Expert Opinion

Dose accuracy of a reusable insulin pen using a cartridge system with an integrated plunger mechanism

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Pen injection devices are a common method of administering insulin for patients with diabetes. Pen devices must comply with guidelines prepared by the International Organization for Standardization, which include device dose accuracy and precision. OptiClik® (sanofi-aventis) was developed to fulfil unmet needs of patients with diabetes, including: easier cartridge changing, clearer dose display and readability, and a larger dose of insulin to be delivered with a single injection. In this paper, the authors report on the dose accuracy of the OptiClik pen device, which uses a novel cartridge system with an integrated plunger for easier cartridge changing. The authors show that OptiClik accurately delivers a required dose of insulin, which is maintained over the lifetime of the pen. OptiClik offers a significant contribution to the treatment of diabetes.

Keywords: delivery device, insulin, insulin delivery, insulin pen, OptiClik®, Type 1 diabetes, Type 2 diabetes

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1. Introduction

The prevalence of diabetes is increasing worldwide and is projected to double between 2000 and 2030 to an estimated 4.4% of all age groups [1]. Despite the increasing evidence supporting the earlier and more aggressive use of insulin in Type 2 diabetes [2-4], barriers to the initiation of insulin exist, including fear of injections, the inconvenience of a vial and syringe and the lack of social acceptance of injections [5].

Insulin pens have the potential to improve compliance among patients with diabetes; compared with vial and syringes, these devices offer substantial improvements in compliance, freedom and flexibility for all insulin-using patients [5-7]. Furthermore, pens may provide more accurate dosing, which could improve blood glucose control and long-term outcomes [6,7]. Compared with a vial and syringe, a clear preference for pen devices has been shown [8,9].

In this paper, the authors provide an overview of the insulin pen market and why insulin pens were developed to overcome problems associated with the traditional vial and syringe method of insulin administration. The unmet needs in the pen market and how OptiClik® (sanofi-aventis) fulfills some of these needs are also discussed. Finally, this article describes findings from the OptiClik development programme; the programme was performed to demonstrate that this insulin device complies with guidelines developed by the International Organization for Standardization (ISO) for insulin pen devices.

2. The insulin pen market

Insulin pens were developed to address some of the key limitations associated with using a vial and syringe, which include the need for more accurate dosing, a

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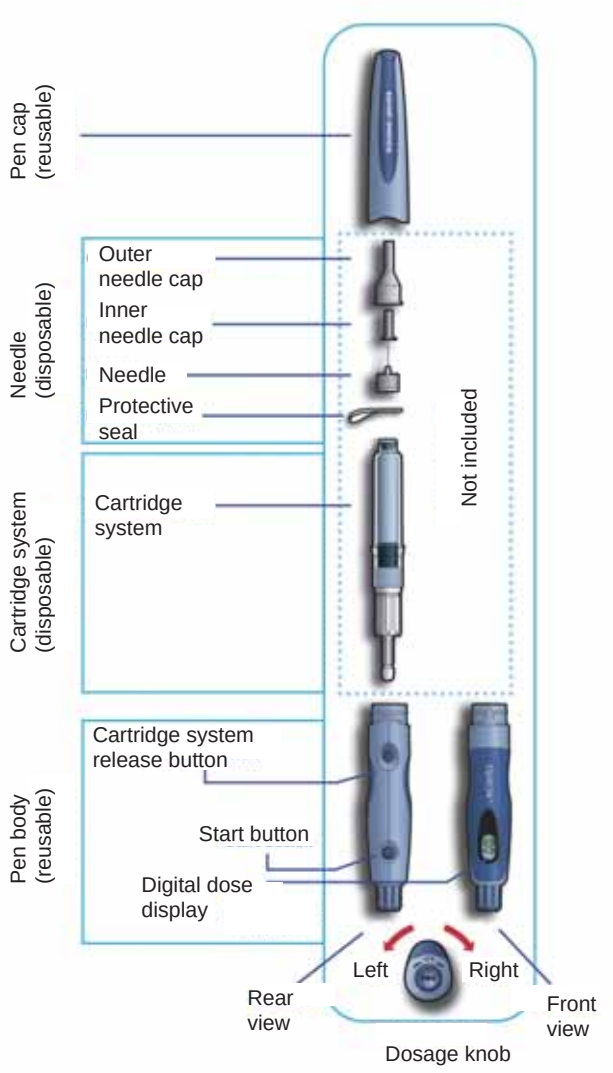

Figure 1. The OptiClik® pen device.

reduced fear of needles and facilitation of insulin administration. The first pens were introduced in the 1980s and, since then, the market has seen an increase in the number of devices that are available for patients, including reusable and disposable pens, and devices tailored to the needs of specific patient populations, such as those with visual or manual dexterity disabilities.

