Expert Opinion

Development of the SoloSTAR® insulin pen device: design verification and validation

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Background: SoloSTAR® (SOL; sanofi-aventis, Deutschland, GmbH) is a new, disposable insulin injection pen device for use by people with type 1 or type 2 diabetes to administer long- or short-acting insulin. *Objectives*: To discuss factors that have underlined the design process of the SOL device. In addition, to highlight the studies that shaped the direction of its development, such as addressing the unmet needs of people with diabetes, which included a need for better differentiation features and a lower injection force compared with existing prefilled disposable pen devices. *Results*: The development of the SOL pen device was an iterative process involving both patients and the design team, which has lead to a manufacturable, tailor-made pen device. Patients' needs have been taken into account in the pen design; there are numerous differentiators on the device, which avoids confusion between insulin types. Furthermore, the SOL device has a lower injection force compared with other marketed pen devices. Finally, studies have shown that the SOL device is more accurate, easier to use and is preferred by patients over other pens on the market. *Conclusions*: The SOL device has undergone rigorous user and laboratory testing, which has captured evolving improvements to better meet the needs of people with diabetes.

Keywords: design, development, device validation, device verification, diabetes mellitus, engineering, insulin pen device, long-acting insulin, short-acting insulin

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1. Introduction

SoloSTAR® (SOL; sanofi-aventis, Deutschland, GmbH) was developed for use by people with type 1 or type 2 diabetes for the administration of long- or short-acting insulin. Both SOL devices were approved in Europe in 2006 and for the long-acting insulin pen, approval was given in the United States in 2007. SOL is a disposable insulin pen device with a 3 ml capacity (300 units of insulin) designed for use once or several times a day (**Figure 1**). Studies have found that these products are easy to use [1-3], easy to teach [4], they dose accurately and have a lower injection force than both the FlexPen® (FP; Novo Nordisk, Bagsvaerd, Denmark) and the Lilly disposable pen device (LP; Humalog®/Humulin® pen; Eli Lilly and Company, Indianapolis, United States) [5,6].

The SOL pen device was effectively developed from the ground up and the development process took into consideration not only laboratory testing (design verification) and user testing (design validation), but also extensive human and ergonomic factors, which will be discussed here using two case studies to illustrate the stages in the process. Design verification and validation were fed into an iterative design process at every stage of development from initial concept design through proof of principle and proof of concept. As a result, the SOL pen device is an intuitive, easy to use device [1] with a similar user interface (i.e., common mode of operation) as other pen devices, but also fulfils patients' needs to a degree that

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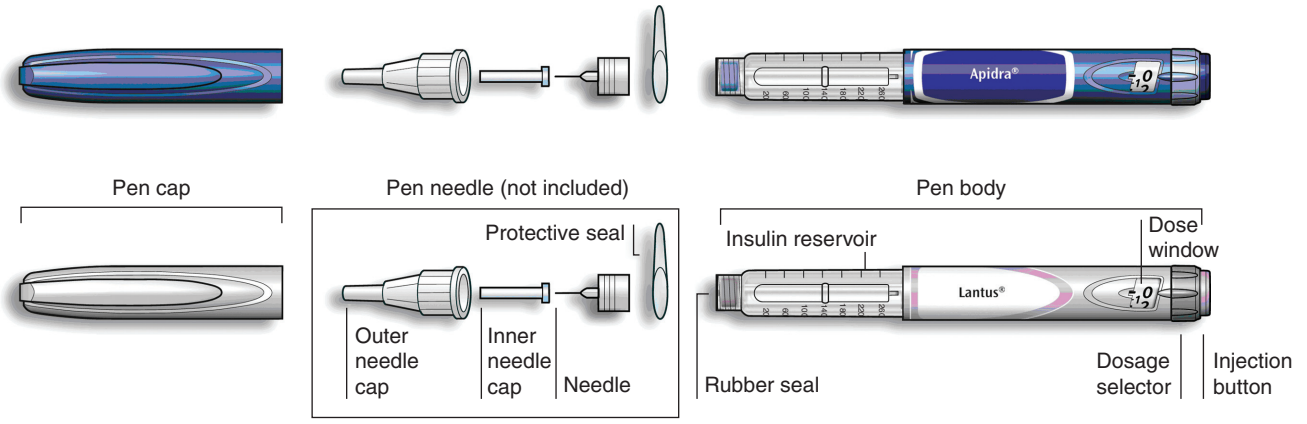

Figure 1. Schematic diagram of the Lantus® SOL (insulin glargine) and Apidra® SOL (insulin glulisine) products.

advances SOL close to the ideal mechanical disposable device. Indeed, some of the features such as addressing the unmet needs of the patient, which included better differentiation features and a lower injection force compared with existing devices that will be discussed, were identified during the development programme in user testing and subsequently incorporated into the end product.

