# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209988Orig1s000

# OTHER REVIEW(S)

**Department of Health and Human Services**
**Public Health Service**
**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Office of Medical Policy**

# PATIENT LABELING REVIEW

| | |
|---|---|
| Date: | September 21, 2022 |
| To: | Brian Proctor<br>Regulatory Project Manager<br>**Division of Cardiology and Nephrology (DCN)** |
| Through: | LaShawn Griffiths, MSHS-PH, BSN, RN<br>Associate Director for Patient Labeling<br>**Division of Medical Policy Programs (DMPP)** |
| From: | Shawna Hutchins, MPH, BSN, RN<br>Senior Patient Labeling Reviewer<br>**Division of Medical Policy Programs (DMPP)**<br><br>Charuni Shah, PharmD<br>Regulatory Review Officer<br>**Office of Prescription Drug Promotion (OPDP)** |
| Subject: | Review of Patient Labeling: Instructions for Use (IFU) |
| Drug Name (established name): | FUROSCIX (furosemide injection) |
| Dosage Form and Route: | injection, for subcutaneous use |
| Application Type/Number: | NDA 209988 |
| Applicant: | scPharmaceuticals Inc. |

# 1 INTRODUCTION

On April 8, 2022, scPharmaceuticals Inc., re-submitted for the Agency's review an original New Drug Application (NDA) for FUROSCIX (furosemide injection) injection, for subcutaneous use. The proposed indication of FUROSCIX (furosemide injection) is for use for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure who display reduced responsiveness to oral diuretics and do not require hospitalization. This NDA was originally submitted on August 18, 2017, but received a Complete Response (CR) letter, issued by the Agency on December 3, 2020.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on July 25, 2022 for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for FUROSCIX (furosemide injection) injection, for subcutaneous use. DCN had originally requested that DMPP and OPDP also review the Applicant's submitted Patient Package Insert (PPI), however, on September 15, 2022, DCN informed DMPP-OPDP that a review of the PPI was no longer requested.

# 2 MATERIAL REVIEWED

- Draft FUROSCIX (furosemide injection) IFU received on April 8, 2022 and received by DMPP and OPDP on September 15, 2022.
- Draft FUROSCIX (furosemide injection) Prescribing Information (PI) received on April 8, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 15, 2022.
- DMPP FUROSCIX (furosemide injection) IND 118919 IFU review dated July 31, 2019.

# 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6$^{th}$ to 8$^{th}$ grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8$^{th}$ grade reading level. In our review of the IFU the target reading level is at or below an 8$^{th}$ grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

## 4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

## 5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** September 21, 2022

**To:** Maryann Gordon, M.D., Medical Officer
Division of Cardiology and Nephrology (DCN)

Brian Proctor, Regulatory Project Manager (DCN)

**From:** Charuni Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Melinda McLawhorn, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Furoscix® (furosemide injection), for subcutaneous use

**NDA:** 209988

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In response to DCN's consult request dated July 25, 2022, OPDP has reviewed the proposed product labeling (PI) and Instructions for Use (IFU) for Furoscix® (furosemide injection), for subcutaneous use. This supplement provides for a new indication, diuretic indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure

**PI**: OPDP's comments on the proposed labeling are based on the draft version received by electronic mail from DCN on September 12, 2022, and are provided below. OPDP has no comments at this time.

**IFU:** A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed and comments on the proposed IFU will be sent under separate cover at a later time.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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CHARUNI P SHAH
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | September 7, 2022 |
| Requesting Office or Division: | Division of Cardiology and Nephrology (DCN) |
| Application Type and Number: | NDA 209988 |
| Product Name, Dosage Form, and Strength: | Furoscix (furosemide) Injection, 80 mg/10 mL (8 mg/mL) |
| Product Type: | Combination Product (Drug-Device) |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | scPharmaceuticals Inc. |
| FDA Received Date: | April 8, 2022 and May 11, 2022 |
| OSE RCM #: | 2017-1762-2 |
| DMEPA 2 Team Leader: | Hina Mehta, PharmD |

# 1 REASON FOR REVIEW

As part of the approval process for Furoscix (furosemide) Injection NDA 209988, we reviewed the proposed Furoscix prescribing information, (b) (4) instructions for use, carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

## 1.1 BACKGROUND INFORMATION

Furoscix (furosemide) is a proposed combination product with an 80 mg/10 mL (8 mg/mL) single-dose pre-filled cartridge co-packaged with a single-use on-body infusor. It is proposed for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure who display reduced responsiveness to oral diuretics and do not require hospitalization.

The NDA was originally submitted on May 15, 2018 and received a Complete Response (CR) due to device, drug product quality, clinical, and Human Factor (HF) deficiencies. We completed a Human Factor validation study, labels and labeling review as part of the submission.[a] On June 30, 2020 a class 2 resubmission was submitted to address the deficiencies including a HF validation study report. We completed a Human Factor study report and labels and labeling review as part of the review of the resubmission.[b] As the device was modified subsequent to the HF study, our recommendations included a request to update the use-related risk analysis and submit results of another HF study if needed. The application received another CR on December 03, 2020 for device related issues. Subsequently, a Type A meeting was held on January 28, 2021 to discuss the device related issues in the CR letter. At the meeting it was determined along with Center for Device and Radiological Health (CDRH) that submission of additional human factors data would not be necessary.[c]

# 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |

[a] Thomas, S. Human Factor Validation Study, Label and Labeling Review for Furoscix (NDA 209988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 15. RCM No.: 2017-1762 and 2017-1764.

[b] Little, C. Human Factor Study Report and Labels and Labeling Review for Furoscix (NDA 209988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 16. RCM No.: 2017-1762-1 and 2017-1764-1.

[c] Proctor, B. Preliminary Meeting Minutes (NDA 209988) Silver Spring (MD): FDA, CDER, OSHEN, DCN (US); 2021 FEB 19. Available from: https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805d3ed1&showAsPdf=true

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container label, carton labeling, prescribing information, (b) (4) and instruction for use for Furoscix (furosemide) to identify deficiencies that may lead to medication errors and other areas of improvement. We note the instructions for use were updated based on the recommendations from the last review cycle.

We identified areas of the proposed labels and labeling that could be revised to improve clarity and readability of important information. For the Division, we note lack of clarity in the dosage form information and instructions on the use of the device in the Prescribing Information. For the Applicant, we recommend revisions to the contents statement, strength statement to remove the extra spacing, aligning the storage statement with the prescribing information, and to the language for the recommended dosage statement.

These factors may confuse the user and inadvertently lead to medication errors. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed (b) (4) is acceptable from a medication error perspective. We identified areas in the proposed container labels, carton labeling, PI, and instructions for use that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide recommendations in Section 4.1 for the Division and Section 4.2 for scPharmaceuticals Inc. to address our concerns.

### 4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration Section

a. We recommend revising the [redacted] bullet to reference the "Full Prescribing Information" [redacted] for clarity.

2. Dosage Forms and Strengths Section

a. We recommend including the dosage form of the product and including information to state the drug is co-packaged with the device. Revise to read "Injection: 80 mg/10 mL (8 mg/mL) in a single-dose prefilled cartridge co-packaged with a single-use on-body infusor. (3)".

B. Prescribing Information

1. Dosage and Administration Section

a. We recommend including some high-level instructions on how to use the device in Section 2.2 Important Administration Instructions. We recommend including the following:

"Load the prefilled cartridge of FUROSCIX into the on-body infusor and close the cartridge holder.

Peel away the adhesive liner on the on-body infusor and apply to the clean, dry area of the abdomen between the top of the beltline and the bottom of the ribcage that is not tender, bruised, red or indurated. The distance from the top of the beltline to the bottom of the ribcage should be at least 2 ½ inches.

Start the injection by firmly pressing and releasing the blue start button.

Do not remove until the injection is complete (signaled by the solid green status light, beeping sound, and the white plunger rod filling the cartridge window.".

2. Dosage Forms and Strengths

a. We recommend including the dosage form and a description of the drug product. Revise to read "Injection: 80 mg per 10 mL as a clear to slightly yellow solution in a single-dose prefilled cartridge for use only with supplied single-use on-body infusor.".

3. How Supplied/Storage and Handling Section

a. We recommend including information to state the drug is co-packaged with the device. Revise to read "80 mg/10 mL carton containing prefilled cartridge co-packaged with one on-body infusor".

C. Instructions for Use

1. We recommend revising the title of the instructions for use for clarity as follows:

Instructions for Use

On-Body Infusor for

FUROSCIX (fue roe' six)

(furosemide injection) for subcutaneous use

Single-Use, On-Body Infusor and 80 mg/10 mL (8 mg/mL) Prefilled Cartridge

2. We recommend revising the storage information to remove the dash and align the information with that in the Prescribing Information. Revise to read "Store at 68° to 77°F (20° to 25°C). Do not refrigerate or freeze.".