The key advantages seen with the insulin pen over the vial and syringe system include improved patient acceptability and compliance [10], reduced injection pain [11], increased convenience and lifestyle flexibility, reliability and accuracy of dosing [10,12,13], as well as simplification of insulin administration. These benefits have been seen in previously insulin- (and pen-) naive patients [8], in children and elderly populations [9,12,14,15], and in those patients with visual [16] or dexterity [17,18] disabilities.

The range of pens that are available has led to numerous studies comparing the efficacy and safety of available devices, as well as further assessment of patient needs. Although insulin pens offer numerous well-documented benefits over vials and syringes, patients face a number of challenges when using insulin pen devices. First, as visual impairments are common in elderly patients and in patients with long-term poorly controlled diabetes [16], dose displays should be made to be as easy to read as possible. Second, reusable pen devices necessitate the change of the insulin cartridge, which can be complicated. As diabetes is associated with impaired hand function and limited joint mobility [17,18], the change of cartridge should be simple. Third, insulin pens should be comfortable to use and easy to hold. Finally, with the growing prevalence of Type 2 diabetes and obesity, increasingly more patients are required to administer larger doses of insulin in order to maintain glycaemic control; therefore, there is a need for a device that delivers larger doses of insulin in a single injection.

Therefore, OptiClik was developed to fulfill the needs of patients with diabetes, including: easier cartridge changing, clearer dose display and readability, better ergonomics for easy handling, and a larger dose of insulin to be delivered with one injection than was possible with most of the other devices.

3. OptiClik® pen

The OptiClik pen is a medical device for the measurement and administration of doses of insulin. OptiClik was introduced in the US in early 2005, and in Japan and Europe in 2005 and 2006, respectively. OptiClik is a reusable pen injector designed for use once or several times each day, with a life of 3 years before a replacement is necessary. The electronic module shuts the pen off when the lifetime is reached and a warning is given 4 weeks before the lifetime expires to ensure a new pen can be obtained in time.

OptiClik is comprised of four main components (Figure 1): the pen body, cartridge system, needle system and pen cap. The main pen body contains the dose-selection knob, electronic module and battery, digital display and the start button and cartridge-release button.

OptiClik has a number of unique features that were designed to address the unmet needs of insulin users. Unlike other reusable pen devices, the plunger mechanism is part of the cartridge and not part of the pen body. As a result, cartridge changing entails a simple push; an audible click informs the user that the cartridge is secured in place. The benefit of this is an easy-to-change cartridge, at a press of a button.

The user-friendly digital LCD dose display shows the status of the pen and current dose in large, easy-to-read, numbers. Dose increments are set and displayed in steps of one unit. The dose is adjusted by the dose-selection knob and audible clicks inform the user at each dose increment. The maximum dose of OptiClik is 80 U, which is important as most of the other devices have maximum doses of 70 U or less. This feature thus

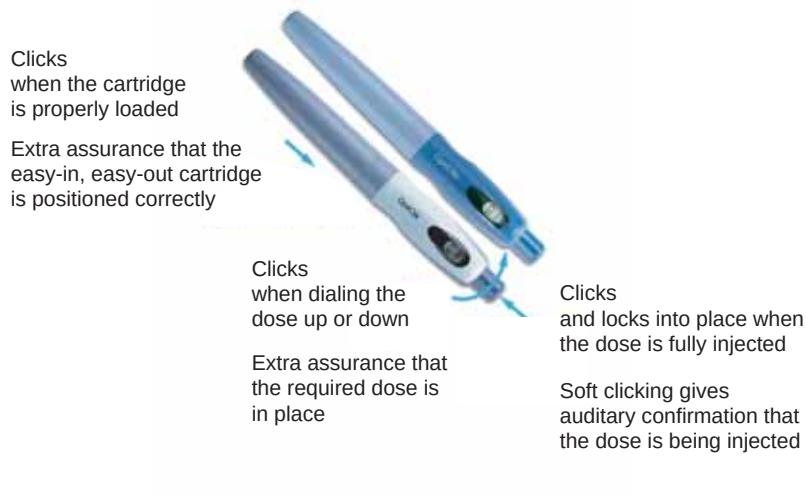

Figure 2. Audible features of the OptiClik® pen device.

allows patients to deliver doses > 70 U in a single injection, rather than with two (or more) injections, which would be required with many of the other devices.

