

Value Innovation

Novo Nordisk – simplifying life for diabetics

Caselet written for INSEAD by Henrik Nielsen

November 2001

Nielsen Innovation SARL

Le Point Cardinal
10 Passage Ronsin
77300 Fontainebleau
France

Tel +33 1 64 69 07 31
Fax +33 1 64 69 07 15

Novo Nordisk – simplifying life for diabetics



NovoPen® 3



NovoLet®



Innovo®



In 1985, a new era for diabetes patients started : Novo Industri, the Danish insulin producing company, introduced the NovoPen. Before, life for diabetics had been quite complicated. Many of the patients needed to inject insulin several times a day, and this meant carrying syringes and vials everywhere and to administer the doses in an accurate way.

Jørn Rex, who then was in charge of the development of the NovoPen, explains: “Novo’s Marketing Director, Sonnic Fryland, asked me one day to come to his office. He had just read an article in “The Lancet” about a modified syringe holder, which the English Doctor, John Ireland, had created. The syringe holder could give a series of injections with a predetermined dosage from a prefilled syringe, but the mechanism was home made and not easy to use. Sonnic asked me, if I thought it would be possible to design a fountain pen with a built-in insulin dosing system ?” In the beginning nobody at Novo believed in the idea. For many, it was simply regarded as an extra cost on top of the price of the insulin products. The authorities, which in most European countries reimburses the patients insulin costs, were not expected to accept any increase in price.

But at the same time, several research studies indicated that Short-Acting insulin, taken just before a meal, 3-4 times a day, would give less complications later in life, than would one shot per day of Slow-Acting insulin. Using syringes and vials could be accepted at home, but nobody wanted to fiddle around with syringes and needles outside their home.

Henrik Jul Nielsen, PhD, MD of Nielsen Innovation SARL, prepared this caselet in conjunction with Professor W. Chan Kim and Professor Renée Mauborgne.

© INSEAD, 2001

Therefore a pull in the market was created, and the patients liked the convenient pen and the improved treatment of diabetes.

The NovoPen was designed as a fountain pen, containing a cartridge with insulin, allowing the patient to carry, in one self-containing unit, what corresponds to, up to, a week-use of insulin. The pen had an integrated click mechanism allowing, even blind patients, to control the dosing.

From Insulin producer to diabetes care company

NovoNordisk was created in 1989 by a merger of Novo Industri, founded in 1925, and Nordisk Gentofte, founded in 1923. Both had long traditions in hospital and laboratory research, especially in the field of insulin. Until the merger, these two Danish companies had been second- and third-largest producers of insulin in the world, after the leader Eli Lilly & Co. After the merger, they were number one, providing nearly 45% of the global demand.

The major product in the new group was insulin, accounting for 65% of the total revenues. In 2000 this number had increased to 70% and the revenue tripled to 20.8 billion DKK.

The remaining turnover of approximately 30% stems from other business areas, such as Industrial Enzymes (demerged as a separate company in 2000), Coagulation Disorders, Human Growth Hormone and Hormone Replacement Therapy.

Novo Industri started developing the first NovoPen in the beginning of the eighties, and the first version was introduced in 1985. This was the start of a new strategy. Before the NovoPen, Novo Industry was mainly producing insulin in bottles or vials. After the NovoPen, Novo Industry progressively widened its business focus to become a “diabetes care company”. In 2001 the mission statement of the NovoNordisk says : “Our aspiration is to defeat diabetes by finding better methods of diabetes prevention, detection and treatment...”.

Innovation in no-man's-land

The new business scope led to a range of products, aiming at making the administration, dosing and carrying of insulin easier. Novo Nordisk set out to occupy the land between the patient/user and the drug supplier. Before, the drug suppliers were happy to supply insulin to the patient in vials, and to focus the R&D effort on new and better insulin. This left the patient with the quite complex task of handling syringes, needles, insulin and of administering doses according to his/her needs. This is a phenomenon, seen in (or in-between) many industries ; the delicate interface between two domains of expertise is often left untouched for long periods – as long as there is room for innovation within each domain. But innovation in the field of both insulin and syringes had climbed to the top of the s-curves, to

a point where the payoff from further investments is expected to give little results. In the case of insulin, “purity” had been a major innovation parameter for several years, but Novo had already created the first “human monocomponent” insulin, and introduced it in 1981, and little progress in this direction could be made. Syringes had also been optimized in terms of materials, costs, manufacturing process... and a fusion of the two areas became attractive.

