Focused Usability Test of colour-blind individuals' ability to differentiate between Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® pen-injectors and cartons

PDS290-UT117-2013 (UT117)

Usability Test Report

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Title page

Title of Usability Test	Focused Usability Test of colour-blind individuals' ability to differentiate between Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® pen-injectors and cartons
UT ID	PDS290-UT117-2013 (UT117)
Generic Name	PDS290 prefilled pen-injector
Test Sites	Denmark, Germany
CRO	[redacted]
Sponsor	Novo Nordisk A/S
International Medical Director	[redacted]
International Trial Manager	[redacted]
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List of abbreviations

Abbreviation	Definition
CRO	Contract Research Organisation
CHMP	Committee for Medicinal Products for Human Use
EMA	European Medicines Agency
GLP-1	Glucagon-Like-Peptide-1
HCP	Healthcare professional
HFE	Human Factors Engineering
IFU	Instructions for Use
PDS290 prefilled pen-injector	Protein Delivery System 290 prefilled pen-injector
PRAC	Pharmacovigilance Risk Assessment Committee
RMA	Risk Management Analysis Input to Usability Test
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
UT	Usability Test

Executive summary

In order to fulfil Novo Nordisk's commitment to the European Medicines Agency (EMA) to assess if patients with Type 1 Diabetes Mellitus (T1DM) or Type 2 Diabetes Mellitus (T2DM) suffering from red-green colour-blindness can differentiate the two Tresiba® FlexTouch® variants – 100 units/mL and 200 units/mL – and NovoRapid® FlexPen® from each other, Novo Nordisk retained [redacted] to conduct a focused post-approval usability test (UT117) on this group of patients' ability to differentiate between the aforementioned prefilled pen-injectors and cartons.

UT117 test

A total of 22 red-green colour-blind individuals with T1DM or T2DM who currently self-administer insulin daily participated in the focused usability test UT117. The test results demonstrated that 20 participants successfully differentiated between the aforementioned prefilled pen-injectors and their respective packages (i.e. cartons) without committing any use errors, close calls or experiencing any operational difficulties. Only 2 participants (out of 22 participants) committed a total of 1 use error and 1 close call. Based on the root cause analyses, the two incidents were primarily attributed to test artefact (i.e. the participants' [redacted] carton selection task) rather than the design (including colour) of the prefilled pen-injector and the carton, and therefore they would be unlikely to occur in a real life setting. In addition, the time spent on the carton and the pen-injector selection tasks indicated that the colour-blind patients were fully able to differentiate between the different cartons and prefilled pen-injectors. Based on the UT117 test results, Novo Nordisk concludes that the participants' red-green colour-blindness did not impact their abilities to differentiate between the different prefilled pen-injector products.

Safety

Since Tresiba® FlexTouch® has been approved and marketed worldwide; a cumulative number of 2,843,208 Tresiba® FlexTouch® have been released from Novo Nordisk as of Q2 2014. A review of the Novo Nordisk post-market surveillance data reveals that no adverse event reports related to mix-up due to colour-blindness have been received in connection with the use of Tresiba® FlexTouch®.

Residual risks

The residual risk has been evaluated as part of the Human Factors Engineering (HFE) process in accordance with ISO 14971:2007 (3). Taking into account the current state-of-the-art of the device and the root cause analysis of the single use error (see section 4.2), the risk analysis concludes that no additional risk mitigations to the user interface, labelling, or training are required. The residual risk is assessed to be acceptable and is outweighed by the benefits offered by the device.

In conclusion, the participants' red-green colour-blindness did not impact their abilities to differentiate between the prefilled pen-injectors and cartons. Tresiba® 100 units/mL FlexTouch® and Tresiba® 200 units/mL FlexTouch® are considered safe and effective for the intended users including patients with red-green colour-blindness, uses, and use environments. Therefore, the test results fulfilled Novo Nordisk's commitment to the EMA to ensure that individuals suffering from red-green colour-blindness can differentiate between different packages (i.e. cartons) and their perspective prefilled pen-injectors.

1 Intended users, uses, use environments, and training

1.1 Intended users

The intended users of the two Tresiba® FlexTouch® variants (100 units/mL and 200 units/mL) include patients with diabetes, caregivers and healthcare professionals (HCPs). The characteristics of the user groups are listed below:

- Adult patients (age 18-64) with T1DM or T2DM who perform their own injections
- Elderly patients (age 65+) with T1DM or T2DM who may have various impairments (e.g. limited vision, hearing, dexterity and cognitive ability), but are still able to perform their own injections (e.g. when using their own vision-aids)
- Caregivers who are not clinicians, but perform injections on a patient (e.g. spouses, relatives and friends)
- HCPs who prescribe/dispense prefilled pen-injector products and/or teach others how to perform injections, including:
    - Pharmacists who dispense prefilled pen-injectors
    - Physicians and physician's office staff (e.g. doctor's assistants and nurse practitioners), who prescribe prefilled pen-injectors to their patients and/or demonstrate during office visits how to use prefilled pen-injectors
    - Diabetes education nurses who help patients manage their diabetes, and may train patients in the use of prefilled pen-injectors, either in an office or at a home visit
    - In-patient nurses who perform injections on patients during hospitalisation

