



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: June 17, 2013

FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID

THROUGH: Ron Kaye, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID

CC: Molly Story, Human Factors and Accessible Medical Technology Specialist, DAGID

TO: Leigh Pratch, Regulatory Project Manager, /CBER/OBRR/DBA/RPMB
The response was found acceptable.

SUBJECT: **BLA STN 125466/0**
Applicant: Novo Nordisk Inc.
Drug: Antihemophilic Factor (Recombinant), Plasma/Albumin Free (NovoEight)
Device: Turoctocog alfa ---(b)(4)--- Delivery System
Intended Use: treatment of bleeding episodes
CDRH CTS Tracking: ICC1300210; CON1310207

QuynhNhu Nguyen, Combination Products Human Factors Specialist

Molly Story, Human Factors and Accessible Medical Technology Specialist
for Ron Kaye, Human Factors and Device Use-Safety Team Leader

CDRH Human Factors Review

Overview and Recommendations

The Office of Blood Research and Review, Center for Biologics Research and Evaluation, requested a Human Factors consultative review of a BLA submission (BLA # 125466, Sequence 0000, and dated 10/15/2012). The submission contained a Human Factors validation test protocol and report on the Turoctocog alfa ---(b)(4)--- Delivery System. Turoctocog alfa is a clotting factor VIII product that is used for prevention and treatment of bleedings. With the currently marketed NovoSeven[®] RT the vial adapter is supplied separately and is not packaged with the drug. The main difference in handling of the --(b)(4)-- and the existing NovoSeven[®] RT is that the handling steps for extraction of the diluent from a vial to the syringe are eliminated through the use of the syringe containing diluent in the --(b)(4)--.

Review of the Human Factors (HF) validation study report showed that there are some issues that need to be addressed with respect to potential dosing errors and contamination, as well as, issues that needed to be clarified with respect to the potential clinical consequences in order to determine whether additional design/Instructions for Use (IFU) modifications and risk mitigations are necessary. Four deficiencies were identified and transmitted to Novo Nordisk. Subsequently, Novo Nordisk provided a response to these deficiencies on April 4, 2013. Additional modifications were made to the IFU to address the concerns raised in the deficiencies. The reviewer does not believe that the IFU modifications required retesting. **As a result, the response was found acceptable. There are no further questions on the human factors component.**

CDRH Human Factors Review

Combination Product Device Information

Submission Number: BLA STN 125466/0

Applicant: Novo Nordisk, Inc.

Drug Constituent: antihemophilic factor (recombinant) plasma/albumin free (NovoEight)

Device Constituent: Turoctocog alfa --(b)(4)-- delivery system

Intended Use: treatment of bleeding

Review Materials:

Container Closure System, Human Factors Validation Report, Conclusive Report

------(b)(4)-----

CDRH Human Factors Involvement History

Date	Involvements
11/26/2012	CDRH HF was requested to review the "Human Factors" study submitted as part of the BLA. This review identified four deficiencies that were transmitted to Novo Nordisk.
5/16/2013	CDRH HF was requested to review Novo Nordisk's response to the deficiencies. This review found that the response was acceptable.

Summary of Review Materials and Reviewer Discussion

Previous review of this submission identified four deficiencies associated with the study results for the HF validation study report. The following provides the reviewer's evaluation of Novo Nordisk's response to those deficiencies.

Deficiency 1: You reported one count of a haemophilia HCP drawing the full amount of mixed drug instead of the calculated dose, which could lead to dosing errors (underdosing/overdosing). You also reported one count of an ER nurse while preparing a 3mL calculated dose, they first emptied 1 ml of solvent from 4ml prefilled syringe prior to reconstitution, which we were not clear of potential clinical consequence. Both of these counts were observed while the participants were performing the calculated dose scenario. Review of your Instructions for Use revealed that the critical task of drawing draw out a specified volume of the reconstituted drug into the syringe (less than the full contents of the reconstituted solution) does not appear to adequately draw the reader's attention to that task. Please revise your Instructions for Use to address this concern.