The new range of pens developed by Novo included increasing degrees of intelligence and simpler use. After the NovoPen, which was a pen containing an insulin cartridge and dial-a-dose function, came the NovoLet in 1989, a prefilled insulin delivery pen. In 1999 came the Innoovo, an integrated electronic memory and cartridge-based delivery system. It was designed to manage the delivery of insulin, thanks to a built-in memory and display of dose, last dose, elapsed time... The main purpose was to reduce risk and eliminate worries about missing injections.

Europe and Japan conquered – in USA the battle has just begun...




Today the success of the NovoPen and the later insulin delivery systems is striking : In Europe 64%, and in Japan 72%, of all sales of insulin is in prefilled devices or pens. In USA the same number is only 3% !

Why this big difference in use of convenient pen devices, between the markets ? First, Eli Lilly has 80% of the market for insulin in USA and Becton Dickinson commands 63% of the entire insulin delivery system market. Neither of the two sees the insulin pen market as a profitable business. Second, the way treatment is administered. Europe has more of a team approach, led by an endocrinologist with a diabetes educator involved. There is in Europe and Japan a trend towards more frequent injections per day (3-4), which again makes the convenience of the pens more apparent. In USA most people only inject themselves once or twice a day. Third, the cost can be a factor, especially for individuals without health insurance. Per unit of insulin delivered, injecting insulin via pens is more expensive than injecting with syringes.

But Eli Lilly has now taken the first step toward widespread use of pens in USA. In 2001 Eli Lilly introduced a line of three prefilled pens.

Novo Nordisk insulin delivery products

Since the introduction of the first NovoPen in 1985, Novo Nordisk has introduced new insulin delivery devices at regular intervals. The Major Innovations are :

	Product	Description
1985 - NovoPen	NovoPen® 3 	Insulin pen with cartridge “Dial-a-dose. Push the button to inject”
1989 - NovoLet	NovoLet® 	Prefilled, disposable insulin syringe with dosing system
1999 - Innovo	Innovo® 	Delivery system with memory. Uses std. cartridges Displays: - dose and elapsed time since last injection - last dose
200? – AERx	Inhaler system under development and testing. Joint venture with Aradigm.	Inhaler with liquid insulin. Synchronizes with patient’s breathing cycle.

Financial consequences of the innovation

“It’s hard to measure the impact of these innovations, when you already have the lion’s part of the market”, says Novo Nordisk’s Jørn Rex. Today Novo Nordisk has 20% of the insulin market in USA, 65% in Europe and 80% in Japan. Eli Lilly is the market leader in USA and Aventis is a challenger in the insulin market in Europe. 70% of Novo Nordisk’s turnover comes from diabetes care, whereas the two major competitors Eli Lilly and Aventis, who are multi-product companies, are four to eight times bigger. Therefore Novo Nordisk does not benefit from a larger group’s advantage

in terms of distribution and industrial synergies. The most tangible benefit Novo Nordisk has had from their more user friendly delivery systems and total diabetes care, is probably that they have been able to maintain their leading position in front of the two giants.

	Total Annual Revenues ¹ of Group, 2000 (bio. \$)	% of World's insulin market ²
Novo Nordisk	2.8	45%
Eli Lilly	12.0	40%
Aventis	22.3	5-10%

Inhaling is the future

It is very likely that, in a near future, insulin will not be injected via a needle. New systems are under development, which allow the patients to say goodbye to the needle. Insulin will be inhaled as 1-3 micron particles, into the lungs, either as a liquid or as a powder. Other solutions consist of spraying it as bigger particles into the mouth. The inhaler systems are now in Phase III clinical trials, and although some problems have still to be solved, they are expected in the market very soon. The long-term consequences (allergies, pulmonary complications...) of these new systems are not fully known today, and therefore their penetration is expected to be slow. But there will certainly be a strong market pull. More than 30% of the diabetics have "needle-phobia" and the absorption via the lungs is much quicker, which means the patient can start eating immediately after taking the insulin, and does not have to wait 20 minutes as today.

All the major insulin producers have made joint ventures with partners to develop the dispenser systems:

	Partner	Technology
Novo Nordisk	Aradigm	Liquid. Inhaler, synchronized with patients breathing cycle
Eli Lilly	Alkermes	?
Aventis + Pfizer	Inhale Therapeutic Systems	Powder. Inhaler

¹ Source : Annual Reports of the Groups

² No official data are available. Figures are estimates from newspaper articles

Value curves

In the following, the value curves for the four Novo Nordisk innovations will be discussed. See page 9-12.