If the user selects too high a dose, the dose can be reduced simply by dialing down. This feature is in contrast to some devices that require the patient to dispel (and therefore waste) insulin if the dose is overdialed. For other devices, the user is instructed to remove the cartridge, press the dose-administration button and reinsert the cartridge if they misdial. Therefore, OptiClik offers the patient the opportunity to correct a misdialed dose without either wasting insulin or having to remove and replace the cartridge system.

With OptiClik, clicks are audible when inserting a new cartridge, at each dose increment and at dose administration, providing the user with audible and tactile feedback that the pen device is working correctly and that the dose has been correctly administered (Figure 2). These features are particularly beneficial to patients with visual impairments.

However, these innovations are meaningless if the pen is not designed for effective handling. OptiClik has been designed to fit the hand comfortably for increased stability and control during injections.

As pen devices are subjected to varying degrees of wear and tear over their lifetime, perhaps the most important feature of an insulin administration device is that insulin is administered with a high level of accuracy and that this accuracy is maintained throughout the lifetime of the device.

4. Technical testing of the OptiClik® pen

During the development of OptiClik, the pen was tested for adherence to ISO standards to establish correct mechanical function and robustness.

4.1 What are the International Organization for Standardization guidelines?

The ISO is a regulatory body that governs the standardisation of technical products and creates a set of criteria that devices should meet in order to gain certification. The ISO standards 11608-1, -2 and -3 are applicable for insulin pen devices, needles and cartridge systems, respectively. Compliance with ISO guidelines is required by the relevant medical devices authorities before the pen and associated accessories can be introduced to the market.

For people with diabetes, these guidelines provide assurance that all insulin delivery devices that comply are of high quality, reliable, efficient and comparable in function. Furthermore, these tests verified the design and performance of OptiClik.

4.2 Insulin pen testing

Possibly the most important aspect of any insulin pen is whether it can accurately deliver a predetermined dose of insulin. If an insulin pen proves to be inaccurate with dosage, the patient can experience acute or chronic complications. For example, if the pen delivers unexpectedly high doses of insulin, the patient is at increased risk of hypoglycaemia [19]. However, if, over a period of time, the pen consistently delivers unexpectedly low doses of insulin, the patient's ability to maintain adequate glycaemic control may be impaired, increasing his or her risk of developing of micro- and macrovascular complications [20].

4.3 Dose accuracy testing

To ensure the complete pen system met the three guidelines for pen devices (ISO standard 11608-1), needles (11608-2) and cartridges (11608-3), OptiClik pens were fitted with insulin glargine cartridges and with Becton Dickinson and

Ypsomed needles (0.33 × 12 mm), for all of the dose accuracy tests. Separate pens were used for each test.

Dose accuracy tests were initially performed at three temperatures (standard = 20°C; cool = 5°C; hot = 40°C) to approximate the range of temperatures to which OptiClik may be exposed to during use.

Dose accuracy tests were also performed after pens were stored in cold (-40°C), hot (70°C) and cyclic atmospheric conditions (96 h in changing temperature and humidity). Furthermore, as the care for a pen varies between people, and as it is common for pens to be dropped, preconditioning tests also included a drop from a height of 1 m at three different orientations and after vibration according to ISO test standards. Pens were also tested after exposure to electromagnetic radiation and electrostatic discharge.

Dose accuracy tests were also performed after pens were subjected to accelerated lifetime testing. For this test, five injections per day were performed by each pen and dose accuracy tests were performed after the equivalent of 4.5 years of simulated continuous use.

All of the dose accuracy tests were performed in conjunction with visual and functional inspection to ensure that there were no defects that may affect dose delivery and accuracy.

In this paper, the authors report the results of the ISO tests that were performed in ambient conditions (20°C) and after accelerated lifetime testing to demonstrate the accuracy of the pen in normal day-to-day use and during the lifetime of the pen.

4.4 Results

In accordance with the ISO guidelines, dose accuracy tests were performed on the required number of pens in ambient conditions (Figure 3A) and after accelerated lifetime (Figure 3B). With a dialed dose of 40 U, the mean dose (± standard deviation) delivered was 39.88 ± 0.20 and 39.81 ± 0.22 U, respectively. With a dialed dose of 80 U, the mean dose delivered was 79.75 ± 0.32 and 79.74 ± 0.30 U, respectively, demonstrating the low variability in dose accuracy and that doses were within the ISO-specified range. Furthermore, no visual or functional defects were evident after each test. Similar results were observed for all of the dose accuracy tests in all conditions, and after preconditioning.

4.5 Discussion of dose accuracy testing results

The results of the ISO tests demonstrate that OptiClik is robust and stable during its lifetime; the dose accuracy of a 4.5-year-old pen is equivalent to that of previously unused pens. These results provide reassurance to the patients that the pen is reliable over time and that the dose selected will be delivered. Furthermore, the dose accuracy and precision of the pens were within the ISO-specified range in all of the tests.

