Case Insulin pen systems

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Introduction to insulin pen systems.

An injector pen is a device used for injecting medication under the skin. The primary difference between injector pens and traditional vial and syringe administration is the easier and more convenient use of an injector pen by people with low dexterity, poor vision, or who need portability to administer medicine on time. Injector pens also decrease the fear or adversity towards self-injection of medications, which increases the likelihood that a person takes the medication as prescribed.

In general, the injector pen is less painful and easier to use, and the scale is easier to read, compared to the conventional vial/syringe. Needle phobia may be decreased by the shorter needles (6–10 mm) found in the pen device compared with the conventional syringe (12 mm).

Injector pens (called insulin pens) are commonly used for injections of insulin and insulin analogs, that are injected repeatedly by a person with diabetes over a relatively short period of time. Many other medications are also available as injector pens, including other injectable medicines for diabetes, high cholesterol, migraine prevention, and other monoclonal antibodies.

Pen systems for injection of insulin was first introduced in the 1980s. Insulin pens contain insulin in cartridges. A new needle is used for each administration. There are different kinds of insulin pens. Insulin is injected into the fat just below the skin. It works quickest when injected into the belly (abdomen). Other injection sites include the back part of the upper arms, the buttocks and the top and outer sides of the thighs.

Diabetes patients do a huge number of injections over lifetime. Type 1 diabetes patients making 4 injections per day do 73,000 injections over 50 years and they may do 1-4 blood glucose measurements per day and thus 3,600 – 15,000 pricks over 10 years.

Design

An injector pen consists of a chamber or cartridge of medication, a tip to attach a needle, and a piston or plunger to inject the dose. Some pens, including most insulin pens, include dials to adjust the dose of the injection before each administration. Dials enable more accurate dose measuring than traditional vial and syringe administration, especially for low doses of insulin. Injector pens

which have dials to adjust dosages may also include a clicking sound or other method to confirm the dose adjustment.

The insulin product chain is thus composed of: the drug substance (insulin), the formulation, the primary container and the device.

Some pens may include a cartridge filled with medication which can be replaced when empty to enable reuse of the pen itself, whereas other pens are designed to be disposed of after their prefilled chamber is depleted. Injector pens designed for single use may also be autoinjectors, which do not require the user to press a plunger to inject the dose.

All injector pens other than those designed for single use require the use of single-use replaceable pen needles for each injection. These pen needles come in various lengths to accommodate varying depths of subcutaneous tissue under the top of the skin. Pen needles are designed for single use subcutaneous injection of medication and are not designed to be reused for more than one administration. The needles are generally manufactured with an outer protective plastic shell, which is used by a person to attach the needle to the pen, and an inner plastic shell protecting the needle itself.

Today, pen needles are manufactured at shorter needle lengths than required for typical vial and syringe administration, which decreases the pain associated with injection. They are available in multiple lengths and gauge of needle, including 3.5mm, 4mm, 5mm, and 8mm lengths, and 31 through 34 gauge. Over time, needles have also had bevels designed which decrease the force required to penetrate the skin, which decreases the pain associated with injection and may increase the acceptability of self-injection. Furthermore, pen needles are designed for insertion at a 90-degree angle to the skin, as opposed to normal syringes which are designed to be injected at an angle. Pen needles generally do not require pinching of the skin for proper administration, unlike historically used syringes.

The mechanical design must be robust and thus less sensitive to variation and more likely to meet quality requirements.

History of devices

The first injection of insulin was conducted on January 11, 1922, to a 14-year-old boy with the use of reusable glass-bodied syringes started a new era of diabetes management. Syringe was the only possible way of delivering insulin in clinical practice for the next several decades. This method of administration had several and serious disadvantages including poor dose accuracy, lack of social acceptance, and fear of injections. These inconveniences of the vial and syringe led to the manufacture of insulin pens.

The first injector pen was introduced in 1985, by Novo Nordisk to administer insulin products. After their introduction, insulin pens had a slow adoption in the United States, with only 2% of insulin being injected via pen in 1999. A major barrier to adoption in the United States was the increased up-front cost of insulin pens compared to traditional injections. Pen adoption in the United States accelerated after studies showed that the higher up-front cost of insulin pens was

offset by the increase in compliance, which decreased overall healthcare costs. Historically, pen needles were manufactured in lengths up to 12.7mm. Over time, pen needles designed for insulin pens have become shorter, and a 4mm long needle is considered sufficient for most people to administer subcutaneously correctly.