1.1.1 Focused user group

As per the request from the European Medicines Agency (EMA) to perform *"a study/a survey with the objective of investigating the impact of red-green colour blindness on the ability to discriminate between the packages and the prefilled pen devices of the two different strengths of Tresiba as well as bolus insulin products marketed in colour schemes relevant in red-green colour blindness.",* the focused usability test PDS290-UT117-2013 (UT117) was conducted. UT117 was designed in order to investigate if the focused user group of diabetic patients with red-green colour-blindness and treated with insulin can differentiate the two Tresiba® FlexTouch® variants (i.e. 100 units/mL and 200 units/mL) and NovoRapid® FlexPen® from each other. For the rationale for including the specific products in the test, please refer to section 3.1.

1.2 Critical differences in capabilities between multiple user populations

1.2.1 Physical and cognitive differences

The physical and cognitive characteristics of the intended users (including patients, caregivers, HCPs) are not expected to impact their ability to use the prefilled pen-injectors.

In UT117 the user group was focused on diabetic patients with red-green colour-blindness who might not be able to use colours to differentiate between the products in the same way as non-colour-blind patients. However, during product development, Novo Nordisk has implemented multiple differentiation parameters on both the prefilled pen-injectors and the cartons. As such, even if the users lack the ability to use one of the parameters (e.g. colour), the user will still be able to select the correct product based on other differentiation parameters (e.g. product name, text font, product design graphics on carton and graphics on prefilled pen-injector), and therefore colour-blind users can still clearly differentiate Novo Nordisk products from other products and between Novo Nordisk products. Overall, the Tresiba® 100 units/mL FlexTouch® and Tresiba® 200 units/mL FlexTouch® have been designed to be capable of accommodating all intended users.

1.3 Intended uses and operational context of device use

1.3.1 Intended use

Tresiba® 100 units/mL FlexTouch® and Tresiba® 200 units/mL FlexTouch® are intended for subcutaneous injection of insulin degludec (with the invented name Tresiba®) for patients with T1DM or T2DM.

Once the product is prescribed to the patients, the patients can either inject themselves or be injected by a caregiver after proper training in the correct use of the prefilled pen-injector.

1.3.2 User requirements

It is the prescribing physician who makes the judgement if a person is qualified to use the Tresiba® 100 units/mL FlexTouch® or Tresiba® 200 units/mL FlexTouch®. It is expected that the prescribing physician evaluates the individual's ability to perform an injection correctly according to the Instructions for Use (IFU), as well as taking the following requirements into consideration when making the judgement:

Education:

- The user must be able to read and understand "Westernised Arabic" numerals for dose setting

Language understanding:

- The user should be able to read the IFU in the local language, or alternatively understand and be able to demonstrate proper handling after an explanation of the IFU

Impairment:

- People who are blind or have severe visual problems and cannot read the dose counter should not use the PDS290 prefilled pen-injector. These users should be assisted by a person (caregiver) who has functional eyesight and is trained to use the PDS290 prefilled pen-injector

Knowledge (after training):

- The user must have basic knowledge of treatment with insulin
- The user must have basic understanding of hygienic aspects of injection treatment and injection techniques

Experience:

- The user must, in the opinion of their prescribing physician, have received sufficient training in order to correctly use the Tresiba® 100 units/mL FlexTouch® or Tresiba® 200 units/mL FlexTouch®

Notably, the levels of experience and training are expected to vary between users depending on various parameters including the type of user, former experience and level of formal training at the starting point of the therapy. As stated in the IFU, the user should not use the Tresiba® 100 units/mL FlexTouch® or Tresiba® 200 units/mL FlexTouch® without proper training.

1.3.3 Intended use environment

Where to use

- Primary use - for self-treatment, in a home environment
- Secondary use - for hospital/physician's office or dispensing at the pharmacy

Storage

- Due to the nature of the drug, an unused prefilled pen-injector must be stored in a refrigerator (2-8°C) until use or expiry. It must be kept away from the cooling elements in the refrigerator and must not freeze. The patient information leaflet for each insulin type specifies the exact shelf-life time allowed
- After the first use, the prefilled pen-injector should be stored according to the specific patient information leaflet for each insulin type

- In order to protect the drug from light, the cap of the prefilled pen-injector should be kept on at all times when the prefilled pen-injector is not in use

Environment

- The prefilled pen-injector can be used in a non-sterile environment
- The prefilled pen-injector is designed to operate under a wide temperature range. However, the prefilled pen-injector should not be used in environments that are not suitable for the specific insulin product as specified in the patient information leaflet/IFU
- The prefilled pen-injector is not intended for use in environments that could damage the drug (e.g. long exposure to direct sunlight or at elevated temperatures)

1.4 Training intended for users and provided to test participants

1.4.1 Training in normal use

The prefilled pen-injector products can be prescribed to the patient by a physician, based on a clinical assessment. According to the IFU, the patient should be trained in the use of the prefilled pen-injector; including training in identifying the specific drug that they are prescribed. It is the physician's responsibility to assess if the patient is sufficiently trained so that they are capable of following the instructions provided by the manufacturer and delivering the intended dose in a safe and effective way.