4.2 RECOMMENDATIONS FOR SCPHARMACEUTICALS INC.

We recommend the following be implemented prior to approval of this NDA:

A. Primary Carton Labeling Trade and Physician Sample

1. As currently presented the principal display panel does not contain the established name and dosage form after the proprietary name. We recommend including the established name and dosage form. In addition, we recommend removing the (b) (4) .
2. As currently presented for the strength statement there is an extra space in the parenthesis that is not needed. Revise "80 mg/10 mL (8 mg/ mL)" to "80 mg/10 mL (8 mg/mL)".
3. We recommend revising the carton contains statement for clarity, consistency with the PI, and to remove unnecessary information. We recommend revising to "1 X 10 mL prefilled cartridge

   1 X On-Body Infusor

   2 X Alcohol Prep Pads

   1 X Instructions for Use"
4. We recommend removing " (b) (4) on all the panels of the carton. As currently displayed, it may be misinterpreted as part of the proprietary name.
5. Revise the statement (b) (4) on the side panel 3 to "Recommended dosage: See Prescribing Information.".
6. We recommend including the statement to include the ingredients. Please include "Each single-use on-body injector with prefilled cartridge delivers a 10 mL solution containing: 80 mg furosemide…..".
7. Revise the storage information for consistency with the prescribing information. Revise to read "Store at 68° to 77°F (20° to 25°C); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.".

B. Cartridge Carton Labeling

1. Revise the statement [redacted] (b) (4) on the side panel 3 to "Recommended dosage: See Prescribing Information.".
2. We recommend including a space between the numerical strength and units in the "each mL contains" statement. Revise "8mg" to "8 mg" for ease of readability.
3. Revise the storage information for consistency with the prescribing information. Revise to read "Store at 68° to 77°F (20° to 25°C); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.".

C. Cartridge Container Label

1. Revise storage to remove the dash and align with the prescribing information.

D. Tyvek Lid Labeling

1. Revise [redacted] (b) (4) to read:

   On-Body Infusor for

   Furoscix

   (furosemide injection)

   80 mg/10 mL (8 mg/mL)

   For subcutaneous use

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Furoscix received on April 08, 2022 from scPharmaceuticals Inc..

| Table 2. Relevant Product Information for Furoscix | |
|---|---|
| Initial Approval Date | N/A |
| Active Ingredient | furosemide |
| Indication | treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure who display reduced responsiveness to oral diuretics and do not require hospitalization |
| Route of Administration | Subcutaneous |
| Dosage Form | Injection |
| Strength | 80 mg/10 mL (8 mg/mL) |
| Dose and Frequency | The recommended dose of FUROSCIX is 80 mg administered over 5-hours subcutaneously (30 mg over the first hour followed by 12.5 mg per hour for the subsequent 4 hours) using the pre-programmed, single-use on-body infusor with prefilled cartridge. (b) (4) |
| How Supplied | 80 mg/10 mL carton containing prefilled cartridge co-packaged with one on-body infusor |
| Storage | (b) (4) Do not refrigerate or freeze. |

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 30, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Furoscix. Our search identified two previous reviews[d,e], and we considered our previous recommendations to see if they are applicable for this current review.

[d] Thomas, S. Human Factor Validation Study, Label and Labeling Review for Furoscix (NDA 209988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 15. RCM No.: 2017-1762 and 2017-1764.

[e] Little, C. Human Factor Study Report and Labels and Labeling Review for Furoscix (NDA 209988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAY 16. RCM No.: 2017-1762-1 and 2017-1764-1.

APPENDIX G. LABELS AND LABELING

## G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following Furoscix labels and labeling submitted by scPharmaceuticals Inc..

- Container label received on April 08, 2022
- Carton labeling received on April 08, 2022
- Professional Sample Carton Labeling received on May 11, 2022
- Instructions for Use received on April 08, 2022, available from \\CDSESUB1\EVSPROD\nda209988\0058\m1\us\114-labeling\draft\labeling\label-0063-ifu-word.docx
- Prescribing Information (Image not shown) received on April 08, 2022, available from \\CDSESUB1\EVSPROD\nda209988\0058\m1\us\114-labeling\draft\labeling\label-0071-pi.pdf
- (b) (4)

## G.2 Label and Labeling Images

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[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

## Memorandum

**Date:** December 11, 2020

**To:** Wayne Amchin, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)

**From:** Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Furoscix Infusor (furosemide), Drug-device combination product

**NDA/BLA**: 209988

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This memo is in response to DCN's labeling consult request dated July 16, 2020. Reference is made to a Complete Response letter that was issued on December 3, 2020. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DCN submit a new consult request during the subsequent review cycle. If you have any questions, please contact Zarna Patel at 301-796-3822 or zarnapatel@fda.hhs.gov.

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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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|---|---|
| Date of This Review: | November 16, 2020 |
| Requesting Office or Division: | Division of Cardiology and Nephrology (DCN) |
| Application Type and Number: | NDA 209988 |
| Product Type: | Combination Product |
| Drug Constituent Name and Strength | Furoscix (furosemide) injection, 80 mg/10 mL (8 mg/mL) |
| Device Constituent: | On-body Infusor |
| Rx or OTC: | Rx |
| Applicant/Sponsor Name: | scPharmaceuticals Inc. |
| Submission Date: | June 30, 2020 |
| OSE RCM #: | 2017-1762-1 and 2017-1764-1 |
| DMEPA Safety Evaluator: | Colleen Little, PharmD |
| DMEPA Team Leader: | Lolita White, PharmD |
| DMEPA Associate Director for Human Factors (Acting): | Jason Flint, MBA, PMP |
| DMEPA Deputy Director: | Danielle Harris, PharmD |

# 1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 209988 for Furoscix (furosemide) injection.

## 1.1. PRODUCT DESCRIPTION

This is a combination product with a proposed single-use, disposable, pre-programmed, on-body infusor device constituent part that is intended to treat congestion due to fluid overload in adult patients with worsening New York Heart Association (NYHA) Class II and Class III heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization. The combination product is not indicated for chronic use. See Appendix A.

## 1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On May 15, 2018, we reviewed the proposed labels, labeling, (b) (4), and human factors (HF) validation study results for Furoscix under NDA 209888.[a] We concluded that the HF data did not support a conclusion that the proposed product can be used safely and effectively by the intended users for its intended uses and use environments. Thus, we recommended that the Applicant conduct adequate root cause analyses for all use errors that could lead to harm (including compromised or delayed care), implement adequate risk mitigation measures, update the use-related risk analysis, and sufficiently test the effectiveness of the mitigations in a new HF validation study. Subsequently, on June 11, 2018, NDA 209988 received a Complete Response (CR) due to device, drug product quality, clinical, and HF deficiencies.[b]

On March 28, 2019, in response to the June 11, 2018 CR letter, the Applicant submitted a meeting request under IND 118919 to discuss their proposed drug-device combination product and to seek agreement on the updated development program for the new to-be-marketed Furoscix Infusor. The Applicant stated the improved device is equivalent in function to the original device design, but includes certain design features that address issues noted in the June 11, 2018 CR letter (e.g. pre-filled cartridge, simplified use steps, dose delivery notification, and fault notification (b) (4)).[c]

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[a] Thomas, S. Human Factors Validation Study, Label and Labeling Review for Furoscix (NDA 209988). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 15. RCM No.: 2017-1762 and 2017-1764.

[b] Proctor, B. Complete Response for NDA 209988. Silver Spring (MD): FDA, CDER, ODE1, DCRP (US); 2018 JUN 11. Available from: https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af8049f3f1&_afrRedirect=910955291663321

[c] Type C Meeting Request for Furoscix (IND 118919). Burlington (MA): scPharmaceuticals, Inc.; 2019 MAR 28. Available from: \\CDSESUB1\evsprod\ind118919\0037\m1\us\12-cover-letter\cover.pdf

We provided preliminary comments to acknowledge the Applicant's plan to submit their HF validation study protocol for Agency review prior to the commencement of their new HF validation study to demonstrate safe and effective use of the redesigned Furoscix infusor.[d]

On July 2, 2019, the Applicant submitted a HF protocol under IND 118919. Our review of the HF validation study protocol identified several areas of concern. We communicated our recommendations to the Applicant in an HF Validation Study Protocol Advice letter.[e]

On August 29, 2020, the Applicant submitted a response to our August 28, 2019 HF Validation Study Protocol Advice Letter stating that they agree with our previous recommendations for the use-related risk analysis (URRA), Instructions for Use (IFU), and general recommendations. In response to our recommendation to use a consistent training decay period for all participants in the trained arm, the Applicant proposed a 24 hour training decay period, with some minor variation due to scheduling constraints. We determined that the Applicant's approach was acceptable and we recommended that they document the participants who varied from the standard 24 hour training decay period in the HF study report.[f]

Additionally, we acknowledged the Applicant's "alternate approach" for the Reading Comprehension portion of the HF study; however, we continued to recommend that the Applicant design the knowledge assessment portion of the study in such a manner that allows the participants to locate the critical information in the IFU on their own and demonstrate their comprehension of the information associated with critical knowledge tasks in order to evaluate those tasks which cannot be directly observed as use tasks.

On June 30, 2020, the Applicant submitted a Class 2 resubmission under NDA 209988 to address the deficiencies in the June 11, 2018 CR letter. The resubmission also included a HF validation study report, which is the subject of this review.