Summary and Evaluation of Novo Nordisk's Response to Deficiency 1: Novo Nordisk reported that both reported cases, the HCP and the ER nurses, were considered to be close call. The HCP stated that she was nervous but she immediately realized her mistake after drawing up the medication. If she did not realize her mistake and injected 4mL instead of the intended volume, it would have resulted in an injection of 133% of the intended dose. She successfully completed all tasks in the subsequent scenario. Similarly, the ER nurse realized her mistake, indicated that she would check with her colleague, and corrected the amount to be injected. Novo Nordisk further reported that there were three cases of overdosing reported in the clinical study; however, no adverse events or medical consequences were seen. In addition, as recommended by FDA, Novo Nordisk has revised the IFU to adequately draw the reader's attention to the task of drawing out a specific volume of the reconstituted drug into the syringe. This response was found acceptable.

Deficiency 2: You reported several counts of performance that could lead to contamination (two counts of an adult participant touching the top of the syringe while removing air bubbles; and four counts of 1 child/adolescent, 2 haemophilia HCPs, and 1 ER nurse of not cleaning the rubber stopper with an alcohol swab). Six counts of ER nurses removing the vial adapter with fingers from protective cap, but did not touch fluid path. We suspect that these actions might also lead to contamination. Review of your Instructions for Use revealed that it does not communicate the negative consequence of contaminating the product while assembling the components, and the importance of cleaning the rubber stopper, not touching the syringe while removing air bubbles, and not using fingers to remove the vial adapter. Please revise your Instructions for Use to address this concern.

Summary and Evaluation of Novo Nordisk's Response to Deficiency 2: As recommended by FDA, Novo Nordisk has revised the IFU to communicate the negative consequence of contamination, and emphasize the importance of reducing contamination risk. This response was found acceptable.

Deficiency 3: You reported four counts of ER nurses did not remove the protective cap correctly leading to removal and then remounting of the adapter. The success criteria specified that the participant would not be able to continue if this task fails. Unclear if participants did not remove the protective cap correctly would be considered as task failures. Please provide a clarification.

Summary and Evaluation of Novo Nordisk's Response to Deficiency 3: Novo Nordisk reported that there were two nurses (4 instances) who did not remove the protective cap correctly but were able to continue with successful preparation of the kit without touching the fluid path of the vial adapter, and therefore did not lead to task failures. This response was found acceptable.

Deficiency 4: You reported multiple counts of assembling the components not according the sequence specified in the Instructions for Use. However, you did not discuss whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user. Please note that if any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences. Please provide a clarification.

Summary and Evaluation of Novo Nordisk's Response to Deficiency 4: Novo Nordisk stated that while participants utilized an alternative sequence than described in the IFU, there were no negative consequences to the patient or the user. This response was found acceptable.

Appendix 1: Previous CDRH Human Factors Review

Review Summary

Novo Nordisk has performed human factors engineering (HFE) to validate the --(b)(4)-- delivery system, which is illustrated in the figure 1.

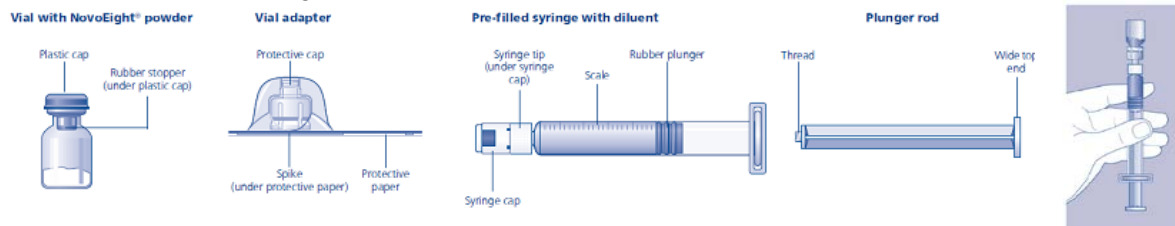


Figure 1: Graphical Depiction of the --(b)(4)-- User Interface Components (left) and after assembly (right)