1.4.2 Introduction to products in the focused usability test

In UT117, all the participants were tested on differentiating the products without any handling of the prefilled pen-injector (i.e. without performing injections); therefore none of the participants received any formal training in the use of the prefilled pen-injector. Instead, they were given a short introduction to the drugs and prefilled pen-injectors by a Danish or German interpreter who has been trained and qualified by Novo Nordisk. The introduction included a brief description of each product’s name, strength and insulin type. The introduction reflects the expected clinical practice.

In real life, there would be some delay between the time when the user is introduced to a product and the time when they use the product in the home environment. Therefore, a suitable delay of minimum 30 minutes between introduction and test was ensured in the test.

To ensure effectiveness and consistency between participants, the Contract Research Organisation (CRO) staff member judged the participants’ competency to use the two Tresiba® FlexTouch® variants upon completion of the introduction. In case a participant was judged not to be sufficiently qualified for using the two Tresiba® FlexTouch® variants or ineligible for the test (e.g. have an

insufficient red-green colour vision deficiency), the reason for exclusion was documented in the CRO report (4).

2 Device user interface

2.1 Description of the device user interface

The PDS290 prefilled pen-injectors including the two Tresiba® FlexTouch® variants are based on the same user interface concept as the currently marketed prefilled pen-injector FlexPen® for insulin delivery and Victoza® pen for Glucagon-Like-Peptide-1 (GLP-1) analogue delivery, which is a pen-shaped injector with a prefilled cartridge. The intended dose is given by turning the dose selector to select the dose, pressing the dose button until the dose counter returns to "0", and keeping the needle under the skin for 6 seconds to ensure that the full dose is delivered.

In UT117, the user interacts with the design features that function as differentiation parameters for assisting the user, when differentiating the prefilled pen-injectors and cartons. A list of the differentiation parameters is shown below:

Prefilled pen-injector differentiation parameters

- Colour[1]
  - Pen colour
  - Product colour coding
  - Cartridge holder, dose button colour and label colour
- Visual (Text + form)
  - Product name
  - Product name placement on label
  - Graphic label design
  - Text font, size and contrast
  - Company name[2]
- Dimensions and mechanical appearance of the pen
  - Prefilled pen-injector geometry
  - Dose button displacement
  - Tactile elements
  - Dose guidance (colour, pointer, numbers, units)

[1] "Product colour coding" is limited as a differentiation parameter for colour-blind users.

[2] "Company name" is not considered as a differentiation parameter, since the products selected in the focused usability test UT117 only included Novo Nordisk products. Please refer to section 3.1 for the rationale for the selection of the products.

Carton differentiation parameters

- Text and font
  - Product name
  - Strength indication
  - Company name[2]
- Visual (Graphic design)
  - Colour coding[1]
  - Illustrations
- Dimensions and mechanical appearance of the pen
  - Functionality and size of box

2.2 Summary of the operational sequence of the user interface

When differentiating the prefilled pen-injector products, the following user steps/primary operation functions may be carried out:

- **Step 1:** Pick the correct carton/prefilled pen-injector
- **Step 2:** Remove the cap
- **Step 3:** Verify via label and cartridge holder that it is the correct prefilled pen-injector

Graphical depictions of FlexTouch® prefilled pen-injectors: Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® are shown in Figure 3-1.

[1] "Product colour coding" is limited as a differentiation parameter for colour-blind users.

[2] "Company name" is not considered as a differentiation parameter, since the products selected in the focused usability test UT117 only included Novo Nordisk products. Please refer to section 3.1 for the rationale for the selection of the products.

3 Focused usability test

3.1 Rationale for test type and products selected

As per the request by the EMA, described in section 1.1.1, the usability test UT117 only focused on differentiation tasks without any handling tasks. In order to select relevant products to be included in the focused usability test, Novo Nordisk has performed a dedicated differentiation analysis as described in the *Risk Management Analysis Input to the Focused Usability Test UT117* (RMA) (1). The differentiation analysis included the two Tresiba® FlexTouch® variants (100 units/mL and 200 units/mL), and a range of commonly used bolus insulin products available in prefilled pen-injectors on the market. The focus of the differentiation analysis was to investigate if any of these prefilled pen-injectors and cartons can pose a risk of mix-up for red-green colour-blind users.

Based on all the differentiation parameters listed in section 2.1, the products have been assessed and given a score to evaluate the similarities between different products seen by red-green colour-blind users in a simulated scenario. The inclusion criterion was that if the product reached a score of 3 or more on a scale from 0 to 10, the product was determined to be relevant and included in the usability test. With respect to the risk of mix-up for red-green colour-blind users, the differentiation analysis concluded that the most relevant prefilled pen-injectors to include in the test were two Tresiba® FlexTouch® variants (in green colour scheme) and NovoRapid® FlexPen® (in red/orange colour scheme) which is the most common bolus insulin in prefilled pen-injector on the market. Inclusion of other bolus insulins would not improve the possibility of detecting potential use errors.