On September 20, 2020, the Applicant submitted a Device Improvement Report[g] under NDA 209988, which provided a high-level overview of device modifications made to

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[d] Proctor, B. Preliminary Meeting Comments (IND 118919). Silver Spring (MD): FDA, CDER, ODEI, DCRP (US); 2019 JUN 13. Available from: https://darrts fda.gov/darrts/faces/ApplicationHistoryContent/viewApplicationHistoryContent?_afrRedirect=1679448665484862&_afrPage=3

[e] Patanavanich, S. Human Factors Validation Study Protocol Advice Letter for Furosemide (IND 118919). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 28. Available from: https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af805117c0&_afrRedirect=1168253653405215

[f] Little, C. Review of Response to Human Factors Validation Study Protocol Advice Memorandum for Furosemide (IND 118919). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 DEC 13. RCM No.: 2019-1403-1.

[g] Device Improvement Report for Furoscix under NDA 209988. Burlington, MA: scPharmaceuticals Inc.; 2020 SEP 29. Available from: \\CDSESUB1\evsprod\nda209988\0040\m1\us\112-other-corr\request-advice-29sep2020.pdf

address a previous FDA recommendation for an alarm to notify the patient of an incomplete dose delivery. The device modifications were made to the previously validated device and the Applicant has not submitted any additional data to support the modifications.

## 2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

| Table 1. Materials Considered for this Review | |
|---|---|
| Material Reviewed | Appendix Section (for Methods and Results) |
| Product Information/Prescribing Information | A |
| Background Information<br>Previous HF Reviews (DMEPA and CDRH) | B |
| Background Information on Human Factors Engineering (HFE) Process | C |
| Human Factors Validation Study Report | D |
| Information Requests Issued During the Review | E |
| Labels and Labeling | F |

## 3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Our assessment of the HF validation study report included in the June 30, 2020, Class 2 resubmission is provided in this section and we have determined the results are acceptable for the tested product. However, during the course of our review, CDRH notified us that device modifications were made subsequent to the HF validation study and the Applicant has not submitted any additional HF data to support the modifications. Thus, we are unable to determine if the modified device is acceptable at this time.

Based on our review of the September 29, 2020 Device Improvement Report submission and discussion with CDRH during internal meetings, at this time, it is unclear whether the device modifications will affect critical tasks related to dose confirmation, alarm identification, and user response to the alarm. Additionally, it is unclear whether the device modifications will require changes to the aspects of the user interface that will require additional HF validation testing. Thus, without review of additional HF data (i.e., use-related risk analysis, comparative analyses, etc.) it is unclear whether the device modifications will introduce any new risks to intended users in the intended use environment. As such, the device modifications in the September 29, 2020 Device Improvement Report submission preclude our ability to determine whether the submitted

HF validation study results demonstrate safe and effective use of the intend-to-market product.

Since we had already started our review at the time we were notified of the device modifications, our high level review of the HF validation report is included in this review. The sections below provide a summary of the study design, errors/close calls/use difficulties observed, and our analysis. We defer to OND to determine whether our corresponding recommendations should be communicated to the applicant at this time.

### 3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

| Table 2. Study Methodology for Human Factors (HF) Validation Study | |
|---|---|
| Study Design Elements | Details |
| Participants | • n=15 untrained patients<br>• n=15 trained patients<br>• n=15 untrained caregivers<br>• n=15 untrained HCPs |
| Training | Trained patient participants received representative training simulating real life that would occur in a healthcare setting. Training took place over 15 to 30 minutes and was conducted by an HCP who regularly works with congestive heart failure patients. |
| Test Environment | The test room was setup to simulate the intended use environments of a home or healthcare facility. |
| Sequence of Study | Trained Arm<br>• Training session<br>• 24 hour training decay period<br>• Simulated- use scenario, Knowledge Tasks, and Post-Interaction Questions<br>o During the simulated-use scenario, the On-Body Infusor issued an alarm and participants were observed as to whether or not they noticed the alarm and then they were asked to identify what the alarm meant and what they would need to do to respond to it. |

| | |
|---|---|
| | o After the alarm scenario, devices were switched out and participants were asked to continue to allow the infusion to deliver just as if no alarm had occurred.<br>• Root cause analysis<br>• Reading Comprehension and Knowledge Tasks<br>• Root cause analysis<br>• IFU Feedback<br>Untrained Arm<br>• Self-familiarization<br>• Simulated- use scenario, Knowledge Tasks, and Post-Interaction Questions (see above)<br>• Root cause analysis<br>• Reading Comprehension and Knowledge Tasks<br>• Root cause analysis<br>• IFU Feedback |

3.2 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

| Identified Issues and Recommendations | | |
|---|---|---|
| | **Identified Issue, Subjective Feedback, Root Cause Analysis and Mitigations** | **DMEPA's Analysis and Findings** |
| 1. | For the knowledge task to identify the application site, there was one use error. One untrained caregiver participant identified the fattiest part of the arm as an acceptable application site.<br><br>The subjective data and the Applicant's root cause analysis attributed this use error to labeling confusion; (b) (4) | Based on the Applicant's URRA, if this task is omitted or not performed correctly there is risk of under-diuresis, user annoyance, or discomfort caused by skin aggravation. Thus, we are concerned with the residual risk for this error.<br><br>We agree with the Applicant that the (b) (4) contributed to this error. However, our review of the study results identified subjective feedback that indicated including the (b) (4) in the IFU may cause confusion, which may lead to selection of the wrong application site.<br><br>Our review of the IFU finds (b) (4) (b) (4) (b) (4) Thus, we disagree with the Applicant's proposed mitigation and find that (b) (4) can be further improved to minimize the risk of the selection of the wrong application site due to misinterpretation (b) (4) (b) (4)<br><br>We acknowledge the Applicant's proposed labeling mitigation. However, based on our overall assessment, we find that the IFU can be further improved to mitigate the risk of selection of the wrong |

| | | |
|---|---|---|
| | | application site. Thus, we have identified additional labeling mitigations to address risk of this use error. We provide recommendation #2 in Table A to address this concern. We have determined that the (b) (4) will not introduce any new or unique risk in the intended user group in the intended use environment. |

ANALYSIS OF OTHER TASK ERRORS

The HF validation study showed use errors, (e.g. failures, difficulties, and close calls) with the following 4 critical tasks and 4 non-critical tasks, however our assessment of these user errors finds the residual risk is acceptable and thus are not the focus of this review. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no recommendations to further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks:

- Remove the protective adhesive liner
- Push the blue start button
- Respond to the alarm
- Do not use the on-body infusor with other medicines other than Furoscix
- Clean the tip of the cartridge prior to inserting it into the cartridge holder
- Clean the application site with an alcohol wipe
- Wash hands before administration
- Dispose of the used on-body infusor and cartridge together into a FDA-cleared sharps container

3.4. LABELS AND LABELING

Our review of the labels and labeling identified areas that are vulnerable to medication error. We provide our high level recommendations in Table A for the Applicant. We defer to OND to determine if these recommendations should be communicated to the Applicant at this time.

| Table A: Identified Issues and Recommendations for scPharmaceuticals Inc. (entire table to be conveyed to Applicant) | | | |
|---|---|---|---|
| | Identified Issue | Rationale for Concern | Recommendation |
| General (for all Labels and Labeling) | | | |
| 1. | As proposed, your logo interferes with the proprietary name, Furoscix, on your proposed labels and labeling. | The use of images or logos immediately before or after the proprietary name may lead to misinterpretation of the proprietary name. In this instance, we are concerned the name may be misinterpreted as Ofuroscix or Ufuroscix as the logo appears to be part of the proprietary name. | We recommend that you revise the presentation of the proprietary name and the logo so that the logo does not interfere with the presentation of the proprietary name. For example, consider a larger space between the logo and the proprietary name, or address by other means. |
| Instructions for Use | | | |
| 2. | Your IFU can be improved to decrease risk of wrong site of administration medication error. In your HF validation study, one participant identified the fattiest part of the arm as an acceptable application site. Your root cause analysis attributed this error to labeling confusion; specifically, (b) (4) (b) (4) Figure M of Step 4 in the IFU. We acknowledge that you have revised Figure M to minimize confusion. However, we have identified additional labeling mitigations to address this error. | We are concerned that as proposed, Figure M may imply (b) (4) which may lead to selection of the wrong administration site. | Remove (b) (4) from Figure M for Step 4. |

| | | | |
|---|---|---|---|
| 3. | Your IFU can be improved to better illustrate one infusor is to be applied per dose. We acknowledge that Step 4.1 states that users should select (b) (4) (b) (4) site. However, we note that Figure M under step 4 includes two green infusors to identify the appropriate application sites. | We are concerned that users may misinterpret the shapes used to identify the appropriate application sites to imply that two devices should be used at once which may lead to overdose medication error. | Revise Step 4.1 (b) (4) (b) (4) to "Select one site…" to clarify that only one device is required. |

## 4. CONCLUSION AND RECOMMENDATIONS

We find the results of the HF validation study submitted on June 30, 2020 acceptable for the tested device. However, during the course of our review, CDRH notified us that device modifications were made subsequent to the HF validation study and the Applicant has not submitted any additional HF data to support the modifications. Thus, it appears the tested device is not representative of the intend-to-market device. Furthermore, it is unclear whether the device modifications will affect critical tasks or require changes to the IFU that will require additional HF validation testing. Thus, additional HF information is necessary to determine whether the modified device can be used safely and effectively.