The majority of insulin pens are proprietary devices and are developed to work with specific insulin analogs from the same manufacturer. Insulin pens are as previously outlined classified into two categories: being reusable (durable) or prefilled (disposable). The reusable insulin pen is loaded by the patient with replaceable insulin cartridges, and the prefilled insulin pen has the insulin reservoir cartridge already installed and the pen is discarded when the cartridge is empty. Both types of insulin pens can contain a maximum of 3 ml of insulin (30) and can deliver insulin in 0.5-, 1-, or 2-unit (U) increments up to 160 U with the use of a needle, that has to be attached to the insulin pen.

Reusable insulin pens from Novo Nordisk

In 1985, Novo Nordisk launched the first reusable insulin pen injector called NovoPen® to overcome barriers of the vial and syringe and started a series of NovoPen® insulin injectors. The new device was a combination of the syringe and insulin vial in one mechanism, resembling a fountain pen. NovoPen® contained a disposable, replaceable 1.5-ml insulin cartridge connected with a single-use needle and one-unit incremental dosing which was ready to use whenever needed. This allowed patients to administer multiple, preprandial injections discreetly, and their daily schedule became more flexible. First studies related to insulin pen comprised only several patients in 1995, but as the development of the devices has grown up, also the number of patients studied increased to several hundreds per study in 2002 and up to several thousands in 2020. Initially, insulin cartridges dedicated to insulin pen contained short-acting insulin for numerous injections before meals and basal insulin was injected with conventional syringes.

Soon after, in 1988 a new insulin pen NovoPen® 2 was presented to administer NPH and premixed insulins. Analogically as with short-acting insulins, majority of patients using the device to administer basal or mixed insulin preferred to continue the therapy with pens.

In 1992, NovoPen® 3 was launched which had a maximum dose that could be administered at one time which increased to 70 U (from 36 U with NovoPen® 2) and the dialed doses could be reset without insulin waste.

Soon after, in 1996 NovoPen® 1.5 was released which had a smaller insulin cartridge and was shorter in length, followed by NovoPen® 3 Demi to administer 0.5 U dose increments in 1999 and NovoPen® Junior in 2003 which was designed with vibrant colors and developed specifically for children with diabetes.

In 2005, NovoPen® 4 was introduced which required reduced force to perform an injection, which had dose increments of 1.0 U and a maximum dose of 60 U. Moreover, NovoPen® 4 was reported

as simpler to learn and easier to use for both insulin-naïve patients and patients currently using NovoPen® 3 patients. Following the release of NovoPen®s, other manufacturers have also introduced reusable insulin pens, including the HumaPen® range (Eli Lilly and Company, Indianapolis, IN, USA) and the OptiPen® Pro, OptiClik®, and ClikSTAR® pens (Sanofi, Bridgewater, NJ, USA) The inconvenience of the first insulin pens related to no possibility of dialing backward without wasting insulin, but the thing changed with the introduction of NovoPen® 3 and HumaPen Ergo®. With time, the option of insulin-free dialing forward and backward became a prevailing way of setting the insulin doses.

In recent years, further improvement in insulin pen function has been made and there are several ones which possess the memory function of the last dose taken. In 2007, Eli Lilly released the world's first digital insulin pen with memory function, namely, HumaPen Memoir. Soon after, in 2010, Novo Nordisk launched NovoPen® Echo, the first insulin pen with memory function and half-unit dosing feature. Most of the insulin pens available in the market have the feature to deliver insulin in 1-unit increments, and only a few may deliver insulin in half-units.

Prefilled (disposable) insulin pens

Prefilled (disposable) insulin pens, like reusable ones, are loaded with 3 ml (300 U) of insulin, and some of the patients find it easier to operate than the reusable insulin pens, because there is no need to replace the cartridge. In 1989, Novo Nordisk launched the world's first disposable, prefilled insulin pen namely NovoLet® followed by FlexPen® introduced in 2001 and Next Generation FlexPen (NGFP) in 2008 and FlexTouch®, a reengineered version of the FlexPen® with a novel injection mechanism, in 2011. Competing products were also launched, Humaject in 1995, HumalogPen in 1998, SoloStar in 2007 and LillyKwikpen in 2009.

Novo Nordisk have also developed new NovoFine® needles from 12 mm needles in 1985 to 4 mm in 2014.

The durable injectors are being re-used with a change of cartridge. These devices can be more sophisticated and globally less expensive. The disposable injectors are disposed when emptied. They are simpler to use but has a higher cost and possess an environmental wastage issue.

Smart insulin pens.