The prefilled pen-injectors and cartons of the aforementioned three products are shown in Figure 3-1 and Figure 3-2, respectively.

Prior to the test, the test plan for the focused usability test UT117 was submitted to the EMA and endorsed by the EMA with respect to the detailed test setup and products selected (refer to EMA7182656/2014 Fax with CHMP adoption of PRAC conclusion received on 28th March 2014).

Figure 3-1 **From top to bottom: prefilled pen-injectors (without pen caps) for Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® (English neutral labelling)**

Figure 3-2 **From left to right: cartons for Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® (English neutral labelling)**

3.2 Number and type of test participants and rationale for how they represent the intended user populations

In order to fulfil the characteristics of the focused user group as described in section 1.1.1, a total of 22 red-green colour-blind individuals with either T1DM or T2DM who currently self-administer insulin daily using an insulin pen-injector or insulin pump, participated in the focused usability test UT117. The specific number of participants was chosen in order to achieve 20 participants who completed the test successfully (i.e. without committing any use errors, close calls or experiencing any operational difficulties[1]). A summary of the participants' demographic information is listed in Table 3-1. An overview of the insulin types being used by the participants is presented in Table 3-2. An alphanumeric code (i.e. [redacted]) was used as participant ID to refer to the individual participant.

Table 3-1 A summary of participants' demographics in the usability test UT117

User group	Number of participants	Age (range and mean)		Gender		Current insulin delivery device		
		Range	Mean	Male	Female	Prefilled pen-injector	Durable pen-injector	Insulin pump
Patients with diabetes	22	33-78	61	21	1	7	10	5

Table 3-2 Insulin types being used by participants included in the usability test UT117

Insulin Type	Product name	Number of participants who reported using the insulin product(s)
Bolus insulin	NovoRapid®	7
	Humalog®	4
	Liprolog®	2
	Insuman Rapid®	1
	Apidra®	1
	Actrapid®	1
Basal insulin	Levemir®	7

[1]Originally, the test plan (2) described that the usability test will be carried out until 20 participants have completed the test without committing any errors. However, during the course of the usability test, the requirement was tightened to 20 participants who completed the test without committing any use errors, encountering any close calls, or experiencing any operational difficulties (4).

Insulin Type	Product name	Number of participants who reported using the insulin product(s)
	Lantus®	3
	Insulatard®	2
	Berlinsulin®	2
	Protaphane®	1
Premix insulin	Huminsulin Profil III	1

3.3 Test goals and critical tasks

As agreed with the EMA (section 1.1.1), the objective of the focused usability test was to determine if this specific group of patients with red-green colour-blindness and on insulin treatment were able to differentiate between Tresiba® 100 units/mL FlexTouch® and Tresiba® 200 units/mL FlexTouch® and to differentiate the two Tresiba® FlexTouch® variants (both in the green colour scheme) from a bolus insulin (i.e. NovoRapid® FlexPen® in the red colour scheme). The test results provided data for subsequent analysis in the risk management process with the purpose of documenting whether the device can pose any risks of mix-up for this specific user group.

As analysed and described in the RMA (1), the critical tasks in the focused usability test included the critical steps that were related to potentially serious use errors with risk severity S4-S5 (as per definitions in section 3.6).

3.4 Use scenarios studied

The use scenario(s) studied in the focused usability test UT117 were based on the results of the risk analysis described in the RMA (1). All participants were required to perform 1 carton differentiation task and 1 prefilled pen-injector differentiation task with each of the three products: Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch®, and NovoRapid® FlexPen® (i.e. a total of 3 carton differentiation tasks and 3 pen-injector differentiation tasks per participant). All the participants were divided into two groups; either “Group A” or “Group B” performed a different set of the 6 differentiation tasks, presented in a random order. The time each participant used for completion of each differentiation task were recorded. For the detailed description of the tasks, please refer to the *Focused Usability Test of colour-blind individuals' ability to differentiate between Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch®, and NovoRapid® FlexPen® pen-injectors and cartons Test Plan* (2).

3.5 Technique for capturing unanticipated use errors

Unanticipated use errors can be captured during the test by the test personnel via their in-depth knowledge of the use of the device. All test sessions were video-recorded. If unanticipated use errors were observed, their root cause were analysed equivalent to all the anticipated use errors based on the subjective feedback from the participants during and post-test.

3.6 Categorisation and definition of use errors, close calls and operational difficulties

All use errors have been divided into the following 3 groups defined by the severity class of the hazards associated with each user step as shown below (1).