DMEPA defers comprehensive review of labels and labeling until the next review cycle. We provide high level recommendations for the proposed labels and labeling below and defer to OND to determine if these recommendations should be issued to the Applicant at this time. We also provide letter ready comments to the applicant in section 4.1.

### 4.1 RECOMMENDATIONS FOR SCPHARMACEUTICALS INC.

We acknowledge your human factors (HF) study report included with your June 30, 2020, Class 2 resubmission. However, your Device Improvement Report submitted on September 29, 2020 indicates that your proposed device was modified subsequent to the HF study. We expect your HF validation study to be conducted with your intend-to-market device. Furthermore, it is unclear whether the device modifications affect critical tasks associated with the safe and effective use of the device or require changes to your Instructions for Use (IFU). Thus, additional information is necessary to determine whether the modified device can be used safely and effectively.

We recommend you update your comprehensive use-related risk analysis taking into consideration the device modifications. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Based on the aforementioned information and data, you should determine whether you need to submit the results of another human factors (HF) validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. If you determine that another HF validation study does not need to be submitted for your product, submit your risk analysis, comparative analyses, and justification for not submitting another HF validation study to the Agency for review when you respond

to the application deficiencies. The Agency will notify you if we concur with your determination.

The comparative analyses should include a labeling comparison, a comparative task analysis, and a physical comparison between the user interface that was validated in your HF validation study and your modified user interface for the purposes of identifying what differences exist between the user interfaces.

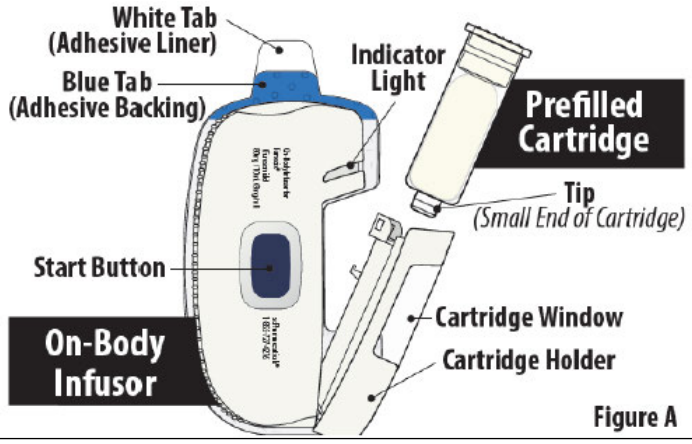
If you determine that you do need to submit a HF validation study for your product, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

In addition, our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table A and we recommend that you implement these recommendations prior to resubmission of this NDA.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 6 presents relevant product information for Furoscix that scPharmaceuticals Inc. submitted on June 30, 2020.

| Table 6. Relevant Product Information | |
|---|---|
| Initial Approval Date | N/A |
| Therapeutic Drug Class or New Drug Class | diuretic |
| Active Ingredient (Drug or Biologic) | furosemide |
| Indication | For the treatment of congestion due to fluid overload in adult patients with worsening New York Heart Association (NYHA) Class II and Class III heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization. FUROSCIX is not indicated for chronic use. |
| Route of Administration | subcutaneous administration via the Infusor (Furoscix Infusor) |
| Dosage Form | injection |
| Strength | 80 mg/10 mL (8 mg/mL) |
| Dose and Frequency | The 80 mg dose of FUROSCIX is administered over 5-hours (30 mg over the first hour followed by 12.5 mg per hour for the subsequent 4 hours) using the pre-programmed, single-use on-body infusor with prefilled cartridge. |
| How Supplied | One single-use FUROSCIX® On-body Infusor, one 80 mg/10 mL prefilled cartridge, two alcohol pads, one IFU |
| Storage | (b) (4) Do not refrigerate or freeze. |
| Container Closure/Device Constituent | FUROSCIX® On-body Infusor   Figure A |

| | |
|---|---|
| Intended Users | Patients, caregivers, HCPs |
| Intended Use Environment | in-home or healthcare clinic environment |

## APPENDIX B. BACKGROUND INFORMATION

### B.1 PREVIOUS HF REVIEWS

#### B.1.1 Methods

On September 21, 2020, we searched the L:drive and AIMS using the terms, IND and NDA to identify reviews previously performed by DMEPA or CDRH.

#### B.1.2 Results

Our search identified 1 previous review[f] since the date of our last search[h], and we confirmed that our previous recommendations were implemented or considered.

## APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

## APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\cdsesub1\evsprod\nda209988\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edema-chf-liver-kidney\5354-other-stud-rep\human-factors\rpt-0333-hf-summative.pdf

## APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On July 23, 2020, we issued an Information Request (IR) to request five placebo only intend-to-market samples. The Sponsor's response to the IR was acceptable.

## APPENDIX F. LABELS AND LABELING

### E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[i] along with postmarket medication error data, we reviewed the following Furoscix labels and labeling submitted by scPharmaceuticals Inc received on June 30, 2020.

- Cartridge Container label
- On-Body Infusor Label

[h] Little, C. Human Factors Validation Study Protocol for furosemide under IND 118919. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 AUG 28. RCM No.: 2019-1403.

[i] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- (b) (4)
- Cartridge Carton Labeling
- (b) (4) Carton Labeling
- Instructions for Use available from \\CDSESUB1\evsprod\nda209988\0034\m1\us\114-labeling\114a-draft-label\label-0063-ifu.pdf
- Prescribing Information (Image not shown) available from \\CDSESUB1\evsprod\nda209988\0034\m1\us\114-labeling\114a-draft-label\label-0071-pi-word.docx

E.2 Label and Labeling Images

Cartridge Container label

(b) (4)

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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DANIELLE M HARRIS
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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** June 18, 2018

**To:** Brian Proctor, Regulatory Project Manager
Division of Cardiovascular and Renal Products (DCRP)

Michael Monteleone, Associate Director of Labeling, DCRP

**From:** Zarna Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** James Dvorsky, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for Furoscix Infusor (furosemide) 80 mg/10 mL, Drug-device combination product

**NDA/BLA**: 209988

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This memo is in response to DCRP's labeling consult request dated August 29, 2017. Reference is made to a Complete Response letter that was issued on June 11, 2018. Therefore, OPDP defers comments on the proposed labeling at this time, and requests that DCRP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Zarna Patel at (301) 796-3822 or zarna.patel@fda.hhs.gov.

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/s/

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ZARNA PATEL
06/18/2018

**HUMAN FACTORS VALIDATION STUDY, LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

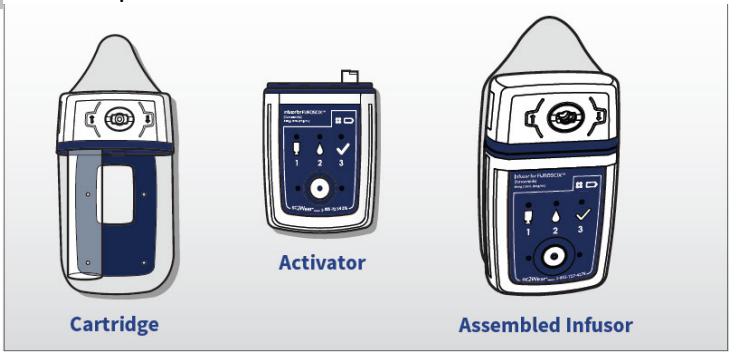
| | |
|---|---|
| **Date of This Review:** | May 16, 2018 |
| **Requesting Office or Division:** | Division of Cardiovascular and Renal Products (DCRP) |
| **Application Type and Number:** | NDA 209988 |
| **Product Name and Strength:** | Furoscix (Furosemide) Injection (b) (4), 80 mg/10 mL (8 mg/mL) |
| **Product Type:** | Combination Product |
| **Rx or OTC:** | Rx |
| **Applicant/Sponsor Name:** | scPharmaceuticals, Inc. |
| **Submission Date:** | August 23, 2017 |
| **OSE RCM #:** | 2017-1762 and 2017-1764 |
| **DMEPA Primary Reviewer:** | Sarah Thomas, PharmD |
| **DMEPA Team Leader:** | Chi-Ming (Alice) Tu, PharmD, BCPS |
| **Associate Director for Human Factors:** | Quynh Nhu Nguyen, MS |
| **DMEPA Deputy Director:** | Danielle Harris, PharmD, BCPS |

## 1 REASON FOR REVIEW

As a part of the NDA submission, scPharmaceuticals submitted labels, labeling, (b) (4) and human factors (HF) validation study results for Furoscix, which is a furosemide formulation optimized for subcutaneous delivery via an infusor. The Division of Cardiovascular and Renal Products (DCRP) has requested that we review the HF validation study results, labels, labeling, (b) (4) submitted by scPharmaceuticals, Inc. to determine if they are acceptable from a medication error perspective.