1.1 What are design verification and validation?

The core of design verification and validation is best described by two simple questions: 'Did I design the product right?' must be answered positively to pass design verification; 'Did I design the right product?' needs to be evaluated in design validation. Design verification is a laboratory-based exercise and involves the assessment of device function, including individual components, from a technical perspective. International standards have to be fulfilled and compliance proven. In addition to parameters set by the International Organization for Standardization (ISO), other parameters are defined as part of the design brief and, therefore, are implicit in the verification process. One such factor is the injection force of the device. Testing operating forces and torques has become state of the art and has been included to verify the end product against the design brief. The aim of design verification is to quantitatively ensure the individual components and the device fulfils the technical requirements.

For design validation it has to be demonstrated that the user can operate the device and that it answers their needs, and that the collection of objectives (i.e., design brief) is achieved. There are many ways to understand the degree of overlap of user requirements and device functionality. Ergonomics and human factors specialists can be consulted, as well as medical advisors who oversee large numbers of patients. However, to best validate a product, it has to be bought to the user. User surveys and studies in clinical settings, which were performed continuously during the development, are appropriate means to get direct feedback and understand the degree of overlap, and demonstrate that the end product fulfils the needs of the users as reflected in the design brief.

1.2 Why was a new insulin pen device needed?

The use of the vial and syringe is still relatively common in some regions, particularly in the US. It had been estimated that in the US, only 14% of patients using insulin were using insulin pen devices (prefilled pens or cartridges) as a percentage of total insulin use, whereas in Europe, 92% of patients were using insulin pen devices [7]. However, it has been demonstrated that switching from the vial and syringe to insulin pens results in increased medication adherence and reduced treatment costs [8]. There are several prefilled and reusable insulin pen devices now on the market, although availability may vary in some regions/countries. Each device offers the patient specific advantages compared with the other pen devices. However, despite the multitude of pens available, there remains scope for further development of insulin pen devices in response to unmet patient needs. Some of these unmet needs will be discussed here, in relation to the development of the SOL pen device.

1.3 Original development requirements/design brief

The original design specification of the SOL pen device was based on the feedback from users with respect to existing devices plus research to understand the basic needs of customers (2001/2002). Here, users are considered to be patients as they inject insulin using the pen, as well as doctors, nurses and pharmacists as they prescribe, train and/or advise the patients on the pen. In addition, human factors analysis by means of a literature search provided basic requirements. The intent was to provide a pen device with better characteristics than the FP and the LP, as those were the most commonly used prefilled pen devices on the market at the time. Factors such as maximum length, diameter and injection force provided an integral part of the initial specification. Refinement of the requirements was done on the basis of human factor and ergonomic analyses.

1.4 Guidelines and standards for insulin pen devices

Insulin pen devices are subject to several regulatory guidelines developed by the national/international medical regulatory bodies, for example, FDA and the European Agency for the Evaluation of Medicinal Products (EMEA). Before approval from the FDA and EMEA can be sought, pen devices and related materials must also meet several criteria specified by ISO, in particular, ISO 11608-1 for insulin pen devices [9].

The guidelines for insulin pen devices cover not only specific aspects of device use, such as dose accuracy or visibility of the selected dose, but also that the pen device doses correctly after storage in a range of environmental conditions (e.g., temperature and humidity), functions properly after being dropped from a height of 1 m at various orientations and that labels or other distinguishing marks are durable during use. However, factors such as injection force and design features such as colour and size are not covered by the ISO standards. Thus, for the design verification and validation of the SOL pen device, tests were performed to ensure it met the ISO guidelines and that it met the more stringent targets that were set internally. Furthermore, user testing was carried out to ensure that the SOL pen device was intuitive to use by the intended population.

1.4.1 Unmet needs

1.4.1.1 Insulin dose

Increasing doses of insulin are required over time to overcome the insulin resistance and relative insulin deficiency. Indeed, many patients need to administer individual doses of insulin > 60 units, the maximum dose of many insulin pen devices, thus necessitating several injections. As a result, the design brief of the SOL pen device included the recommendation of a maximum dose of 80 units.

1.4.1.2 Hand function and injection force characteristics

Limited joint mobility of the hand, commonly referred to as cheiroarthropathy, is frequently observed in patients with diabetes, particularly elderly patients, which may occur as a result of connective tissue disorders or diabetic neuropathy, and is characterised by low grip strength and/or limited dexterity [10-15]. As a result, the recommendation in the design brief was for the SOL pen device to have a lower injection force than other prefilled devices available at the time, as well as a short dial extension length to reduce the mechanical strain on the user's thumb. Indeed, one would anticipate that a short dial extension with low force requirements would be easier to use for most of the patients.

1.5 Overview of the SOL pen design verification and validation process

Numerous concepts were initially investigated; all could fulfil the design brief, but used different mechanical principles. Complex designs, such as an odometer mechanism for displaying the dose, were investigated, as well as toothed rod type mechanisms and simple tampo-printed dose scales. Of the proposals mentioned earlier, very few were selected after mechanism concept evaluation, which used quality function deployment techniques (QFD). These techniques ensured end user requirements were the main focus of selection. Extra parameters, such as complexity, technical risk or perceived patent infringement risk, were taken into consideration.