A use error is a case in which a participant performs a task in an incorrect manner that will not lead to the intended outcome:

- Use errors related to handling (S1 and S2) with no potential for harm or impact on the prescribed therapy
- Non-serious use error (S3) is a use error which potentially can be associated with a non-serious adverse event
- Potentially serious use error (S4 and S5) is a use error which potentially can be associated with a serious adverse event

For identifying the use errors, a list of potential use errors and use error criteria extracted from the Use Error Risk Analysis is demonstrated in Appendix B (1).

In addition to use errors, close calls and operational difficulties observed in the focused usability test UT117 were also reported as per definitions below:

A close call is a case in which a user almost commits a use error, but “catches” him- or herself in time to avoid making the use error.

An operational difficulty is a case in which a user appears to struggle to perform a task. Such a struggle might be indicated by multiple attempts to perform the task; anecdotal comments about the task’s difficulty; facial expressions and vocalisations suggesting frustration or confusion.

This report evaluates and assesses root causes for the use errors, close calls and operational difficulties (if any), and provides a discussion of the potential clinical consequences.

4 Test results and analysis

4.1 Task completion

In UT117, 20 participants successfully performed the carton and pen-injector differentiation tasks without committing any use errors, close calls or experiencing any operational difficulties. Therefore, the test results fulfilled Novo Nordisk's commitment to the EMA to ensure that individuals suffering from red-green colour-blindness can differentiate between different packages (i.e. cartons) and their respective prefilled pen-injectors such that the prefilled pen-injectors can be used safely and effectively.

4.2 Use errors

4.2.1 Selected incorrect pen-injector carton

1 ([redacted]) out of 22 participants selected an incorrect pen-injector carton from the refrigerator during the carton differentiation task. This use error occurred during [redacted] task. The participant chose the NovoRapid® FlexPen® carton arbitrarily rather than consciously choosing a product based on the task given. The use error was analysed being not related to the colour or design of the pen-injector carton.

Use error description

The participant retrieved the NovoRapid® FlexPen® carton from the refrigerator, rather than selecting the Tresiba® 200 units/mL FlexTouch® carton.

After reading the task instruction, the participant expressed confusion about the task's goal and asked how to calculate [redacted] dose based on the different dose strengths [redacted] learned about during the introduction session. The test administrator clarified that [redacted] only needed to perform the task written on the task card, at which point [redacted] reviewed the task instruction again. The participant then retrieved the NovoRapid® FlexPen® carton from the refrigerator, removed the IFU from the carton, and began reviewing the IFU. After nearly a minute, the test administrator asked the participant what information [redacted] was searching for; the participant responded [redacted] was looking for the number of units [redacted] needed to inject. The test administrator clarified that [redacted] did not need to inject any insulin during the task – only perform the task written on the task card. The participant said [redacted] had selected the correct product, but [redacted] needed to know what kind of needle to use. The test administrator clarified that [redacted] did not need to use any needles to perform the task. The test participant ultimately confirmed [redacted] had completed the task.

During the post-test interview, the participant reported that [redacted] did not fully understand the task's goal; [redacted] was unaware [redacted] needed to select a particular pen-injector carton. Rather, [redacted] thought [redacted] needed to select a pen-injector that was suitable for use (i.e. that was not damaged in any way). Moreover, the participant said [redacted] focused on the latter part of the task instruction (i.e. "… confirm that you have chosen the right product"), rather than the first sentence ("Retrieve a Tresiba® 200 units/mL FlexTouch® carton …"). [redacted] believed that the first sentence in a paragraph typically provides context rather than essential information. [redacted] reportedly chose the NovoRapid® FlexPen® pen-injector carton arbitrarily among the two options and then focused on ensuring the pen-injector's suitability in response to the instruction to "… confirm that you have chosen the right product."

Root cause analysis

Participant [redacted]: the participant's use error has been attributed to the following root causes:

- Test artefact – [redacted] carton selection task. The participant's use error was primarily attributed to test artefact associated with this task being the participant's [redacted] carton selection task. The participant did not seem to understand that the task's goal was to select a particular product among two products present in the refrigerator. However, during the remaining two carton selection tasks and the three pen-injector selection tasks, [redacted] demonstrated that [redacted] understood the goal of retrieving a particular carton/pen-injector, and thus completed the remaining tasks successfully.
- Habit – Prior use of NovoRapid®. The participant's use error was partly attributed to habit. Although the participant reportedly chose the NovoRapid® FlexPen® carton arbitrarily between the two carton options available in the refrigerator, the NovoRapid® FlexPen® carton was underneath the Tresiba® 200 units/mL FlexTouch® carton as shown in Figure 4-1. [redacted] intentionally selected the bottom carton from the two-carton stack. It was concluded that the participant selected this carton because [redacted] used NovoRapid® FlexPen® pen-injectors for about [redacted] years before starting insulin pump therapy [redacted] years ago. As such, it seems as though [redacted] selected the more familiar product.
- Test artefact – nervousness. The participant's use error was also partly attributed to the nervousness that [redacted] seemed to experience when participating in the test session. The participant seemed nervous throughout the introduction and test sessions to the extent that [redacted] struggled to focus on the task at hand and seemed considerably confused.