Price per unit of insulin delivered

The cheapest solution remains the classical syringes and vials, which is approximately 15-20% cheaper than the NovoPen solution. The Novolet is slightly more expensive than the NovoPen and the Innovo. The latter has a quite high initial cost, but it is amortized over a large amount of doses. The unit price for the inhaler system AERx is not accessible, but it is expected that the inhaler itself, which must be a quite complex mechanism, as well as the liquid, will be sold at a higher price than any of the other solutions.

Practicality

How easy the product is to use, once the user has had the first instructions, is an important element – actually, one of the major “raison d’être” for the two pen systems. The NovoLet is more practical to use, mainly because of the absence of cartridges. The Innovo requires more manipulation before each injection and is therefore considered less practical to use.

Practicality was a new key element when the first NovoPen was introduced. Other attempts had been made, such as pump systems, but they have never gained the same success.

Very little is known about the inhaler system, but for the simple reason that no injections are to be made, it is considered as the most practical for the user.

Portability

Being able to carry the insulin delivery system during travels, at the job etc., in a fountain pen sized unit, is another major key element for the pens. With the syringe and vial system, patients are more or less bound to use long-acting insulin, injected once a day. It is now proved, that more frequent injections, just before a meal, is a better treatment in the long term.

The Innovo is considered as less portable than the pens, mainly because of its bigger size.

The Inhaler can be used in almost any place, with very little preparation, and is therefore considered as the most portable of all systems, despite its bigger size.

Instantness

How much time it takes to deliver a dose of insulin is an important factor when it has to be carried out several times a day, and sometimes even in public places.

Here the pens win over the syringe and vial, but also over the Innovo, which involves more “programming” before use. The Inhaler comes out best, because it does not require any preparation of clothing etc.

Intuitiveness of use

How easy the devices are to understand is an important element for many of the patients. Keeping in mind that diabetics can be children or elderly people with reduced ability to see, reduced sensory system etc., there is a constant risk of wrong use (dose count, timing etc.) and it is therefore important that there is no doubt about how the products shall be used. In some cases, the doctors have very little time to instruct the patients, so therefore, the more self-explanatory the device is, the better.

When the NovoPen was introduced, it was easier to learn to use than the syringes and vials. The NovoLet which does not need charging of cartridges is even easier to understand. The Innovo will probably cause some problems, especially for elderly people, who may not understand the information given by the device.

It is not known how the inhaler will look like, so it is difficult to assess its use.

Dosing precision

One big advantage of the two pen systems, as well as the Innovo, is that they help to increase the dosing precision. With a syringe the tolerance can be 15-20%, whereas the new systems have approximately 3% of tolerance. Since the treatment of diabetes requires exact dosing of insulin, this is an important element.

The inhaler system is reckoned to have a poor tolerance, because of its working principle. Due to leaks from the mouth and adsorption of the insulin in the mouth and upper part of the pulmonary system, the exact dose delivered via the lungs can be difficult to control.

Design appeal

The NovoPen is made in noble materials, such as stainless steel, and is designed with an exclusive look. A special model for children “NovoPen-Junior” with fresh colors has also been created. For this reason, it is considered more attractive than any of the succeeding products. NovoLet is a disposable product, which means that the choice of materials and the other functions gives a cheaper impression. Nevertheless there is a coherence between what it expresses and what it is.

Innovo could be anything from a mp3 player to a mobile phone. Despite its advanced technology, it does not express anything fresh or exclusive. From its appearance, it is considered as a less attractive product.

Dosing control

With dosing control is meant how well the device helps the patient to administer his/her doses. A new key element has been created, with the introduction of the Innovo. Using micro-controllers in this kind of products

allows users to successfully start on and confidently manage their insulin therapy. It helps to eliminate worries about missed injections and how much was last administered.

Rapidness of insulin action

This element did not exist until the concept of inhalers was revealed – or it did only depend on the type of insulin used, not on the type of delivery system. With inhalers, the insulin goes directly into the lungs, and gets adsorbed very quickly. For the user this means that he/she does not need to wait 20 minutes after the injection before eating.