The selected concepts were then progressed through the design verification and validation processes. As described earlier, the verification and validation of the SOL pen device followed an iterative process: at each stage of the process, studies were done to assess technical aspects (i.e., the mechanical/physical properties) and user aspects (i.e., feedback from the intended user population). Additionally, structured risk assessment was done at each stage, with the results used for risk management of the device. Failure mode and effects analysis (FMEA) and user task analyses served as tools for risk assessment and provided an approach from two different directions. The FMEA helped us to understand which component failure or feature malfunction could lead to critical loss in performance and the user task analyses highlighted potential ambiguity leading to reasonably foreseeable misuse.

Studies done at each stage of the process assessed not only the pen device itself (block models, proof of principle rigs, proof of concept prototypes and eventually the industrialised pen), but also individual components and features (including dial display, pen colours, label size and format, dose knob, pen cap and clip, overall dimensions). Results of these studies were fed back into the iterative design process, as summarised in **Figure 2**, to ensure the ongoing developments in pen device design and function continued to meet not only the original design specification, but also subsequent suggestions and recommendations leading to an updated design brief to further meet the patients' needs.

As shown in this figure, there are two key areas that govern the design and development process. On the one hand, it is important to understand the patient's needs through a combination of literature research, ergonomics studies and user testing. On the other, it is important to respond to these needs with rational design and adaptation to ensure a solution is found before the next stage of development can be entered. User testing and laboratory-based testing performed at each stage of the development cycle helps ensure that the design is verified and validated.

1.6 Objectives

The design validation process involved nine user studies, which were done with a total of > 2,300 participants, including health-care professionals (nurses and physicians) and people with diabetes. Moreover, 12 ergonomics analyses were done in addition to numerous meetings with health-care professionals (nurses and physicians), which are part of an advisory board that allows medical experts to provide feedback on most aspects of product development. Technical tests of all products and components were performed in advance of each user/ergonomics study to ensure the product and component

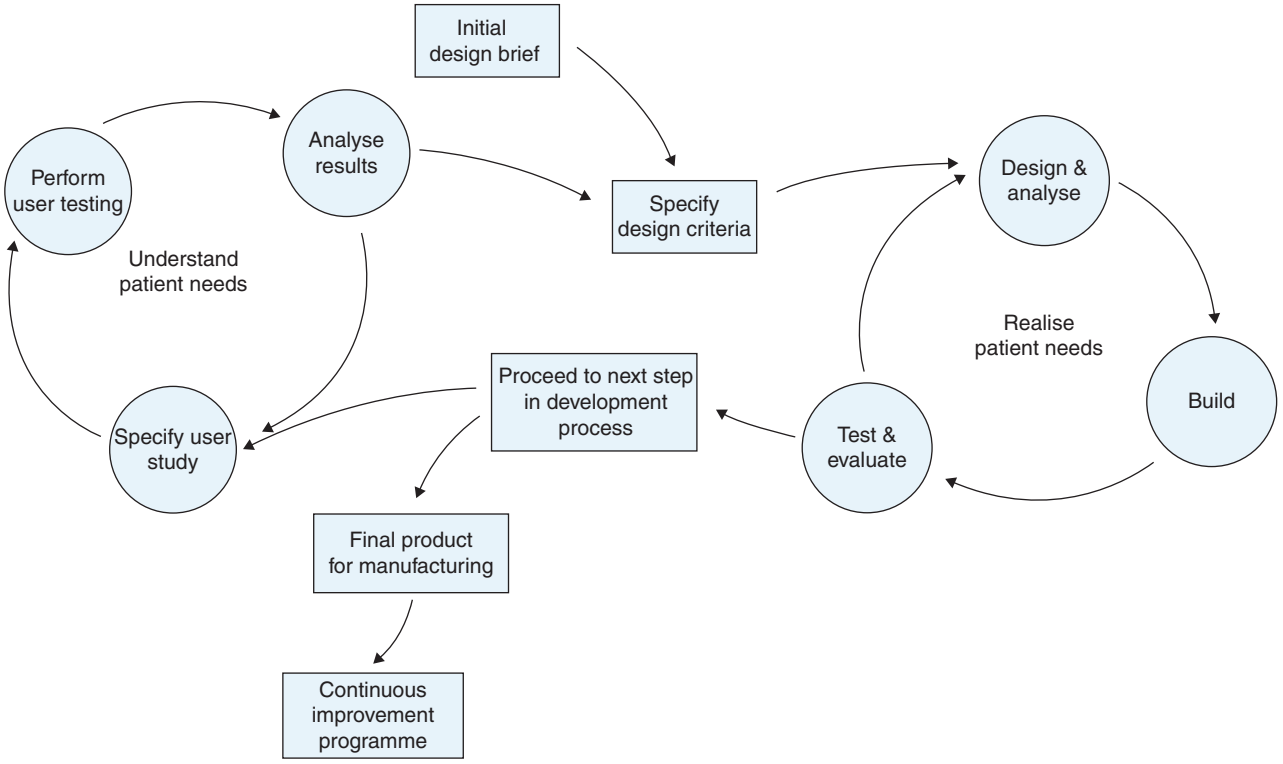

Figure 2. A simplified diagram illustrating the feedback loops for the input of technical testing and user testing results on the design and development of the SOL pen device.