### 1.1 PRODUCT DESCRIPTION

The proposed Infusor consists of two parts: an Activator and a Cartridge. The Activator is the multi-use component, and the Cartridge is intended to be used only one time. Together the Activator and Cartridge form the Infusor device, which is placed on the patient's abdominal wall by a healthcare provider, patient, or caregiver to deliver a fixed dose of 80 mg of Furosemide subcutaneously over 5 hours. The proposed indication is for the treatment of edema associated with congestive heart failure, (b) (4) in adult patients.




### 1.2 REGULATORY HISTORY

As a follow-up to the pre-IND meetings held on September 18, 2013[a] and July 30, 2014[b], scPharmaceuticals proposed a Human Factors (HF) Validation Study Protocol for SCP-101 furosemide injection system in a meeting package on March 16, 2015. DMEPA reviewed this March 16, 2015 HF protocol and consulted Division of Medical Policy Programs (DMPP) to review the instructions for use (IFU). Both DMEPA's HF protocol recommendations and DMPP's IFU recommendations were provided to scPharmaceuticals at the Type B meeting on April 27,

[a] Monteleone, M. Type B Pre-IND Meeting Minutes for scF Administration System (furosemide patch pump). Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2013 October 7. IND 118919.

[b] Amchin, W. Type B Pre-IND Meeting Minutes for Subcutaneous Furosemide Administration System (scFAS). Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2014 August 28. IND 118919.

2015.[c,d] Our recommendations provided advice on participant training, the training program, and the study design relating to not re-using participants already exposed to the proposed product for testing. We also recommended that the Sponsor clarify the tasks and comprehensive use-related risk analysis, as well as definition for success and failure for each task, etc.

On June 4, 2015, scPharmaceuticals submitted a revised HF study protocol. The Division of Cardiovascular and Renal Products requested that we review the revised Human Factors Validation Study Protocol for the SCP-101 furosemide injection system to ensure the protocol is adequately designed to assess if the intended population is able to use the product safely and effectively. We found the revised Human Factors Validation Study Protocol acceptable from a medication error perspective in OSE Review# 2015-1332. We provided two additional clarifications to ensure the reasons for patient/caregiver disqualification would be recorded and to ensure that DMEPA and DMPP would have an opportunity to review the revised HCP IFU and Patient/Caregiver IFU prior to study initiation.[e]

We completed a label and labeling review with DMPP in 2016, providing recommendations for the IFU/QRG and labels and labeling.[f] We then completed a follow-up label and labeling review memo in 2016 with additional recommendations for the IFU and Quick Reference Guide (QRG).[g] Last, we provided Human Factors-related comments during a pre-NDA meeting in 2017 that scPharmaceuticals should fix the device issues observed in the Product Design Clinical Validation study prior to attempting further Human Factors testing.[h]

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[c] Childers, A. Type B Guidance Preliminary Meeting Comments for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2015 APR 23. IND 118919.

[d] Childers, A. Type B Guidance Meeting Minutes for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2015 May 19. IND 118919.

[e] Gao, T. Human Factors Protocol Review for scFurosemide. IND 118919. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 July 2. RCM No.: 2015-1332.

[f] Thomas S. Label and Labeling Review for Human Factors Validation Study for Furoscix (IND 118919). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 FEB 25. 60 p. OSE RCM Nos.: 2016-79 and 2016-150.

[g] Thomas S. Label and Labeling Review Memo for Human Factors Validation Study for Furoscix (IND 118919). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 AUG 31. 5 p. OSE RCM Nos.: 2016-1430.

[h] Childers, A. Type B Guidance Meeting Minutes for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2017 JUNE 1. IND 118919.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

| Table 1. Materials Considered for this Label and Labeling Review | |
|---|---|
| **Material Reviewed** | **Appendix Section (for Methods and Results)** |
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B |
| Human Factors Study | C |
| ISMP Newsletters | D-N/A |
| FDA Adverse Event Reporting System (FAERS)* | E-N/A |
| Other | F-CDRH HF Review |
| Labels and Labeling | G |

N/A=not applicable for this review

## 3 HUMAN FACTORS VALIDATION STUDY RESULTS

The sections below provide our evaluation of the HF study design, use errors observed, and our analysis of the HF validation study results.

### 3.1 EVALUATION OF STUDY DESIGN

scPharmaceuticals conducted 4 summative HF studies to test patient, caregiver, and healthcare provider (HCP) use of the infusor in three different, anticipated use scenarios (See Table 2 below). The objectives of studies 123, 128, and 133 included 1) confirming no unanticipated serious use errors, 2) confirming essential and critical tasks can be performed safely and effectively, and 3) confirming the product design meets user needs. There were 4 key outcomes assessed for effective use in the studies: 1) Fill the infusor reservoir with drug, 2) Apply the infusor correctly on the abdominal belt with simulated skin pad, 3) Initiate drug delivery, and 4) Confirm infusion session was successful. Each of these HF studies included at least 15 representative users in each distinct user group, such as healthcare providers (doctors, nurses, and pharmacists), heart failure patients, or caregivers. HF studies were conducted in simulated home, clinic, and/or exam rooms. Per scPharmaceuticals, the product was evaluated for safe use with respect to serious use errors defined by the applicant as any deviation from the instructions that is not corrected by the participant and could lead to harm of severity 4-5 (4: severe harm; 5: catastrophic harm).[i] The example of severity harm score of 4 provided by

[i] Definition of critical task per the "Applying Human Factors and Usability Engineering to Medical Devices" Guidance for Industry and Food and Drug Administration Staff (https://www.fda.gov/downloads/MedicalDevices/.../UCM259760.pdf): A user task which, if performed

scPharmaceuticals is using the infusor with a different drug (not Furoscix). scPharmaceuticals only identified one critical task in the HF studies, which was the comprehension of a warning in the labeling for use of the infusor with other medications. We note that Study 126 was conducted to evaluate the changes made to the IFU as a result of study 123; study 126 consisted of IFU knowledge tasks and no simulation was performed in study 126.

Table 2. Overview of the 4 Human Factors Validation Studies Conducted by scPharmaceuticals

| Study Report # | 123 (PCG-1 Study) | 126 (PCG-2 Study) | 128 (HCP Study) | 133 (PCG-3 Study) |
|---|---|---|---|---|
| Date conducted: | April 2016 | October 2016 | November 2016 | May 2017 |
| Scenario | Pre-acute[j] scenario #2. HCP trained and supervised patient/caregiver to prepare, fill, and apply pump. Following a 90 min training decay period, patient/caregiver start infusion once at home, monitors, and dispose pump after infusion is complete. | | Pre-acute scenario #1. HCP prepare, fill, apply pump to patient, infuse, monitor, and dispose pump. | Post-acute[k] scenario #3. HCP administered 1st dose, trains patient/caregiver. Following 1 day training decay, patient discharged with cartridge kit to complete future treatment at home. |
| Simulated Environment | Home use | Home use | Clinic/exam room | Home use |
| Subjects (n) | Patient (n=18) | Patient (n=7) | Doctors (n=17) | Patient (n=16) |

incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care.

[j] scPharmaceuticals defines the Pre-Acute Scenario as follows: "A patient becomes mildly or moderately symptomatic and contacts their managing HCP. They receive an appointment and travel to the clinic/hospital for examination by their HCP. After an examination, the HCP prescribes the sc2Wear Infusor and it is dispensed by the clinic or on-site pharmacy. The Infusor is prepared, filled and applied to the patient by the HCP. In one variation, the patient receives treatment while they remain in the clinic under HCP observation. In this variation, the HCP is the primary user, starting infusion, monitoring infusion progress, and dispositioning the Infusor after infusion is complete. Afterwards, the patient returns home, keeping the reusable portion of the system (i.e., the Activator) for future use. In a second variation, the patient returns home before starting the infusion. In this variation, the HCP is the primary user for the preparation and application steps then the patient and/or caregiver is the primary user, starting infusion, monitoring infusion progress, and dispositioning the Infusor after infusion is complete. Afterwards, the patient keeps the Activator for future use."

[k] scPharmaceuticals defines the Post-Acute Scenario as follows: "A patient becomes acutely symptomatic and contacts their managing HCP. The patient is directed to the ER/hospital by their HCP. ER/Hospital staff examine the patient and begin IV administration of Furosemide. When the patient's condition is stabilized the ER/Hospital staff prescribe the sc2Wear Infusor and it is dispensed by the hospital pharmacy. The ER/Hospital staff is responsible for all interactions with the device from preparation through disposition and may use that session to train the patient and caregiver. The patient is then discharged with additional Cartridge Refill Kit(s) and instructions to complete treatment at home. Afterwards, the patient keeps the Activator for future use."

| | Caregiver (n=15) | Caregiver (n=8) | Nurses (n=18)<br>Pharmacists (n=17) | Caregiver (n=16) |
|---|---|---|---|---|
| Scope of study | Simulated tasks, & IFU comprehension | IFU comprehension | Simulated tasks, & IFU comprehension | Simulated tasks, & IFU comprehension |
| Device modifications | • No needle<br>• Empty vial<br>• Delivery duration (b) (4) | n/a | • No needle<br>• Empty vial<br>• Delivery duration (b) (4) | • Delivery duration (b) (4) |

Our evaluation of the overall study design finds that the study participants and the simulated use environments are appropriate; however, we identified some concerns with the study design. Specifically, we disagree with the Applicant's identification of critical tasks. (b) (4) (b) (4) (b) (4). We acknowledge this is a change in assessment from our prior review of the Applicant's proposed use-related risk analysis and human factors protocol under IND 118919.[l] This change in assessment is based on clinical input from the review team during this NDA 209988 review cycle suggesting that use-errors that lead to delay in treatment, partial treatment, or treatment omission could result in the need for medical intervention and possible hospitalization.