Painlessness

One third of diabetics have “needle-phobia”, and it is evident that any system, which can avoid using needles, is a great plus. This element was more or less created with the introduction of inhalers. Nevertheless, the pen systems are given a higher value than the syringes, mainly because of the psychological aspects related to preparing and using syringes.

Conclusion

After the merger in 1989, Novo Nordisk became the world’s largest supplier of insulin. Already before this merger, Novo Industri had developed the first NovoPen, and the new group has since then continued to build on this advance, by continuously introducing new portable delivery devices.

Thanks to these delivery devices, Novo Nordisk has become a “diabetes care company” instead of an insulin supplier, and has brought the focus away from the direct cost of the insulin. With the introduction of the NovoPen in 1985, the competing solution, syringes and vials became irrelevant. The value curve was at all points above the traditional solution.

In the succeeding innovation, the NovoLet, the level of all key elements were raised again, except for the very subjective “design appeal”.

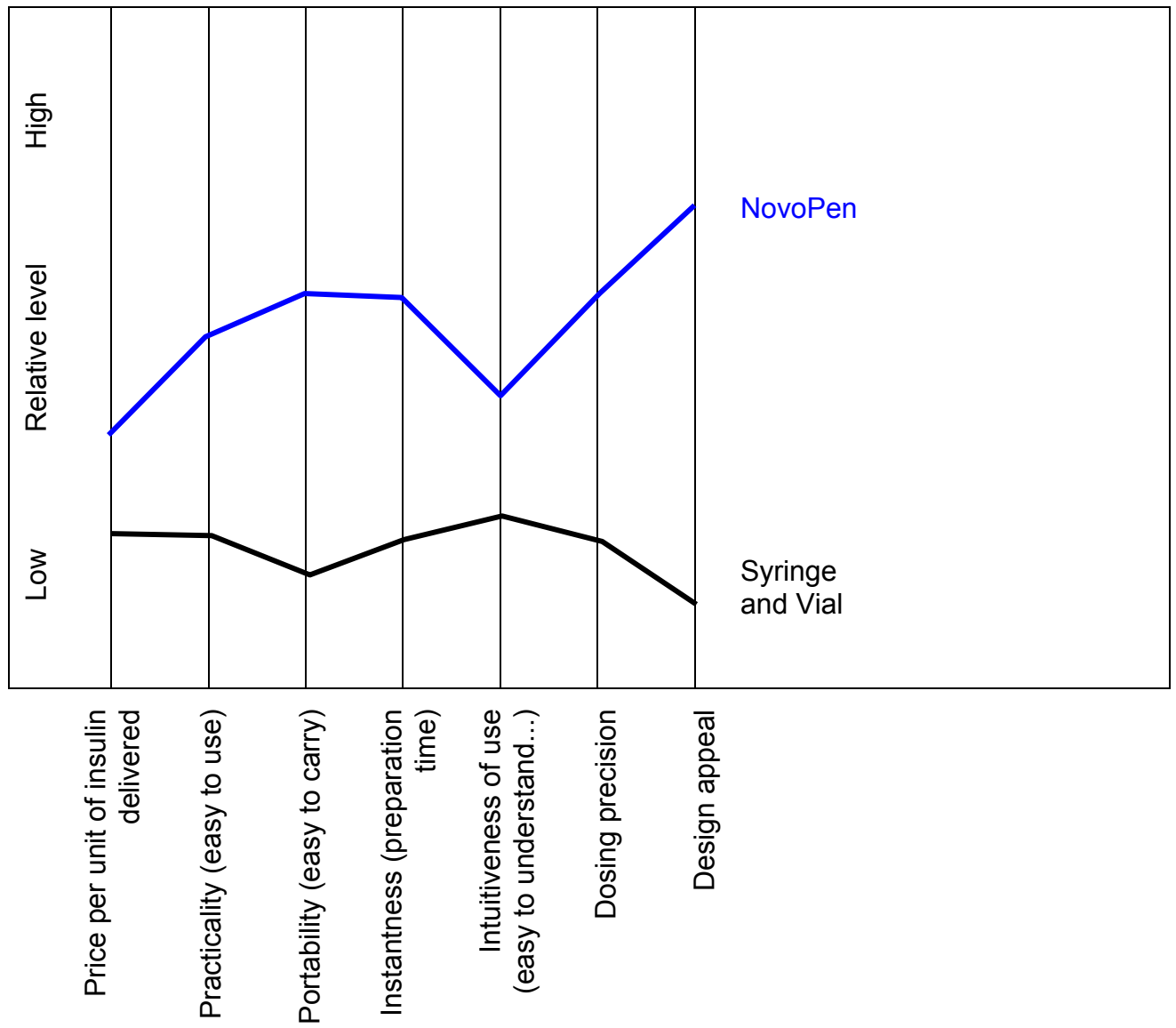
With the introduction of the Innovo, the value of all key elements fell below those of the NovoPen, except for “Dosing Control”, which is a new key element and the “raison d’être” of this product. For this reason, the Innovo becomes a niche product, appealing only to people receptive to this factor.