met the design brief and ISO guidelines. It is not the aim of this paper to discuss all details of the extensive test programme (in excess of several 10,000 pen devices and components were tested). Instead, we have focused on two key events that helped shape the development of the SOL pen device; these two events are exemplary for the development process and systems applied for SOL. An overview of the development method is shown in **Figure 3**. In brief, each stage of the development process involved an iterative approach, and the process was guided by user research as well as laboratory testing.

First, we wish to discuss the rationale for developing the SOL pen devices with distinct body colours specific for the delivery of long- or short-acting insulin devices. Second, we wish to discuss the impact of mechanics on the function of the dose dial extension and injection force. For both characteristics, we will present the results of studies in which these characteristics were identified, provide a summary of the impact on the verification process and the final validation testing.

2. Case studies

2.1 Colour differentiation

Problems with visual acuity are relatively common in diabetes, and may be either age related, such as macular degeneration or cataract formation [16,17], or diabetes related, with onset and progression of diabetic retinopathy [18-20]. People with diabetes, particularly those with type 1 diabetes, but also some with type 2, often use more than one type of insulin to manage the basal and prandial insulin requirements, which can be provided by insulin glargine and insulin glulisine, respectively.

Owing to the differences in typical dose and pharmacodynamic characteristics of basal and prandial insulins, it is important that the delivery devices (pen device or vial) are sufficiently differentiated to ensure a low risk for confusing the two insulin formulations and to minimise the risk of hypoglycaemia. Typically, this may involve some colour applied to the label and dose button of the device along with text and potentially tactile features.

2.1.1 Colour deficiencies

Colour deficiencies in people with diabetes occur primarily as a result of retinopathy [21], which is associated with altered colour perception owing to a reduction of light falling on the retina and the death of cones where the oxygen supply is restricted, or maculopathy, such as age-related macular degeneration, which is associated with an accumulation of fluid in the cone-rich area of the fovea, leading to distorted vision along with altered colour perception [16]. People with poorly controlled diabetes (type 1 or type 2) are at increased risk of developing retinopathy, whereas risk factors for maculopathy include aging, smoking and poor glycaemia