Figure 4-1 A recreation of the Tresiba® 200 units/mL FlexTouch® carton and the NovoRapid® FlexPen® carton positioned in the refrigerator as they were during the task.

Conclusion on UT117 use errors

Based on the root cause analysis, Novo Nordisk concludes that the only use error occurred during the focused usability test was attributed to test artefact – [redacted] selection task, nervousness and [redacted] habit – using NovoRapid® FlexPen® for [redacted] years. Noticeably, this participant has successfully completed all remaining tasks. This use error was not related to the design (including colour) of the prefilled pen-injector or carton and would be unlikely to occur in a real-life setting.

The test results confirmed that the participants' red-green colour-blindness did not impact their abilities to differentiate between different prefilled pen-injectors and cartons.

4.3 Close calls & operational difficulties

1 out of 22 participants experienced 1 close call when performing 1 of the 6 differentiation tasks. This close call occurred during [redacted] task. Eventually, the participant successfully selected the correct pen-injector carton.

Based on the root cause analysis (4), Novo Nordisk concludes that the only close call observed in UT117 was not attributed to the design (including colour) of the prefilled pen-injector or the carton (see Appendix A for details).

None of the participants experienced any operational difficulties when performing the 6 differentiation tasks.

4.4 Task times

The time each participant used for completion of each differentiation task was recorded. Tasks were presented in a random order to control for order effects (i.e. participants were divided into Group A or B, see section 3.4). The average time spent for each differentiation task performed by each group (i.e. the sum of the task time per group/participant number per group, where there were 11 participants per group) was shown in Figure 4-2. The six blue grey vertical bars reflect the average task time of the carton differentiation tasks. The six green vertical bars reflect the average task time of the pen-injector differentiation tasks. The task labels reflect both the selector product and distractor product from which participants selected. For example, the label "C1 (100/NR)" refers to the carton differentiation task in which participants were instructed to retrieve a Tresiba® 100 units/mL FlexTouch® from the refrigerator, and the NovoRapid® FlexPen® was the distractor. The bars on each vertical bar indicate the minimum and maximum task times (i.e. the range).

Overall, the average time for each carton differentiation task ranged from 25 to 41 seconds, while the average time for each pen-injector differentiation task ranged from 11-18 seconds. The time for the carton selection tasks being relatively longer than that for the pen-injector selection tasks was due to more actions involved in a carton selection task (e.g. stand up, approach the refrigerator and open the door of the refrigerator) compared to a pen-injector selection task (i.e. take out a pen-injector from a bin). There is no significant difference in the task time between the two groups, and thus the tasks were not affected by the order. Notably, the longest maximum task time at Task C6 is due to the occurrence of the use error (see section 4.2).

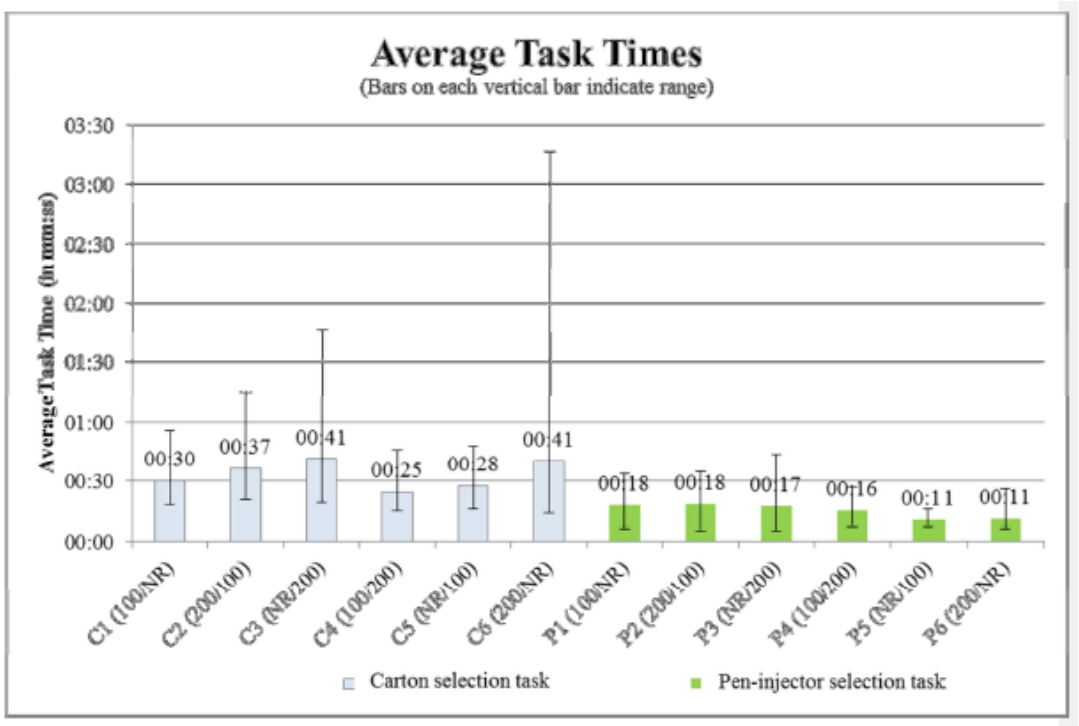

Figure 4-2 Average task time for carton (blue grey) and pen-injector (green) differentiation tasks. Please note that C1, C2, C3, P1, P2 and P3 were the tasks for Group A; C4, C5, C6, P4, P5 and P6 were the tasks for Group B to control for order effect. The bars on each vertical bar indicate the minimum and maximum task times (i.e. the range).