In the future, the inhaler systems are expected to play a key role, and the competitors are certainly waiting for this chance to increase their market share. On the other hand Novo Nordisk has more experience with complete systems, which can be an opportunity, especially in USA, where Novo Nordisk’s market share is small today. With what is known about the inhaler system, there seems to be an increase in all values, except for “Dosing precision”. Two new key elements, “Rapidness of insulin action” and “Painlessness” are introduced.

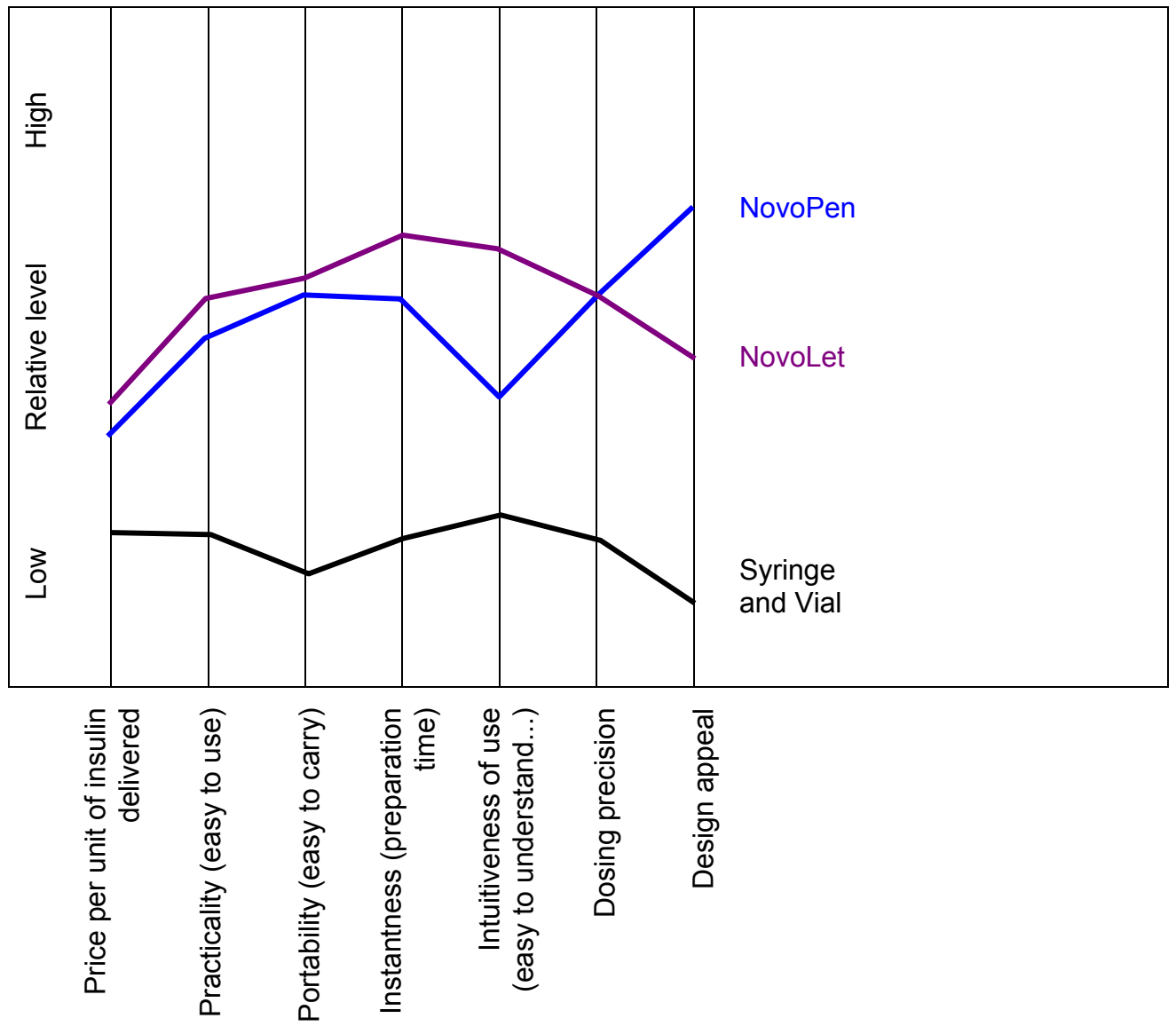
For each new product introduced, Novo Nordisk has either managed to raise the value curve or to introduce new key elements.