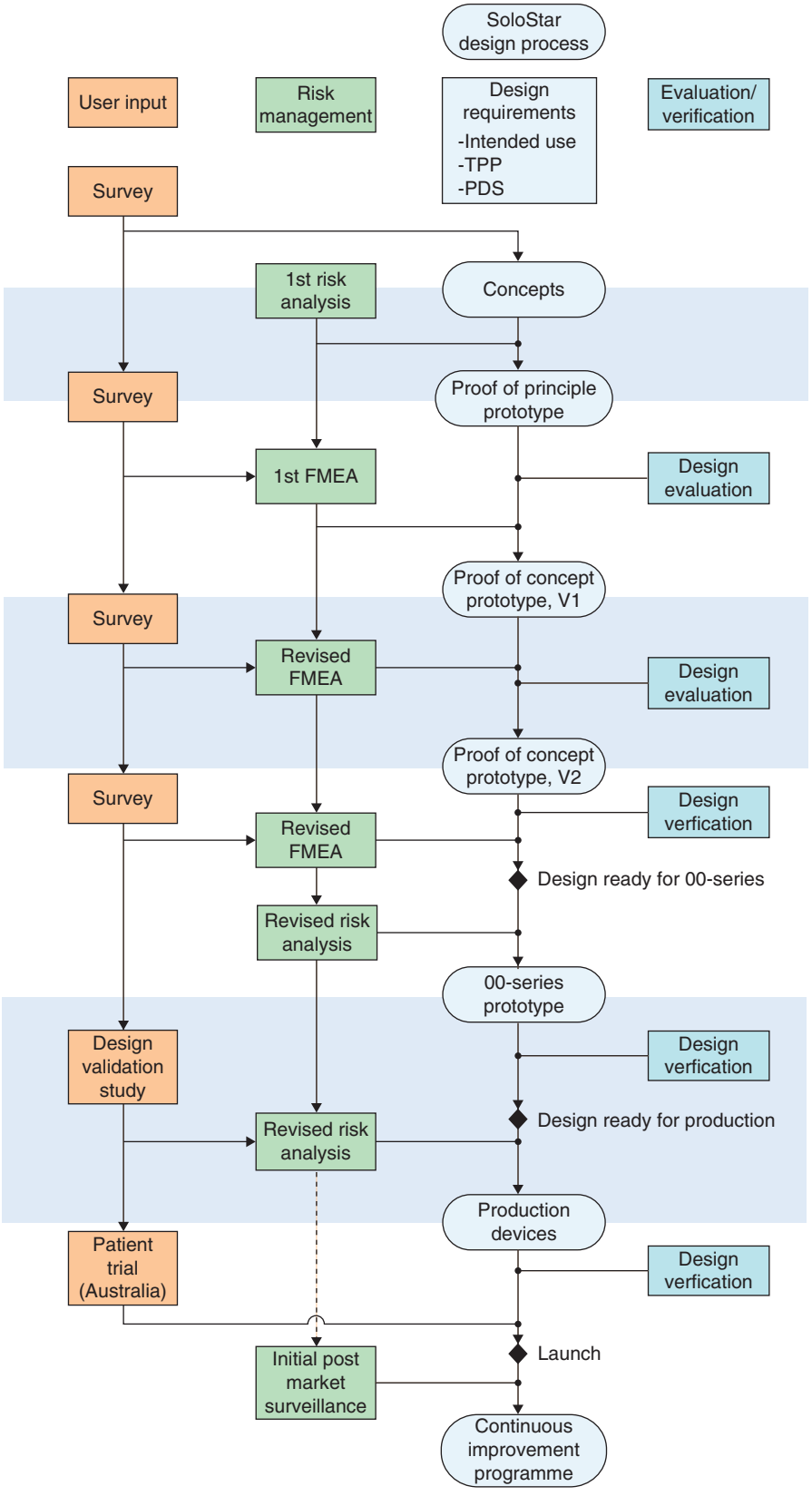

Figure 3. A summary of the key stages of the SOL pen device development process and tests done at each stage.
FMEA: Failure mode and effects analysis; PDS: Product design specification; TPP: Target product profile.

control [22]. In addition, colour perception is altered with aging; as the lens of the eye ages, it becomes less transparent and absorbs more blue light. This results in a slight blue-weak colour deficiency, particularly in adults aged > 30. Inherited colour deficiency, although not related to diabetes, is a significant concern; as many as 8% of Caucasians are thought to be colour deficient, with deuteranopia (impaired middle wave receptor; confusion between red and green) being the most common [23].

2.1.2 *Colour discrimination*

Discrimination of colour is based on three dimensions:

1. Hue: the perceptual quality of light of different wavelengths.
2. Saturation: the purity of a hue, which is reduced as more black, grey or white, is introduced into the hue.
3. Brightness: the amount of light reflected by a surface.

People with normal colour vision are unable to differentiate hue in low lighting levels, whereas people with colour vision deficiencies are restricted in their perception of hues, even at normal lighting levels. As a result, to aid colour discrimination, colours should differ sufficiently on all three dimensions.

2.1.3 *Implications for the treatment of diabetes*

Traditionally, insulin vials and pen devices have relied on text for differentiation of the type of insulin, although colour swatches were also used. The International Diabetes Federation (IDF) introduced a colour coding scheme to help identify certain insulin formulations.

2.1.4 *Study: review of colour pairings based on human factors for two insulin pen devices*

The development of the SOL pen device was initially planned to provide one pen device body colour, with differentiation between the long- and short-acting insulins provided by colours on the label and the dose button, as well as the text on the label. Results of some user and ergonomics/human factors studies indicated that the differentiation provided is sufficient and in line with common practice, but that further means would be beneficial. The results of these earlier studies suggested that there was potential to improve the differentiation of the two insulin pen devices; two distinct colour schemes should be used for pens that deliver the long- or short-acting insulin. A range of body colour options were considered to help differentiate between the two insulins, as well as differentiate within the sanofi-aventis portfolio and relative to pen devices already available on the diabetes market. Therefore, a study was designed to determine the optimal pairings of colours for the two SOL pens.

The team investigated potential options for further colour differentiation; the largest area of the pen device is the pen body itself; hence, it was decided to differentiate the two insulins through distinct pen body colours. A variety of colour options was developed from a technical perspective (what is technically feasible) and analysed as part of the design validation [24], and the optimal colour pairing is shown in **Figure 4**.

2.1.5 *Discussion*

In terms of insulin pen differentiation, the structured development process has proven to be a successful tool to detect user needs (i.e., the need for differentiating features), highlight room for improvement (i.e., introduce body colour as well as labels for differentiation), make the best choices between available options (i.e., optimal colour pairs) and confirm that the optimal solution has been identified (i.e., user testing). As a result of the studies described earlier, the SOL pen device is available in two body colours to aid differentiation between the long- or short-acting insulins (**Figures 1** and **4**), which have been validated in studies with patients with poor visual acuity or colour blindness. Furthermore, the SOL pen device contains several extra features that can help the user discriminate between a SOL pen device that delivers long- or short-acting insulin, including label text and colours, dose injection button colour and tactile features. The use of two differentiated body colours has also been validated in user studies, and the SOL pen device was associated with low risk of confusion in terms of insulin type as well as pen devices from other manufacturers (unpublished observations).