It is also important to note that, with the exception of the self-trained HCP (n=6), all of the remaining participants (b) (4) (b) (4)

### 3.2 ANALYSIS OF HF STUDY RESULTS

[l] Gao, T. Human Factors Protocol Review for scFurosemide. IND 118919. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 July 2. RCM No.: 2015-1332.

[m] The IFU language was revised based on ORP/OCC advice (b) (4) (b) (4) (b) (4) on September 9, 2016. Our review of the HF protocol preceded this advice to change the IFU language.

We evaluated the HF study results to identify areas in the user interface that can be improved to promote the safe use of this proposed product. We also sub-consulted CDRH to review the HF validation studies and we considered their recommendations as part of our review (Appendix F).

As mentioned above, we disagree with the sponsor's categorization of critical tasks (b) (4) (b) (4) (b) (4). Thus, Tables 3-6 below summarize and focus on the use errors associated with critical tasks, including those that could result in delay in treatment, partial treatment, or treatment omission. In addition, Table 3 presents the use errors observed in study report 123 associated with scPharmaceutical's only identified critical task involving comprehension of a warning in the labeling for use of the infusor with other medications. We also note any mitigations implemented by the Applicant to address any of the failures/close calls/use difficulties. The tables also include our assessment of the use errors.

11 pages have been Withheld in Full as b4(CCI/TS) Immediately Following this Page

## 4 HF RESULTS DISCUSSION

The applicant submitted 4 HF studies, conducted sequentially, to support this NDA, and concluded that the 4 studies demonstrate that the proposed Furoscix product can be safely and effectively used for the intended purpose in the intended user population.

Based on our discussions with the clinical team, we disagree with the applicant's selection of critical tasks. We understand that a delay in therapy, partial therapy, or therapy omission could result in the need for medical intervention or hospitalization. Therefore, we focused our analysis on the use-related errors that could result in delay in therapy, partial therapy, or therapy omission (see Tables 3-6 above).

Numerous use-errors occurred in the HF studies, (b) (4) (b) (4) (b) (4). Errors of this nature could result in partial treatment, or treatment delay or omission with the current infusion or with subsequent infusions ( (b) (4) (b) (4). We are most concerned about errors that could occur and go undetected by the patient, thus, leading the patient to believe that the drug was administered.

Because the applicant conducted the HF studies sequentially, it is important to acknowledge that the applicant made modifications to the product design and instructional materials to address some of the errors over the course of the study sequencing. Specifically, for example, the sponsor made modifications to the IFU (b) (4) (b) (4) and revised (b) (4) (b) (4) Of note, while these changes were tested in study 126 (patient/caregiver participants), study 126 consisted of knowledge comprehension questions only, and participants were not required to simulate the use of the device. Despite the labeling revisions, the participants in study 126 still experienced errors and difficulty (b) (4) (b) (4), suggesting the mitigations were not effective. The sponsor cited the root cause of the errors to be "(b) (4) design".

HCPs in study 128 also had difficulty (b) (4). scPharmaceuticals acknowledged that despite the IFU changes, the ability (b) (4) (b) (4) remains difficult for some participants (b) (4) (b) (4). In addition, following study 133, the applicant made additional changes to the instructional materials, including changes to the text and format of the IFU. The changes were not tested and validated in the patients, caregivers, or HCP intended user populations. While the iterative changes are aligned with the principles of HF engineering, it does not appear that final user interface was validated in the intended user populations. Our expectation is that the finalized product user interface be evaluated in a human factors validation study.

As noted above, the applicant concludes that the proposed product is safe and effective for use in the intended population. (b) (4)

(b) (4)

Based on our understanding of the clinical consequences associated with delayed, partial or omitted therapy, as described by the DCRP clinical review team, the data from all 4 HF studies do not demonstrate that the device is optimized for safe and effective use by the intended user populations for the intended users.

## 5 LABELING AND PACKAGING ASSESSMENT

Our review of the materials identified some undefined abbreviations, inconsistent and misleading statements and nomenclature, and missing descriptive information (e.g., NDC numbers, kit components, route of administration, etc.) in the labels and labeling.

## 6 CONCLUSION & RECOMMENDATIONS

The Human Factors Validation Studies identified use errors that could result in delay in treatment, partial treatment, or treatment omission. If patients do not receive the full intended treatment, or treatment is delayed, they would experience a continuation of symptoms. We acknowledge that the applicant did not consider these use errors to be critical to the safe and effective use of the product because the product is not intended for use in emergency situations (i.e., for the treatment of acute heart failure symptoms or pulmonary edema).

However, based on our discussions with the DCRP Review Team, we understand that heart failure patients are fragile and at risk of transitioning into acute decompensated heart failure if therapy is delayed, incomplete, or not received, which may result in the need for medical intervention and possible hospitalization. Furthermore, for most of these use errors, the Applicant did not implement any mitigations. The mitigations that were applied were not validated in all intended user populations. Therefore, the human factors data do not support a conclusion that the product can be used safely and effectively by the intended users for its intended uses and use environments.

Ultimately, we defer to the DCRP review team to determine if the clinical consequences of delayed therapy, partial therapy or therapy omission are acceptable residual risks for this product for the proposed indication. (b) (4)

(b) (4)

(b) (4)

If the DCRP clinical review team finds this residual risk is unacceptable, we recommend that the sponsor evaluate the use-related errors further, revise their use-related risk analysis, implement additional mitigations, and provide data from another human factors study that demonstrates the effectiveness of those mitigations with at least 15 representative users in each distinct user group. Additionally, our review of the proposed labels and labeling identified several areas that can be revised and updated to improve readability and minimize the risk for medication errors. We recommend the Applicant implement our recommendations, prior to conducting another human factors validation study.

Please see our recommendations for the prescribing information (PI) (b) (4) in section 6.1 below. Furthermore, we reviewed the CDRH human factors reviewers' comments (Appendix F), and we have incorporated CDRH's comments and our recommendations in section 6.2 below for scPharmaceuticals.

## 6.1 RECOMMENDATIONS FOR THE DIVISION

Based on our review, we recommend the review team consider the following changes to the Prescribing Information (PI) (b) (4):

A. Prescribing Information and Patient Information
    1. We note inconsistency in the timeframe provided in the PI, (b) (4) and the instructions for use (IFU) for how long patients should expect diuresis to last (b) (4) (b) (4) (b) (4) Clarify how long patients should expect diuresis to last as well as ensure consistency in the provision of information across the labels and labeling.
B. Prescribing Information
    1. Highlights, Dosage and Administration
        a. We recommend adding the following statement after the dosing information: "See Full Prescribing Information for preparation and administration of the injection."
    2. Highlights and Full PI, Dosage Forms and Strengths
        a. Revise the strength presentation so that the total quantity per total volume is provided first followed by the concentration per milliliter[nn]:

[nn] USP General Chapter <1> Injections

(b) (4)

3. Full PI, Section 2, Dosage and Administration
    a. Clarify (b) (4)
    b. (b) (4)
4. Full PI, Sections 3, Dosage Forms and Strengths, and 16, How Supplied/Storage and Handling
    a. Add appropriate information to facilitate identification of the injection dosage form (e.g., color of injection solution and other identifying characteristics).
5. Full PI, Section 16, How Supplied/Storage and Handling
    a. Revise (b) (4) (b) (4) to include all components as well as the quantities of components, as follows:

(b) (4)

    b. We note placeholders for the NDC numbers (b) (4) (b) (4) We request submission of the actual NDC numbers.

(b) (4)

[oo] USP General Chapter <1> Injections

(b) (4)

## 6.2 RECOMMENDATIONS FOR SCPHARMACEUTICALS, INC.

The human factors (HF) data do not support a conclusion that your proposed product can be used safely and effectively by the intended users for its intended uses and use environments. You have not adequately addressed all the use errors from your validation studies that could lead to patient harm due to delay in treatment, partial treatment, or treatment omission. We acknowledge that you did not consider these use errors to be critical to the safe and effective use of the proposed product because the product is not intended for use in emergency situations. (b) (4) (b) (4) (b) (4). However, we disagree because delayed, partial, or omitted treatment may require medical intervention and potential hospitalization.

