be defeated in the laboratory. That's why Novo Nordisk invests millions into research every year. By staying at the forefront of new developments in diabetes treatment, we can offer a wide range of therapies and delivery systems that make life better for millions of people. As such, researchers and scientists must remain committed to innovation and development is crucial in the treatment and care of diabetes. "We must continue to look for even better insulins until a cure for diabetes can be found," states Dr. Etie S. Moghissi who practices endocrinology and diabetes care in Marina Del Rey, California. "As the new generation of insulin evolves, effectiveness and safety should remain the two important paradigms that need to be considered in insulin development."

Novo Nordisk's partnership with the Oxford Centre for Diabetes, Endocrinology and Metabolism enables research and clinical trials that accelerate the search for new treatments. But part of our research focus also lies with organizations such as the world-renowned Hagedorn Research Institute, an independent arm of Novo Nordisk, where the latest advances in stem cell research are being realized. Because we don't think it's enough to be an innovator in diabetes treatment. Our focus is on leading the fight for a cure.

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DIABETES IN THE NEWS

On June 16, 2010, *Diabetes Care* published "Diabetes and Cancer"¹ – a consensus report co-authored by a committee of the American Diabetes Association (ADA) and the American Cancer Society (ACS). The report reviews emerging evidence that suggests a link between diabetes and cancer incidence or prognosis.

According to the report, type 2 diabetes and cancer share many risk factors, but potential biologic links between the two chronic diseases are not completely understood.

While the increased incidence of certain types of cancer in people with diabetes has been known for some time, this report provides an important, extensive, and comprehensive examination of existing data regarding the potential associations between diabetes, diabetes treatments, and cancer.

The ADA/ACS Committee did not identify any new clinical conclusions nor do they make recommendations for changes to treatment guidelines for people with diabetes. What they do call for are better designed studies and more research – an indisputable value to the entire health care community.

1 Edward Giovannucci MD, SCD, David M. Harlan MD, Michael C. Archer MA, PhD, DSC, Richard M. Bergenstal MD, Susan M. Gapstur PhD, Laurel A. Habel PhD, Michael Pollack MD, Judith G. Regensteiner PhD, Douglas Yee MD. Diabetes and Cancer: A Consensus Report. *Diabetes Care*. Volume 33, Number 7. July 2010.