2.2 Ease of injection

The design brief for the SOL pen device required a low injection force and short dial extension to allow easy injection. However, these two factors are inextricably linked in terms of mechanics of operation. Reducing the injection force or the dial extension is relatively simple; however, development of earlier injection devices indicated that reducing the one will normally increase the other. Thus, for the SOL pen device, the challenge was to inject large doses on short strokes at low forces.

To achieve this, the team developed a totally new concept. As the low injection force and short dial extension are conflicting criteria, detailed mathematical modelling of the mechanism concepts was required, as well as stress and material analyses such as Finite Element Analysis or Moldflow. Careful selection of materials was needed both for low friction and high stress resistance.

During the continuous user studies, the benefit of low and consistent injection force was identified to be a key differentiating factor with regard to ease of use. As a result, the injection mechanism was exposed to several stages of the iterative design verification (from a technical perspective) and validation (from a user perspective) process, to ensure the injection force characteristics were as good, or better, than both the FP and LP.

2.2.1 *Study: dose injection force*

The design brief for the SOL pen device defined an injection force lower than FP and LP. In user studies, a variety of injection forces were tested to determine the impact of the different forces on the perception of users; the data helped the team to have a set goal to design an appropriate mechanism to achieve this.

Figure 4. The Lantus® SOL (insulin glargine) and Apidra® SOL (insulin glulisine) products showing the colour pairing (with European labels).

In addition to the earlier-mentioned user studies, the dose injection force characteristics of SOL versus FP and LP have been assessed in two separate studies, and all force characteristics were lower with SOL, particularly peak injection force and mean injection force [5,6].

The mean injection force required to dispense 40 units in 4 sec for the SOL, FP and the LP in these two studies was in the range of 10.7 – 10.8 Newtons [N], 15.5 – 17.1 N and 23.5 – 24.9 N, respectively [5,6]. Peak dose force for the SOL, FP and the LP was in the range of 14.4 – 14.7 N, 22.9 – 25.0 N and 30.9 – 31.8 N, respectively [5,6]. The mean injection force was similar across the two studies; SOL had ~ 40% lower value than LP and ~ 30% lower than that measured for FP [5,6]. These laboratory-based studies are consistent with the subjective assessment by people with diabetes, as more people rated the effort to dispense a 40 unit dose with SOL (63% of participants) as best compared with either the FP (19%) or LP (16%) [25].

2.3 Patient usability of insulin pens

Finally, it is important to consider the end result of the design process; the impact the pen has on patient usability. An open-label study done by Haak *et al.* across four countries (United States, Germany, France and Japan) compared four pen devices (SOL, LP, FP and Pen X [a prototype pen]) in 510 patients with diabetes [25]. A significantly higher proportion of patients correctly prepared the pen and performed an injection into a receptacle with SOL (94%) compared with the FP (90%; $p < 0.05$), LP (61%; $p < 0.05$) and Pen X (64%; $p < 0.05$). Similar results were seen regardless of previous pen use, age and manual/visual impairments. In addition to usability, a higher proportion of patients had an overall preference for SOL (53%) compared with FP (31%; $p < 0.05$) or LP (15%; $p < 0.05$) [25].

3. Discussion

Here, we have provided a brief overview of the design and developmental process to bring the two SOL insulin pen devices that deliver either long- or short-acting insulin from a concept on paper to mass-produced insulin pen devices. The processes involved in the design and development of the SOL pen device can be likened to those involved in developing pharmaceutical drugs, which requires preclinical (i.e., concept design and selection) and Phase I – IV studies (i.e., validation and verification). However, there are significant differences with respect to the iterative process, in which a prototype is tested from both a technical and user perspective, and the resulting data are used to change the design as needed to then go into testing (user and technical); this approach introduces an element of consumer products into the development process. Only a lively dialog with several iterations between users and the development/device design team allowed the SOL pen device to be tailored to suit the patient needs and be manufacturable. The primary considerations in the design brief were to develop an easy to use insulin pen device with an injection force lower than that of other pens on the market. Within a laboratory setting, the SOL pen device has a lower and smoother injection force than both FP and LP [5].

The ease of use of the SOL pen device has also been demonstrated in a single-centre, two-group sequential study [3]. In that study, after a training session on the day before assessment, patients were able to correctly administer three doses of insulin.

As demonstrated in the Haak *et al.* study, more patients correctly used and preferred SOL and FP than the LP and a prototype pen [25]. Similar ease of use and patient preference for the SOL were seen regardless of age, manual dexterity or visual impairments, factors that may have particular importance when considering elderly patients with diabetes, or patients that have peripheral neuropathy, a common complication of diabetes [26,27].

In these three studies, the users injected the dose into a receptacle or injection pad; in the case of the force measurement [5], dose deliveries were performed by a force stand. As these studies do not provide evidence of the usability of the SOL pen device in a clinical setting (i.e., at least once each day for a duration of time), an observational survey of everyday clinical practice was done in Australia to evaluate the usability and safety of SOL, which showed that most of the participants (95%) were very satisfied or satisfied with using SOL to inject insulin [1].