4.5 Subjective post-test ratings

After participants performed all of the hands-on tasks, the test administrator asked each participant to rate, on a 1 to 7 scale (1 = difficult, 7 = easy), the following two pen-injector attributes:

1) The ease of selecting the cartons from the refrigerator
2) The ease of selecting the pen-injectors from the container

Overall, participants perceived the ability to 1) select the cartons from the refrigerator and 2) select the pen-injectors from the container as easy, assigning an average, overall ease-of-selection rating of 6.7 and 6.5, respectively (scale: 1 = difficult, 7 = easy). Although this finding is not presented as evidence of use-safety, it is notable that participants perceived it as easy to differentiate the different packaging and their associated pen-injectors.

5 Conclusion

Since Tresiba® FlexTouch® has been approved and marketed worldwide; a cumulative number of 2,843,208 Tresiba® FlexTouch® (i.e. 100 units/mL and 200 units/mL) have been released from Novo Nordisk as of Q2 2014. A review of the Novo Nordisk post-market surveillance reveals that no adverse event reports related to mix-up due to colour-blindness have been received in connection with the use of Tresiba® FlexTouch®.

The UT117 test results demonstrated that 20 participants successfully differentiated between different packages (i.e. cartons) and their respective prefilled pen-injectors without committing any use errors, close calls or experiencing any operational difficulties. Only 2 participants (out of the 22 participants) committed a total of 1 use error and 1 close call. Based on the root cause analyses, these two incidents were primarily attributed to test artefact (i.e. the participants' [redacted] carton selection task) rather than the design (incl. colour) of the carton or the prefilled pen-injector. Therefore, they would be unlikely to occur in a real life setting. In addition, the time spent on the carton and the pen-injector selection tasks indicated that the colour-blind patients were fully able to differentiate between the different cartons and prefilled pen-injectors, indicating that the colour-blindness did not affect their abilities to differentiate between the different prefilled pen-injector products.

The residual risk has been evaluated as part of the HFE process in accordance with ISO 14971:2007 (3). Taking into account the current state-of-the-art and a root cause analysis of the single use error, the risk analysis concludes that no additional risk mitigations to the user interface, labelling, or training is required. The residual risk is assessed to be acceptable and is outweighed by the benefits offered by the device.

In conclusion, the participants' red-green colour-blindness did not impact their abilities to differentiate between the different prefilled pen-injectors and cartons. Tresiba® 100 units/mL FlexTouch® and Tresiba® 200 units/mL FlexTouch® are considered safe and effective for the intended users including patients with red-green colour-blindness, uses, and use environments. Therefore, the test results fulfilled Novo Nordisk's commitment to the EMA to ensure that individuals suffering from red-green colour-blindness can differentiate between different packages (i.e. cartons) and their respective prefilled pen-injectors.

6 References

1. Risk Management Analysis Input to Focused Usability Test (UT117): Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch® and NovoRapid® FlexPen® prefilled pen-injector V. 2.0. novoDOCS ID 001497415
2. Focused Usability Test of colour-blind individuals' ability to differentiate between Tresiba® 100 units/mL FlexTouch®, Tresiba® 200 units/mL FlexTouch®, and NovoRapid® FlexPen® pen-injectors and cartons Test Plan V. 2.0. novoDOCS ID 001502175
3. Medical devices–Application of risk management to medical devices ISO 14971:2007
4. Post-approval Usability Test CRO Report PDS290-UT117-2013 V. 1.0. novoDOCS ID 001881208

Appendix A Close calls

Initially selected incorrect pen-injector carton

1 ([redacted]) out of 22 participants initially selected an incorrect pen-injector carton from the refrigerator, but after verifying the product name, [redacted] successfully selected the correct pen-injector carton. This close call occurred during [redacted] task.

Close call description

The participant initially retrieved the Tresiba® 100 units/mL FlexTouch® carton from the refrigerator, rather than retrieving the Tresiba® 200 units/mL FlexTouch® carton. The participant then removed a pen-injector from the carton and removed the pen-injector's cap. After the participant reviewed the task instruction and inspected the pen-injector, [redacted] realized [redacted] retrieved the incorrect carton. The participant then returned the Tresiba® 100 units/mL FlexTouch® carton to the refrigerator, retrieved the Tresiba® 200 units/mL FlexTouch® carton, and said the task was complete.