By this innovation strategy, Novo Nordisk has increased the loyalty of its customers, and has remained in a strong competitive position over the much larger competitors.

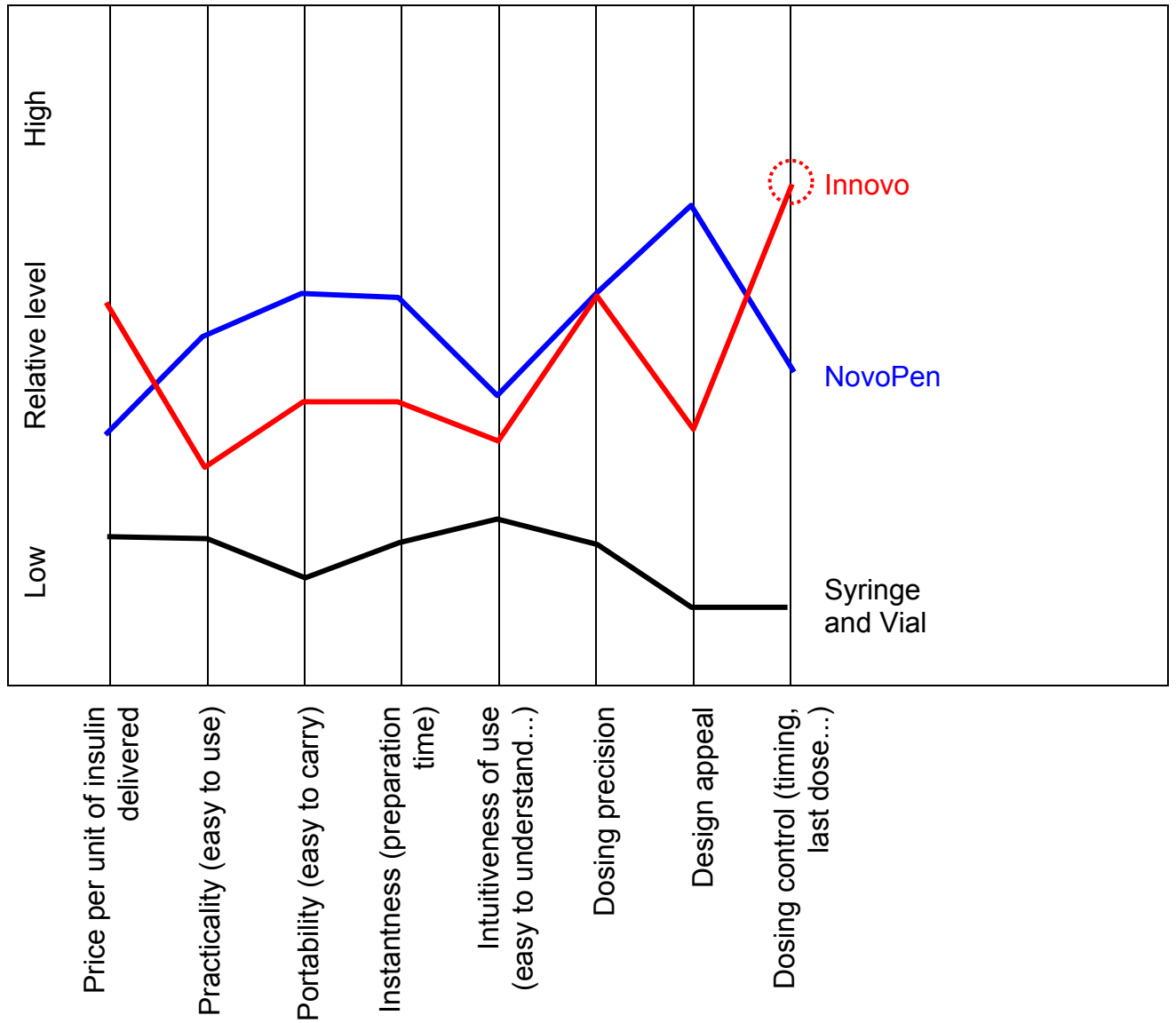
1985: NovoPen vs traditional Syringes and Vials