4. Conclusions

Here, we have presented data from two aspects of the design verification and validation of the SOL pen device and have shown how these have impacted the final production model, which was approved for use in a clinical setting to administer either long- or short-acting insulin. We have presented selected aspects from a wealth of data that we collected through the iterative development process. This comprehensive design verification and validation process with rigorous testing has resulted in a final product that is easy to use with a dose injection force lower than both FP and LP and, in a nonclinical environment, is preferred by more people than the FP and LP. Finally, within a clinical setting, the use of SOL delivering long-acting insulin in 5,983 patients with type 1 or type 2 diabetes was associated with a low incidence of adverse events (0.3%) and adverse reactions (0.15%; such as skin reactions, hypoglycaemia, pruritis), in addition to a low rate of reported technical problems (0.6%; such as leakage, defective dose knob or incomplete dose delivery) [28].

5. Expert opinion

Insulin therapy becomes a necessary part of a patient's disease management in order to reach appropriate glycaemic control in type 1 diabetes mellitus and following disease progression in type 2 diabetes mellitus. Common stressors of injection based insulin therapy affecting people with both types of diabetes include the psychological aspects of injecting an accurate dose and the reproducibility of doing so; this can lead to a decrease in patient compliance to what is an invasive and chronic daily routine.

The traditional syringe and vial approach to the delivery of insulin, although still in large-scale use, particularly in the US, has been improved on by the development and availability of insulin pens. These devices may go some way to lessen the stresses associated with the vial and syringe as they have improved dose accuracy, and are more convenient. In terms of cost effectiveness, although acquisition costs are higher with insulin pens, the annual overall treatment costs are lower in comparison to the vial and syringe [8,29]. Moreover, insulin pens may improve adherence to treatment owing to the ease of use and handling of the devices, in addition to impacting lifestyle issues, such as alleviating the stigma of syringe use.

Several devices are available on the market, each with particular characteristics that provide different advantages, offering a wide choice to patients and health-care professionals. With standardised ISO parameter requirements for approval, insulin pens are technically accurate; however, there are remaining unmet needs, particularly in terms of injection force and dispensing of large doses of insulin. The next generation of pen devices, such as SOL, go beyond providing standardised ISO parameters. The SOL pen incorporated a unique design approach, which combined laboratory-based input as well as end-user feedback at each stage to develop an important, beneficial but manufacturable device. Laboratory tests and clinical use so far have provided sufficient data to show that patient preference for SOL is greater than with other insulin pens, and that SOL has the distinct advantage of a lower injection force compared with other marketed pen devices.

In light of the global trend in the growing numbers of people who are obese, particularly at an early age, the incidence of type 2 diabetes will rise, and the age range of patients affected will increase. It could be anticipated that injection force and pen differentiation will gain greater importance, as this predicted rise of patients with diabetes, particularly in those acquiring the disease at an early age, will increase the number of patients with such complications as limited dexterity, peripheral neuropathy and retinopathy. The interactive and comprehensive design process of SOL has combined both a technical and end-user centred approach, which has aimed to address the potential emerging needs of the patient. The changing needs of this growing population of patients with diabetes over the next decade and beyond will provide both a challenge and an opportunity to further evolve insulin delivery devices.

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Declaration of interest

Andreas Bode is an employee of sanofi-aventis, Deutschland, GmbH, the manufacturer of SoloSTAR®, LANTUS® and Apidra®.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Carter J, Beillin J, Morton A, et al. Usability, participant acceptance and safety of SoloStar in a 3-month observational survey in everyday clinical practice. J Diabetes Sci Technol 2007;1(Suppl 1):A21
2. De Luise M, Beillin J, Morton A, et al. Influence of diabetes type and previous experience of pen devices on acceptance and usability of a new pen: an observational survey on SoloStar use. J Diabetes Sci Technol 2007;1(Suppl 1):A30
3. Schwartz SL, Vlajnic A. Validation of the SoloStar insulin pen. J Diabetes Sci Technol 2007;1(Suppl 1):A159
4. Roberts A, Thornley S. Health care professional-reported usability of SoloStar in a 3-month observational survey in everyday clinical practice. J Diabetes Sci Technol 2007;1(Suppl 1):A151
5. Clarke A, Spollett G. Dose accuracy and injection force dynamics of a novel disposable insulin pen. Expert Opin Drug Deliv 2007;4(2):165-74

•• **This review reports on the key investigations during the development of SOL and highlights dose accuracy and injection force testing in comparison with two other commonly used insulin pens.**

6. Owens DR. Study to compare the injection force required for the following insulin pen devices: Lilly disposable pen, Novo FlexPen, and SoloStar. J Diabetes Sci Technol 2007;1(Suppl 1):A134
7. IMS Health. IMS Midas(TM) June 2007, Quarterly insulin sales volume in units. 2007
8. Lee WC, Balu S, Cobden D, et al. 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. Clin Ther 2006;28(10):1712-25