We acknowledge that you made modifications to the product design and instructional materials to address some of the errors after studies 123 and 133. While the iterative changes are aligned with the principles of HF engineering, it does not appear that final user interface was validated in the intended user populations. Furthermore, despite the mitigations, participants still experienced errors and difficulty using the product, suggesting the mitigations were not effective.

To address this deficiency, the Agency requests that you conduct adequate root cause analyses for all use errors that could lead to harm (including compromised or delayed care), implement adequate risk mitigation measures, update your use-related risk analysis, and sufficiently test the effectiveness of your mitigations in a new HF validation study with at least 15 representative users in each distinct user group. We recommend that you submit your updated use-related risk analysis and human factors validation study protocol for review prior to commencing the study.

We recommend you consider the following as you update your use-related risk analysis and design your HF protocol methodology:

1. Use errors that can cause potential serious harm (including compromised medical treatment, contamination, and infection) should be evaluated as critical tasks[p].
2. Hazards that can cause potential damage to the device (i.e., disengaging the device by force) may not be detected and may result in delay of treatment or treatment omission with subsequent treatments. Implement additional mitigation strategies to

[p] Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

communicate hazardous situations to the users, and ensure your use-related risk analysis and HF protocol evaluate such hazards and associated mitigations accordingly.

3. Ensure the training methodology employed in your future HF testing (including trainers, training materials, and training decay periods) reflect the training that intended users would receive in real-world, and include justification for the training methodology.
4. We expect your HF study report to document subjective feedback collected from study participants for all use errors, difficulties, and close calls (including participant's feedback on potential root cause of the use errors, difficulties, and close calls).
5. We expect your HF study to test the final intend-to-market user interface or provide justification for not testing alterations. Alterations to the device in your HF studies (b) (4) (b) (4)) may have limited testing of the full functionality of the device and effectiveness of the user interface in the simulated studies (b) (4) and confounds the interpretation of the study results. Furthermore, because you made changes to the instructional materials after HF studies 123 and 133, you may not have adequately validated your final user interface (b) (4) in the intended user populations.
6. We expect your HF study to evaluate user ability to understand all warnings, alerts, and troubleshooting the device. We consider user's understanding of critical warnings, alerts, and ability to troubleshoot the device to be critical tasks and should be evaluated in HF validation testing.

Our review of the proposed product's labels, labeling (b) (4) identified areas that should be modified. We recommend you implement the following prior to conducting another HF validation study:

A. General Comments (Labels and Labeling, (b) (4))
   1. (b) (4)). To minimize confusion during its use, we recommend consistently using the same nomenclature across the labels, labeling, device itself, (b) (4) for the Furoscix system and its individual components.
   2. Since the activator component does not contain Furoscix medication, we recommend revising the nomenclature for the activator on the carton labeling ((b) (4) and actual activator device component face and back labeling ((b) (4)) to the following: "Activator for Furoscix." In addition, we recommend revising the additional medication and strength information (b) (4) (b) (4) to the following: "Intended for use with (furosemide injection) 80 mg/10 mL (8 mg/mL)". Also, we recommend revising any reference to the attached cartridge and activator device unit within the IFU, QRG, and other labeling (b) (4) to the following: "Assembled Infusor for Furoscix." (b) (4)

[redacted]. Therefore, revise to clarify the Infusor doesn't contain drug product until after the activator is joined with the cartridge.

3. [redacted], we recommend adding a space between "80mg" so that the numerical dose and units are separated as follows "80 mg." When the numerical dose and unit of measure run together, there is risk of the "m" being mistaken as zero or two zeros which may potentiate a 10- to 100-fold overdose.[q]
4. We note that cell phones can have an impact on the activator if held in close proximity to the infusor. We recommend adding a warning to the IFU, QRG, [redacted] to warn end-users of this potential issue.
5. We note placeholders for the NDC numbers on the Furoscix [redacted] container label and carton labeling, [redacted]. We request submission of the actual NDC numbers.
6. We note warnings in the labeling related to the patients needing to call their healthcare provider if extra urine output does not occur. We recommend adding the specified time point in the labeling [redacted] after start of the infusion at which the patient should contact their healthcare provider if not experiencing diuresis or adequate diuresis. In subsequent Human Factors testing, we recommend testing participant understanding of this warning.

B. Instructions for Use (IFU)

1. In general, ensure that all images of the container labels and carton labeling presented within the IFU are updated with the revised images. [redacted]
2. If space allows, we recommend adding a warning to the IFU regarding use and the consequences of use of the device near cell phones [redacted] In subsequent Human Factors testing, we recommend testing participant understanding of this warning.
3. We note inconsistency [redacted] Provide your rationale for the different descriptions, or revise for consistency.
4. [redacted]

[q] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2016 Feb 11]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

5. We note the IFU does not provide guidance on what to do if all of the medicine is not delivered ( [redacted] (b) (4) Provide relevant instructions in the IFU and QRG labeling on the recommended steps to take if all of the medicine is not delivered from the infusor. We recommend testing these revisions in your future HF study.
6. There were errors in the HF studies involving cleaning of the device or the infusion site. This could lead to an infection in the target patient population with congestive heart failure. Consider revision of the IFU to be more explicit in directing cleaning of the device and infusion site. We recommend testing these revisions in your future HF study.

C. [redacted] (b) (4)

D. [redacted]

E. Furoscix [redacted] (b) (4) Container Label and Carton Labeling

1. We note the format for the expiration date on the container label and carton labeling is "MM/YYYY" and "YYYYMMDD", respectively. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).[r]

[r] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

2. We note there is no barcode provided on the container label or carton labeling. The drug barcode is often used as an additional verification before drug administration in the inpatient setting; therefore, it is an important safety feature that should be part of the label and labeling whenever possible. Therefore, we request you add the product barcode to each individual vial container label and labeling as required per 21CFR 201.25(c)(2). When printed, ensure the barcode is positioned vertically[s] and with enough white space surrounding it[t] so that it is able to be scanned.

F. Furoscix (b) (4) Container Label

1. We recommend relocating the statement "For subcutaneous use only." to the Principal Display Panel (PDP) of the container label.[u]
2. If there is room available, we recommend adding the warning "Protect from light" to the container label.

G. Furoscix (b) (4) Carton Labeling

1. We recommend adding the statement "For subcutaneous use only." to the Principal Display Panel (PDP) of the vial carton labeling.[v]

H. (b) (4)

1. We note that not all of the symbols used on the labeling are defined consistently (b) (4) (b) (4). Define all symbols, or alternatively delete the symbols and spell out the intended meaning.

(b) (4)

[s] Neuenschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60 (8):768-79.

[t] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

[u] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

[v] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf.

(b) (4)

I. Furoscix (b) (4)

(b) (4) Carton Labeling

1. We note the format for the expiration date on the carton labeling is "YYYYMMDD". To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend using a format like either MMMYYYY (e.g. JAN2017) or MMMDDYYYY (e.g. JAN312017).[w]

J. (b) (4)

[w] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Furoscix that scPharmaceuticals, Inc. submitted on August 23, 2017.

| **Table 2. Relevant Product Information for Furoscix** | |
|---|---|
| **Product Name** | Furoscix |
| **Initial Approval Date** | N/A |
| **Active Ingredient** | Furosemide |
| **Indication** | Furosemide is a diuretic indicated in adult patients for the treatment of edema associated with congestive heart failure, (b) (4) |
| **Route of Administration** | Subcutaneous |
| **Dosage Form** | Injection |
| **Strength** | 80 mg/ 10 mL (8 mg/mL) |
| **Dose and Frequency** | 80 mg furosemide dosed over 5 hours: 30 mg over the first hour followed by 12.5 mg per hour for the subsequent 4 hours |
| **How Supplied** | (b) (4) |
| **Storage** | Store at 20° to 25°C, (68° to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from Light. |
| **Container Closure** | Vial |

## APPENDIX B. PREVIOUS DMEPA REVIEWS

### B.1 Methods

On December 14, 2017, we searched the L:drive and AIMS using the terms, scfurosemide, Furoscix, furosemide, NDA "209988", and IND "118919" to identify reviews previously performed by DMEPA.

### B.2 Results

Our search identified FDA's meeting minutes[x], meeting minutes[y], preliminary comments[z] and meeting minutes[aa], and meeting minutes[bb] for Type B meetings with scPharmaceuticals held on September 18, 2013, July 30, 2014, April 27, 2015, and June 1, 2017 respectively. In addition, we identified a Human Factors Protocol review[cc], and two label and labeling reviews. [dd,ee]

We confirmed that most of our previous recommendations were implemented and/or considered. However, some of our previous recommendations from a prior review were not implemented, and so we readdress in section 6.

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[x] Monteleone, M. Type B Pre-IND Meeting Minutes for scF Administration System (furosemide patch pump). Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2013 October 7. IND 118919.

[y] Amchin, W. Type B Pre-IND Meeting Minutes for Subcutaneous Furosemide Administration System (scFAS). Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2014 August 28. IND 118919.

[z] Childers, A. Type B Guidance Preliminary Meeting Comments for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2015 APR 23. IND 118919.

[aa] Childers, A. Type B Guidance Meeting Minutes for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2015 May 19. IND 118919.