Nowadays, the way of health delivery is becoming more digital than ever before where face-to-face visits are often replaced by telephone or video contacts and continuous glucose monitoring or glucometer data can be revived through cloud-based data sharing technology, which was very pronounced in the COVID- 19 era.

Smart insulin pens are digital, connected insulin pens which go beyond memory function and automatically transmit information about time and amount of insulin administered to the user's mobile device and can remind about the insulin dose and help to calculate the bolus. The clinical

data from the smart insulin pen are transferred wirelessly via Bluetooth® technology to an application (app) available for smartphones. Therefore, smart insulin pens require the use of an app to collect the data sent from the pen but eliminate the need for manual self-report logbooks. Thus, smart insulin pens can help to overcome the challenges that users of pen injectors have to deal with on a daily basis. In 2017, the world's first US Food and Drug Administration (FDA)-approved insulin smart pen which uses Bluetooth® technology, namely, InPen™ (Companion Medical, San Diego, Ca, USA), was launched, and in November 2020 its new version was launched by Medtronic. This pen combines the insulin pen with a smartphone app which has the ability to record and store data of insulin injections and recommend doses, as well as display glycemia and related data on the paired smartphone app. InPen™ is designed for use with rapid-acting insulin U-100 Lilly Humalog® and Novo Nordisk NovoLog®. InPen™ is the first of its kind of smart insulin pen that allows to prepare reports for healthcare professionals, reminds about missed doses, and tracks insulin on board, but also alerts the user about an exposure of the device to abnormal (very high or very low) temperatures that may inactivate insulin. What is likewise important, in InPen™ the insulin dose can be increased or decreased in half-unit steps, and therefore the dose administered is very precise. Later on, several new smart insulin pens emerged on the market, namely, ESYSTA® pens (Emperra), Pendiq 2.0 pens (Pendiq), and NovoPen® 6 (Novo Nordisk). Smart insulin pen injectors may help not only patients but also diabetes care teams. They provide accurate information about missed doses as well as injection times in relation to meals and dose sizes, which is useful in making correct therapeutic decisions and providing personalized treatment plans. The first study of clinical outcomes using a smart insulin pen was reported in 2020. This investigation was conducted in Sweden and indicated that among patients with T1DM using smart insulin pens, clinical outcomes improved at lower costs compared to standard care. What is even more important, this research suggested that smart insulin pens have the potential to improve glycemic control and decrease glucose variability.

Ethnography in relation to pen usage

Ethnography is an approach to understanding what, how and crucially why people do what they do, and say what they say. Fieldwork is the main method to collect data. It involves the ethnographer participating in people's daily lives for an extended period of time, watching what happens, listening to what is said, asking questions. A number of ethnographic studies have been conducted with diabetes patients.

Diabetes patients (the customers) vary in several dimensions impacting the way they use the insulin pen systems:

- Age
- Cognitive capacity
- Health system/caretaking support
- Busy lifestyle
- Self-expression
- Complementary therapy
- Personality

- Analytical vs holistic thinking style

Diabetes patients may express different needs in using the insulin pen systems depending on their classification in the above listed dimensions.

Development and commercialisation of devices

Devices are less important for competition, if they are combined with superior insulins. Devices are on the other hand differentiating competitive factors, if they are combined with on par insulins or inferior insulins.

The maturity and development of a device project is monitored through the adoption of several milestones. Milestones may include verification of patient needs in alignment with technical feasibility, establishment of target product profile (TPP), design consolidation and robustness verification and manufacturing implementation verification, regulatory approval, mass production and product launch.

The medical device market encapsulates a market value, accounting for approximately 390 billion USD, which 40% of it is found in the USA, and this volume is expected to increase by 25% or more by 2023. Nevertheless, the expected margin is forecasted to be reduced, in spite of the increase in market size (medidata, 2018). Patient-centricity is an important market trend. The main elements that patient-centred healthcare is based on, are the safety of the patients (e.g., medication precision and adherence), the monitoring of their condition (e.g., smart monitoring wearables, IoT) and their engagement in the management of their condition (e.g., home-health management).

Combination products are being developed in fixed-dose ratios and are generally dosed by units of peptides like insulin, which will administer a proportional amount of another peptide like the GLP-1 agonist as well. Such projects are difficult, takes a long time and are costly. The products may have a dual chamber solution allowing for sequential dosing. Alternatively, the peptides may be pre-mixed with a simultaneously dosing.

The innovation process for new devices may include design thinking processes including brain storming seminars with company employees and with customers.

New innovations focus on injection device connectivity, device material science and big data generation and usage with aspirations of device safety, patient convenience and sustainability in the device value chain.