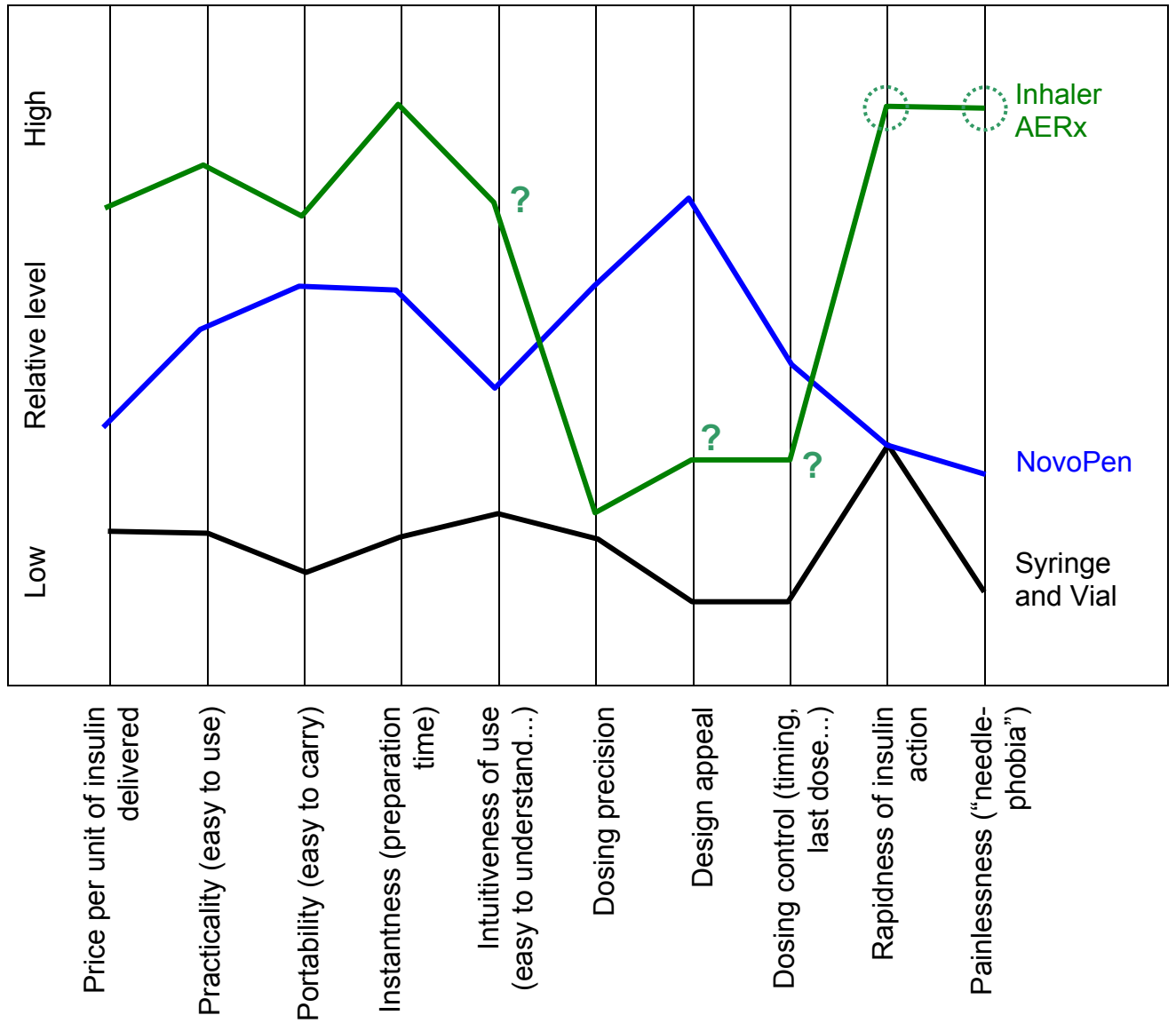
1989: NovoLet vs NovoPen and traditional Syringes and Vials



1999: *Innovo* vs *NovoPen*



+2001: Inhaler AERx vs NovoPen and traditional Syringes and Vials



APPENDICES

What is diabetes and insulin ?