•• **This study reports the benefits provided by insulin injection pen devices for patients converting from the vial and syringe. Importantly, the delivery of insulin using a pen device increases patient adherence to treatment, including fewer adverse medical events, such as hypoglycaemia and the requirement of emergency treatment, compared with insulin administered by means of the vial and syringe. Together with the evidence of cost effectiveness, this gives a further indication that switching from the vial and syringe to an insulin pen can provide the patient and treating physician considerable advantages in terms of the management of diabetes.**

9. International Organization for Standardization. Pen-injectors for medical use – Part 1: Pen-injectors – Requirements and test methods (ISO 11608-1:2000). Geneva, Switzerland: International Organization for Standardization; December 2000
10. Aljahlan M, Lee KC, Toth E. Limited joint mobility in diabetes. Postgrad Med 1999;105(2):99-101, 5-6
11. Casanova JE, Casanova JS, Young MJ. Hand function in patients with diabetes mellitus. South Med J 1991;84(9):1111-3
12. Rosenbloom AL. Limitation of finger joint mobility in diabetes mellitus. J Diabetes Complications 1989;3(2):77-87
13. Savas S, Koroglu BK, Koyuncuoglu HR, et al. The effects of the diabetes related soft tissue hand lesions and the reduced hand strength on functional disability of hand in type 2 diabetic patients. Diabetes Res Clin Pract 2007;77(1):77-83
14. Schady W, Abuaisha B, Boulton AJ. Observations on severe ulnar neuropathy in diabetes. J Diabetes Complications 1998;12(3):128-32
15. Starkman HS, Gleason RE, Rand LI, et al. Limited joint mobility (LJM) of the hand in patients with diabetes mellitus: relation to chronic complications. Ann Rheum Dis 1986;45(2):130-5

• **This article highlights the prevalence of limited joint mobility, a condition associated with patients with diabetes. Impairments in manual dexterity in patients with diabetes can affect the patient's ability to self-inject insulin, and is an important consideration in the development of insulin delivery devices.**

16. Gehrs KM, Anderson DH, Johnson LV, et al. Age-related macular degeneration–emerging pathogenetic and therapeutic concepts. Ann Med 2006;38(7):450-71
17. Whiteside MM, Wallhagen MI, Pettengill E. Sensory impairment in older adults: part 2: Vision loss. Am J Nurs 2006;106(11):52-61; quiz 61-2
18. Aylward GW. Progressive changes in diabetics and their management. Eye 2005;19(10):1115-8

•• **This paper provides a perspective on the prevalence of diabetic retinopathy, and highlights the therapeutics available for treatment and the key unmet needs of patients with this condition.**

19. Wong T, Mitchell P. The eye in hypertension. Lancet 2007;369(9559):425-35
20. Wong TY, Klein R, Amirul Islam FM, et al. Three-year incidence and cumulative prevalence of retinopathy: the atherosclerosis risk in communities study. Am J Ophthalmol 2007;143(6):970-6
21. Fong DS, Barton FB, Bresnick GH. Impaired color vision associated with diabetic retinopathy: Early Treatment Diabetic Retinopathy Study Report No. 15. Am J Ophthalmol 1999;128(5):612-7

•• **This trial highlights that patients with diabetic retinopathy commonly show impairment of colour vision. The importance of this observation has implications in the development of insulin pens, such as the colour differentiation of devices to avoid medication errors.**

22. de Jong PT. Age-related macular degeneration. N Engl J Med 2006;355(14):1474-85
23. McIntyre DA. Colour blindness: causes and effects. Chester: Dalton Publishing; 2002
24. Austin F, Cox G. Lantus SoloStar and Apidra SoloStar pen colors contributes to the differentiation by users with normal vision and by users with impaired color vision. J Diabetes Sci Technol 2007;1(Suppl 1):A4
25. Haak T, Edelman S, Walter C, et al. Comparison of usability and patient preference for the new disposable insulin device SoloStar versus Flexpen, Lilly disposable pen, and a prototype pen: an open-label study. Clin Ther 2007;29(4):650-60
26. Fox C, McKinnon C, Wall A, et al. Ability to handle, and patient preference for, insulin delivery devices in visually impaired patients with type 2 diabetes. Pract Diab Int 2002;19:104-7
27. Petzinger RA. Diabetes aids and products for people with visual or physical impairment. Diabetes Educ 1992;18(2):121-38
28. Schreiber S, Ferlinz K, Donaubauer B. The Reliability and Usability of SoloSTAR® (SOL) Disposable Pen in Clinical Practice

in Germany. Presented at the CDA/CSEM Professional Conference and Annual Meeting, Montreal, Quebec, October 15–18, 2008. Abstract 88

29. Pawaskar MD, Camacho FT, Anderson RT, et al. Health care costs and medication adherence associated with initiation of insulin pen therapy in medicaid-enrolled patients with type 2 diabetes: a retrospective database analysis. Clin Ther 2007;29:1294-305

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