The summative usability test (UT84) included 76 participants from 5 intended user groups participated in this test. These include children (from age 10), adolescents and adults with haemophilia A, caregivers and HCPs (haemophilia HCPs and ER nurses). A minimum of 15 participants from each group were included in this test. After receiving representative training and a 30 minute training decay period, participants were asked to select a specified turoctocog alfa --(b)(4)-- from a refrigerator (differentiation scenario), assemble --(b)(4)-- and reconstitute the specified turoctocog alfa --(b)(4)-- (handling scenario). For the handling each participant performed 1 full and 1 calculated dose scenario. The required dose is calculated depending on patient's weight. The turoctocog alfa product is available in six doses (250, 500, 1000, 1500, 2000 and 3000 IU). In most cases this allows using one or more full vial(s) to prepare and administer the dose needed. In some cases, such as with very young patients, a calculated dose less than the full content of a vial may need to be prepared and administered. For preparation of the calculated dose, the technique described in the Instruction for Use is to withdraw the needed volume of the mixed solution in the syringe using the syringe scale to measure.

The study included three use scenarios:

Differentiation scenario:

- Select the specified product from the refrigerator.
- Find and indicate the product type and expiry date.

Full dose scenario:

The participants were asked to prepare a full dose of reconstituted solution (performed immediately after completing the Differentiation Scenario).

The operation sequence for the proposed product is:

1. Remove the plastic cap from the vial
2. Clean the rubber stopper on the vial with an alcohol swab and allow it to dry before use
3. Remove the protective paper from the protective cap
4. Put the vial adapter onto the vial
5. Remove the protective cap from the vial adapter
6. Connect the plunger rod to the syringe
7. Remove the Tip-Cap from the syringe
8. Screw the syringe onto the vial adapter
9. Inject diluent into vial
10. Swirl the solution to dissolve all powder

11. Draw out the mixed solution into the syringe
12. Push out air bubbles from syringe
13. Unscrew syringe from vial adapter

Calculated Dose Scenario:

The participants were asked to prepare a calculated dose of the reconstituted solution (performed immediately after completing the Differentiation Scenario). For this scenario, participants were asked to repeat all of the steps associated with assembling -(b)(4)- and reconstituting the selected product as listed in the full dose scenario above. However, in this scenario, the participants were required to draw out a specified volume of the reconstituted drug into the syringe (less than the full contents of the reconstituted solution).

The results of the study are summarized as follows:

- One count of a haemophilia HCP drawing the full amount of mixed drug instead of the calculated dose, which could lead to dosing errors (underdosing/overdosing)
- One count of an ER nurse while preparing a 3mL calculated dose, they first emptied 1 ml of solvent from 4ml prefilled syringe prior to reconstitution. Unclear potential clinical consequence.
- Two counts of an adult participant touching the top of the syringe while removing air bubbles, which could lead to contamination.
- Four counts of 1 child/adolescent, 2 haemophilia HCPs, and 1 ER nurse of not cleaning the rubber stopper with an alcohol swab, which could lead to contamination.
- Four counts of ER nurses did not remove the protective cap correctly leading to removal and then remounting of the adapter. The success criteria specified that the participant would not be able to continue if this task fails. Unclear if participant did not remove the protective cap correctly would be considered as task failures.
- Six counts of ER nurses removing the vial adapter with fingers from protective cap, but did not touch fluid path. Unclear potential clinical consequences but have the lowest task priority.
- Multiple counts of assembling the components not according the sequence specified in the Instructions for Use.

While Novo Nordisk has reported that there were one “use error” (which could result in dosing error and patient harm), and multiple “deviations” (which did not result in patient harm), the test results demonstrate that there are some issues that need to be addressed with respect to potential dosing errors and contamination as well as issues that needed to be clarified with respect to the potential clinical consequences in order to determine whether additional design/IFU modifications and risk mitigations are necessary.

Review of the Human Factors validation study report showed that there are some issues that need to be addressed with respect to potential dosing errors and contamination, as well as, issues that needed to be clarified with respect to the potential clinical consequences in order to determine whether additional design/IFU modifications and risk mitigations are necessary.