Diabetes is a disorder caused by reduced production of insulin, or by the body's decreased sensitivity to insulin. Insulin is a hormone produced by the pancreas and is required by cells to utilize blood sugar as an energy source, as it enables this sugar (glucose) to pass from the blood into the cells. Decreased insulin production or sensitivity therefore results in excess sugar and lipids in the blood, some of which is removed by the kidneys. In summary, the metabolism of carbohydrates, fats and proteins is disturbed. Symptoms of diabetes include frequent urination, excessive thirst and fatigue. Two types of diabetes can be distinguished:

Type 1 diabetes develops when there is a severe lack of insulin in the body, and is treated by insulin injections and diet. It is characterized by onset in children and young persons.

Type 2 diabetes develops when the pancreas has maintained its ability to produce some insulin, although in reduced quantities or when it has reduced effect. It is treated by diet alone, or a combination of diet, tablets and injections and is characterized by onset in people over the age of 40.

Novo Nordisk – Milestones

Novo Nordisk was created in 1989 in a merger between two danish companies – Novo Industri a/s and Nordisk Gentofte a/s.

- 1923 Nordisk Insulinlaboratorium (later called Nordisk Gentofte a/s) founded.
- 1925 Novo Terapeutisk Laboratorium (later called Novo Industri a/s) founded
- 1973 Monocomponent Insulin is introduced – the purest insulin available.
- 1981 Human Monocomponent Insulin – the world’s first insulin preparation identical to human insulin, is launched.
- 1985 NovoPen – an injection system similar in appearance to a fountain pen, with replaceable insulin cartridges, is launched.
- 1987 Novo starts production of human insulin with the help of genetically engineered yeast cells.
- 1989 Novo Industri a/s and Nordisk Gentofte a/s merge to become the world’s leading producer of insulin.
- 1989 NovoLet is marketed – The world’s first prefilled insulin syringe.
- 1998 NovoNorm – Novo Nordisk’s new oral treatment for type 2 diabetes – is launched in USA and Europe.
- 1998 NovoNordisk and Aradigm sign worldwide agreement to develop a pulmonary insulin delivery system.
- 1999 A new insulin doser, Innovo is launched in Europe
- 1999 NovoRapid, the first rapid-acting insulin analogue, is launched.
- 2000 The Company’s enzymes business is demerged as a separate company called NovoZymes a/s. Novo Nordisk continues as a focused healthcare company.

Novo Nordisk Insulin Products

Different types of insulin preparations are distinguished by the speed at which the injected insulin is absorbed from the subcutaneous tissue into the blood (onset of action) and by the time it takes for all the injected insulin to be absorbed (duration of action).

Rapid-acting insulin

Rapid-acting insulin are clear solutions containing a modified form of human insulin. The modification results in a faster absorption of the insulin from the injection site, and consequently in a more rapid onset and shorter duration of action than the traditional short-acting insulin. It can be injected immediately before a meal and is considered to better mimic the normal state of insulin release after meals.

Short-acting insulin

This insulin comes also in a clear solution, and like rapid-acting insulin is also intended to be given at meals. An injection should be followed by a meal or snack containing carbohydrates within 30 minutes.

Intermediate-acting insulin

An insulin formulation that contains a substance which delays, or retards, the absorption of insulin. The combination of insulin and a retarding substance usually results in the formation of crystals which give the liquid a cloudy look. Intermediate-acting insulin takes approximately 1 1/2 hours before it begins to have an effect. The largest effect occurs between 4 and 12 hours after the injection, and after approximately 24 hours, the whole dose has been absorbed.

Premixed insulin

An insulin containing a combination of a short-acting and an intermediate-acting insulin in standard proportions. These products eliminate the difficulty some individuals encounter while mixing insulin. The products come in several different premixed combinations containing 10-50% short-acting insulin and 90-50% intermediate-acting insulin

Long-acting insulin

A long-acting insulin having a duration of more than 24 hours and a slow onset.

Tablets

When Type 2 diabetes can no longer be adequately controlled by diet and/or exercise, guidelines recommend that tablets and/or insulin are added to the treatment of Type 2 diabetes. The tablets used for this treatment are the so-called oral hypoglycaemic agents (OHA's).