Compliance at a variety of temperatures ensures that the pen is reliable and can be used in a range of environmental conditions according to the locality of the patient. Furthermore, dose accuracy was not impaired by drops from a height of 1 m, providing confidence for patients that the occasional drop will not impair function and that the dose will still be delivered with accuracy.

Finally, compliance with the preconditioning tests with exposure to electromagnetic radiation and electrostatic discharge show that the pen will perform after passage through, for example, airport X-ray scanners, and will be safe to use on an airplane and on holiday without fear of dose inaccuracy.

The results after accelerated lifetime testing are perhaps the most impressive of the tests and show that OptiClik is very robust and reliable over its lifetime and will not develop inaccuracies over time.

5. Conclusions

With respect to its prelaunch development and testing, OptiClik demonstrated compliance in all aspects of ISO testing, especially those relating to dose accuracy, thus demonstrating the reliability of this insulin device in the accurate delivery of insulin doses. It is important to note that all new devices are required to undergo ISO testing, and that compliance with ISO guidelines provides patients with the assurance they need that the device they are using is reliable. In dose accuracy tests with new pens and artificially aged pens using a dialed dose of 40 U, the dose delivered was 39.88 and 39.81 U, respectively. Using a dialled dose of 80 U, the dose delivered was 79.75 and 79.74 U, respectively. These two tests demonstrate the remarkable accuracy of OptiClik, and that it is very robust and reliable without significant change in dose accuracy over its lifetime. In addition, the low standard deviations of the tests (40 U: 0.20 and 0.22; 80 U: 0.32 and 0.30) demonstrate the low variability between each pen. In order to maintain the safety profile of OptiClik, the device has a built-in system to inform the user at 3 years that a replacement is required. It has been demonstrated that, even exceeding this electronically set lifetime (the equivalent to a simulated use of 4.5 years), the accuracy of OptiClik is almost identical to that of the previously unused pen.

The compliance with dose accuracy tests in a range of artificial environments and after environmental preconditioning demonstrate that the OptiClik is robust and is reliable for use in a range of conditions that users may experience either through choice or necessity. Therefore, patients with diabetes can be confident that OptiClik will deliver the required dose accurately when used according to the instructions provided with the device.

The features of OptiClik (a cartridge with built-in plunger, large easy-to-read LCD display and ergonomic design) make the device suitable for the majority of patients with either Type 1 or Type 2 diabetes, including patients with secondary complications that are commonly associated with diabetes, such as visual impairments [16] and limited dexterity [17,18]. Furthermore, OptiClik offers a maximum dose of 80 U, which is beneficial for patients requiring doses of > 70 U (the maximum dose deliverable by most of the other pen devices).

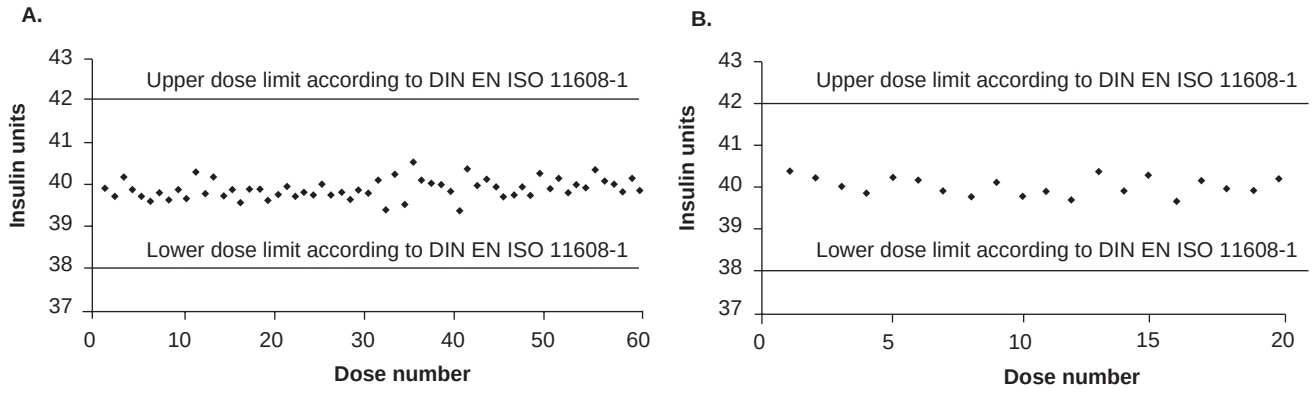

Figure 3. Dose accuracy of OptiClik® in ambient conditions (A) and after lifetime testing (B) to deliver a fixed dose of 40 U.
DIN EN: Deutsche Institut für Normung (English version); ISO: International Organization for Standardization.