[bb] Childers, A. Type B Guidance Meeting Minutes for SCP-101 furosemide injection system. Silver Spring (MD): FDA, CDER, OND, DCRP (US); 2017 JUNE 1. IND 118919.

[cc] Gao, T. Human Factors Protocol Review for scFurosemide. IND 118919. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 July 2. RCM No.: 2015-1332.

[dd] Thomas S. Label and Labeling Review for Human Factors Validation Study for Furoscix (IND 118919). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 FEB 25. 60 p. OSE RCM Nos.: 2016-79 and 2016-150.

[ee] Thomas S. Label and Labeling Review Memo for Human Factors Validation Study for Furoscix (IND 118919). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 AUG 31. 5 p. OSE RCM Nos.: 2016-1430.

## APPENDIX C. HUMAN FACTORS STUDIES

Please see Human Factors Validation Study result reports at the following links for detailed information on study design and reported results:

Pre-Acute Scenario 2 Patient and Caregiver studies:

-Report-123: \\cdsesub1\evsprod\nda209988\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edemachfliverkidney\5354-other-stud-rep\0040-0123\rpt-0123.pdf

-Retest, report-126: \\cdsesub1\evsprod\nda209988\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edemachfliverkidney\5354-other-stud-rep\0072-0126\rpt-0126.pdf

Pre-Acute Scenario 1 study Healthcare Provider study (Report- 128):
\\cdsesub1\evsprod\nda209988\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edemachfliverkidney\5354-other-stud-rep\0041-0128\rpt-0128.pdf

Post-Acute Scenario 3 Patient and Caregiver Home-Use study (Report-133):
\\cdsesub1\evsprod\nda209988\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edemachfliverkidney\5354-other-stud-rep\0074-0133\rpt-0133.pdf

Report 151, Summary document of summative study results:
\\cdsesub1\evsprod\nda209988\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\edemachfliverkidney\5354-other-stud-rep\0151\rpt-0151.pdf

## APPENDIX F. OTHER- CDRH HUMAN FACTORS STUDY REVIEW

Intercenter Consult Request (ICCR):
http://sharepoint.fda.gov/orgs/OSMP/ocp/ICRR/Lists/ICRR%20Forms/Item/displayifs.aspx?List=337aa2e9%2D7692%2D4a76%2Dada9%2Dae967ad4a69b&ID=1926&Web=703664f2%2D33ef%2D4c9f%2Da6f2%2De1f658e187f9

CDRH Review documentation:

NDA209988.furoscix infusor.cdrh-ode revie

CDRH's specific recommendations for HF studies:

6. d. You have not adequately addressed all the use errors from your validation study that could lead to patient harm of under-dosing or lack of therapy. (b) (4) (b) (4) (b) (4). However, it is likely that your patients will be high risk patients, with high mortality rates and acute conditions. Therefore, the Agency requests that you conduct adequate root cause analysis for all use errors that could lead to serious harm, implement adequate risk mitigation measures, and sufficiently test the robustness of your mitigations in a new validation study or provide justification for not doing so. As examples to facilitate your understanding, please consider the following:

i. You described several (b) (4) use errors which went uncorrected in the PCG-1, PCG-2 and PCG-3 studies and would have resulted in the user not completing a critical tasks. For example, in PCG-1 16 users were unable to determine if the Infusor was filled properly and this was left uncorrected, and several HCPs lifted or tilted the device during filling, which was left uncorrected. The Agency disagrees (b) (4) (b) (4). You should revisit the severity level of these errors based on your revised risk analysis and critical task assessment. You should determine if additional design or labeling measures should be implemented to mitigate these errors and, if so, validate these changes.

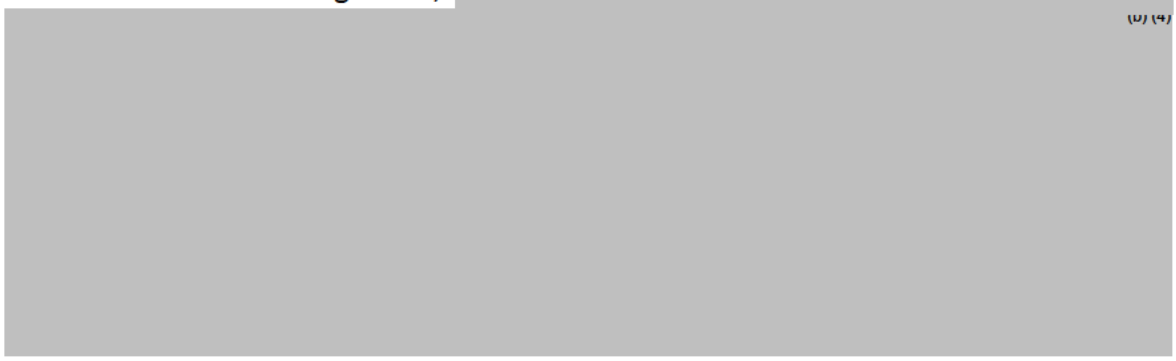
ii. There were several (b) (4) errors with regards to cleaning of the device or the infusion site. This could lead to an infection and in patients with congestive heart failure this is a serious issue. Additionally, this is the type of behavior that may be expected to be forgotten over time. You may need to make changes to the IFU to be more explicit in directing cleaning of the device and infusion site

iii. (b) (4) disengaging the device by force (b) (4) could lead to damage of the device that may not be detected. In this case the user might be unable to reuse the activator resulting in delay or treatment.

e. Study participants had use errors for not disinfecting the vial septum (1 user) and touching the inside of the adapter (3 users). This was rated as a "harm severity (b) (4) (b) (4)" (page 25 of 40). However, the consequences of not using the appropriate technique, stated as "the medication could be contaminated leading to a patient infection," can be very severe or even deadly. Please revise the harm severity of these tasks and ensure that they are identified as critical tasks in your future Human Factors studies.

24. You state that you made design changes to the instructional materials used in PCG-1 after conducting further studies (PCG-2, HCP, PCG-3). In particular, PCG-2 was conducted "to validate the IFU changes made as a result of the PCG-1 study" (pg. 50). However, the PCG-2 study only focused on testing patients and caregiver users on IFU Knowledge Tasks. As the intent of the PCG-1 study was to test the use-scenario of "HCPs train lay users in the preparation and application steps in a simulated clinic environment then lay users started, monitored and completed infusion in a simulated home setting" (pg. 50), you have not properly re-evaluated the changes to the IFU with regards to its effectiveness in training the HCPs. In general, because you have set up your study as multi-legged, you may not have adequately evaluated your final user interface (final instructional material).

25. In Section 5.3.5.4, the Human Factors Report-0133 describes testing performed related to Protocol-0074.
    a. In Table 2, you describe that the "Nurse Trainers" were nurse consultants for ScPharmaceuticals (page 8 of 40). However, it is important that the training in your Human Factors Studies mimics training in the actual use scenario. Unless you intend for your future marketing plan to include that every patient and/or caregiver is trained by a Nurse Consultant from your company, you should perform an additional Human Factors study using a "train the trainer" model. Please be sure to use participants that are representative of the nurses and/or physicians who will be providing training to future patients on your device (i.e. ensure that emergency room nurses and inpatient nurses are included and not only cardiology nurses as were used as stated in Report-0128 (page 11 of 53), etc.).
        i. In Section 6.3.1 "Training Phase," (b) (4)



Please repeat your Human Factors testing with the appropriate trainers as described above (minimum 15 participants) while also ensuring that the training for "patient" and "caregiver" subjects mimics the actual use scenario for the training. The Agency recommends that you incorporate a minimum of 5 days for training decay.

ii. In your future Human Factors testing with properly trained users, it will also be important to ensure that they understand how to troubleshoot the device. For example, if a user needs to stop the pump early and does not know the proper procedure to end the infusion and retract the needle, the patient may be harmed with a needle stick which could lead to a serious infection. Since the training for your Human Factors studies did not mimic the actual use scenario with regards to the trainer and the training itself, the tasks tested in your post-summative protocol will also need to be re-tested. If patients do not understand if the device has been filled properly, fully emptied, as well as any pump errors that may occur, they may not be treated with the drug/device as prescribed by their physician, and this lack of knowledge may cause them harm if there is a significant delay to additional medical treatment. Please include this testing in your future Human Factors studies.

**b.** In Table 5 of Human Factors Report-0133, (b) (4)

(b) (4)

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis[ff] we reviewed the following Furoscix labels and labeling submitted by scPharmaceuticals, Inc. on August 23, 2017.

- Furoscix (b) (4) Container label
- (b) (4)
- Furoscix Cartridge Carton Labeling
- (b) (4)
- Prescribing Information (not shown)
- (b) (4)
- Instructions for Use (IFU) (not shown)

(b) (4)

### G.2 Label and Labeling Images

(b) (4)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

[ff] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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SARAH E THOMAS
05/16/2018

CHI-MING TU
05/16/2018

DANIELLE M HARRIS on behalf of QUYNHNHU T NGUYEN
05/16/2018

DANIELLE M HARRIS
05/16/2018