During the post-test interview, the participant reported that [redacted] initially remembered to retrieve a Tresiba® 200 units/mL FlexTouch® pen-injector but retrieved the Tresiba® 100 units/mL FlexTouch® carton because it was on top of the two-carton stack. However, at one point the participant also indicated that [redacted] did not initially remember that [redacted] goal was specifically to retrieve the Tresiba® 200 units/mL FlexTouch® carton; [redacted] seemed uncertain of the product to select. Upon removing a Tresiba® 100 units/mL FlexTouch® pen-injector from the carton, [redacted] noticed the "100" on the pen-injector's label and realized [redacted] had retrieved the incorrect pen-injector carton.

Based on the root cause analysis (4), Novo Nordisk concludes that the close call was primarily attributed to test artefact (i.e. the participant's [redacted] selection task), rather than the design (including colour) of the prefilled pen-injector carton, and therefore no additional risk mitigations to the user interface, labelling, or training is required.

Appendix B List of potential use errors and use error criteria extracted from the Use Error Risk Analysis (1)

Step to be tested	Risk identifier	HAZOP ID	Non-serious use error (S3) criterion	Potentially serious use error (S4-S5) criterion	Comments
Step 1 Pick the correct carton box / prefilled pen-injector	See "Step 3"	See "Step 3"	See "Step 3"	See "Step 3"	See "Step 3"
Step 3 Verification via label and cartridge holder that it is the correct carton box / prefilled pen-injector	Picks Tresiba® 100 units/mL FlexTouch® Basal insulin – should have been Tresiba® 200 units/mL FlexTouch® Basal insulin	1.B.20 1.B.38	N/A	N/A	Only a use error if participant has retrieved the wrong prefilled pen-injector/carton and confirmed that this (wrong product) is the correct product. Close call if initial selection of prefilled pen-injector/carton box is wrong, but corrected before confirming that the correct product has been chosen. Please note: If the participant omits step 3 (Verification via label and cartridge holder that it is the correct carton box / prefilled pen-injector) but has successfully completed step 1 (Pick the correct carton box / prefilled pen-injector), this shall not be registered as a use error. For a mix-up between Tresiba® 100 units/mL and
	Picks NovoRapid® FlexPen® Bolus insulin – should have been Tresiba® 200 units/mL FlexTouch® Basal insulin	1.B.7 1.B.8 1.B.23 1.B.41	N/A	(see comments column)	
	Picks Tresiba® 200 units/mL FlexTouch® Basal insulin – should have been Tresiba® 100 units/mL FlexTouch® Basal insulin	1.B.15 1.B.30	N/A	N/A	

Step to be tested	Risk identifier	HAZOP ID	Non-serious use error (S3) criterion	Potentially serious use error (S4-S5) criterion	Comments
	Picks NovoRapid® FlexPen® Bolus insulin – should have been Tresiba® 100 units/mL FlexTouch® Basal insulin	1.B.1 1.B.2 1.B.18 1.B.33 1.B.36	N/A	(see comments column)	Tresiba® 200 units/mL it is classified to be without any medical consequence as the dose counter shows the amount of insulin units which will be injected If a user selects a NovoRapid® FlexPen® instead of a Tresiba® 100 units/mL FlexTouch® it is classified as a potential serious use error. If a user selects a NovoRapid® FlexPen® instead of a Tresiba® 200 units/mL FlexTouch® it is classified as a potential serious use error. If a user selects a Tresiba® 100 units/mL FlexTouch® instead of a NovoRapid® FlexPen® it is classified as a non-serious use error. If a user selects a Tresiba® 200 units/mL FlexTouch® instead of a NovoRapid® FlexPen® it is classified as a non-serious use error.
	Picks Tresiba® 100 units/mL FlexTouch® Basal insulin – should have been NovoRapid® FlexPen® Bolus insulin	1.A.11 1.A.17	(see comments column)	N/A	
	Picks Tresiba® 200 units/mL FlexTouch® Basal insulin – should have been NovoRapid® FlexPen® Bolus insulin	1.A.11 1.A.17	(see comments column)	N/A	

Appendix C Batch number of the prefilled pen-injectors, cartons, IFUs and labels used in UT117

Test site	Product	Label	IFU	Carton	Pen-injector
Germany	Tresiba® 100 Enheiten/ml FlexTouch®	8-9560-81-201-1	8-9560-81-001-1	8-9560-81-301-1	CV40018
	Tresiba® 200 Enheiten/ml FlexTouch®	8-9562-81-201-1	8-9562-81-001-1	8-9562-81-301-1	CV40171
	NovoRapid® FlexPen®	8-9670-81-202-5	8-9670-81-003-9	8-9670-81-311-1	DP50711
Denmark	Tresiba® 100 Enheder/ml FlexTouch®	8-9560-42-202-2	8-9560-42-001-4 8-9560-42-010-1	8-9560-42-302-1	CV40018
	Tresiba® 200 Enheder/ml FlexTouch®	8-9562-42-202-2	8-9562-42-001-4 8-9562-42-010-1	8-9562-42-302-1	CV40171
	NovoRapid® FlexPen®	8-9670-42-202-2	8-9670-42-002-3	8-9670-42-302-1	DP50711