The data presented here show that OptiClik is reliable and robust for the accurate delivery of insulin in the treatment of diabetes. Furthermore, the user can be confident that dose accuracy does not change during the lifespan of OptiClik. Therefore, the OptiClik pen device offers a significant contribution to the treatment of diabetes. However, it remains to be seen how patients react to OptiClik in clinical testing and day-to-day use.

6. Alternative technologies

There are five technologies that are available for the administration of insulin. These are the traditional vial and syringe, insulin pens (reusable and disposable), jet injectors, infusion pumps for continuous subcutaneous insulin infusion and, finally, inhaled insulin. Vials and syringes are the cheapest and most established method of insulin administration in the US. However, these are associated with poor accuracy and low patient acceptance. Insulin pens offer high accuracy and convenience compared with the vial and syringe. Insulin pens are the predominant device for insulin administration in Europe, while an increase in use is observed in the US. Insulin pens are available in disposable or reusable configurations according to whether the insulin cartridge can be replaced by the user once empty. Disposable pens can be discarded once the insulin is used to offer greater convenience. Reusable pens have a long lifetime compared with disposable pens, but require a change of cartridges. Jet injectors are needleless systems that use high pressure to penetrate the skin. However, the cost is greater than pen devices and bruising at the injection site is common. Infusion pumps offer the user the greatest flexibility and, coupled with glucose sensors, can control insulin infusion very rapidly. However, infusion pumps are expensive compared with insulin pens. Inhaled insulin offers patients a route of administration that avoids the use of a needle. However, this system will be no more suitable for patients with fear of injections, as needles will be essential for blood glucose monitoring. Additionally, the high cost of inhaled insulin compared with injectable insulins may limit the availability of this new formulation. It remains to be seen how inhaled insulin is perceived once launched and what the long-term clinical experience may be.

7. Expert opinion

The prevalence of diabetes, especially Type 2 diabetes, is steadily increasing: in 2030, it is estimated that 366 million people will have diabetes [1]. As a result of this increase in the diabetes patient population, the authors believe that the reliance on insulin delivery devices and insulin pens, such as OptiClik, will dramatically rise. The largest increase in the number of people with diabetes is likely to be in those who are > 65 years of age [1]. This subpopulation is at an increased risk of co-morbidities, including limited joint mobility and impaired vision, which may or may not be related to diabetes. Another diabetes patient population that is anticipated to grow over the coming years is those with obesity. These patients may require higher doses of insulin to control glycaemic levels compared with leaner counterparts owing to the insulin resistance that is associated with obesity.

Given these two patient profiles, future developments in the devices market are likely to take into consideration the needs of elderly and obese patients. For the elderly population, either reusable pens with a very easy cartridge exchange or disposable pens are preferred. OptiClik offers the patients easy cartridge changing: the cartridge system uses an integrated plunger, releasing the cartridge is at a push of a button and inserting the cartridge is by a simple push. At no stage in this process is it necessary to manipulate the plunger. Therefore, with such a straightforward process, there is little apparent need to introduce further improvements to this process. For obese patients requiring high doses of insulin, future devices may offer patients the ability to administer larger does of insulin with one injection; the OptiClik device already

exceeds most of the other devices by enabling patients to administer up to 80 U in one injection.

OptiClik was developed for sanofi-aventis in order to address many of the unmet needs identified in the devices market. However, not only does our understanding of patient needs continue to increase, but so the typical patient profile is anticipated to change over time. With the expanding and heterogeneous nature of the diabetes patient population, the needs of subpopulations of patients should be identified and catered for.

The authors anticipate that a variety of new devices will be developed and launched by both insulin and devices companies in order to address the needs of the diabetes patient of the future. Two major trends in the development of future devices are also predicted: i) further simplification of the pen, including minimising the injection effort required and maximising ease-of-use; and ii) increased complexity with additional features that provide integrated solutions for diabetes management. To address the issue of simplification, designers will need to find solutions that further reduce the injection force, reduce the dial extension and provide a larger number size. Additionally, as increasingly more patients require higher doses of insulin, devices will need to be able to hold greater volumes of insulin. With respect to the development of devices with increased complexity, the authors anticipate that further integration of electronic features will help address this need. Combining technologies from different devices, such as pens and blood glucose meters, have already been seen, and such devices will increase in complexity to the point where they provide a seamless range of functions for the patient.

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