# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 209988Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118919

**MEETING MINUTES**

scPharmaceuticals, Inc.
Attention: Yverre Bobay
Senior Director, Regulatory Affairs
131 Hartwell Ave., Suite 215
Lexington, MA 02421

Dear Ms. Bobay:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SCP-101 furosemide injection solution.

We also refer to the meeting between representatives of your firm and the FDA on June 1, 2017. The purpose of the meeting was to obtain feedback from FDA on its planned application to support a 505(b)(2) NDA for a combination product.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,
*{See appended electronic signature page}*

Norman Stockbridge, Ph.D., M.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes and sponsor presentation

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

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| **Meeting Type:** | B |
| **Meeting Category:** | Pre-NDA |
| **Meeting Date and Time:** | June 1, 2017, 12:30-2:00 pm ET |
| **Meeting Location:** | White Oak Building 22, Conference Room: 1309 |
| **Application Number:** | 118919 |
| **Product Name:** | SCP-101 furosemide injection solution |
| **Indication:** | treatment of edema associated with CHF |
| **Sponsor Name:** | scPharmaceuticals, Inc. |
| **Meeting Chair:** | Norman Stockbridge, Ph.D., M.D. |
| **Meeting Recorder:** | Alexis Childers, RAC |

**FDA ATTENDEES**

| | |
|---|---|
| **Division of Cardiovascular and Renal Products* | |
| Norman Stockbridge, MD, PhD | Director |
| Michael Monteleone, MS, RAC | Associate Director for Labeling |
| Martin Rose, MD, JD | Clinical TL |
| Melanie Blank, MD | Clinical Reviewer |
| Albert DeFelice, PhD | Supervisory Pharmacology/Toxicology |
| Alexis Childers | Sr. Regulatory Health Project Manager |
| **Office of Clinical Pharmacology* | |
| Ju-Ping Lai, PhD | Clinical Pharmacology Reviewer |
| Sudharshan Hariharan, PhD | Clinical Pharmacology TL |
| **Office of Biostatistics, Division of Biometrics I* | |
| Jialu Zhang, Ph.D. | Statistician |
| **Office of Pharmaceutical Quality* | |
| Thomas Wong, PhD | Chemist |
| Om Anand, PhD | Biopharmaceutics |
| **Office of Surveillance and Epidemiology* | |
| Chi-Ming Tu, PharmD, BCPS | DMEPA Team Leader |
| Janine Stewart, PharmD | DMEPA Reviewer |
| Mona Patel, PharmD, RAC | Senior Risk Management Analyst (DRISK) |
| **Center for Devices and Radiological Health* | |
| Carolyn Dorgan | CDRH Team Leader and Device Reviewer |
| Steven Basile | Engineer |
| **Office of Combination Products, OC* | |

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|---|---|
| Bindi Nikhar, MD | Associate Clinical Director |

**SPONSOR ATTENDEES**
**scPharmaceuticals**

| | |
|---|---|
| John Tucker | CEO |
| John Mohr, PharmD | VP of Medical Affairs |
| Rene Myers, PhD VP, | Clinical Affairs |
| Javier Gonzalez-Zugasti, PhD | VP, Engineering |
| Yverre Bobay | Sr. Director, Regulatory Affairs |
| Lucy Johnston[1] | Project Manager |
| Troy Ignelzi[1] | CFO |
| Abe Ceesay[1] | COO |

(b) (4)

## 1.0 BACKGROUND

Furosemide is a diuretic approved for marketing in the USA for treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease. Currently, there are no approved furosemide products for subcutaneous administration. scPharmaceuticals is developing the Subcutaneous Furosemide Administration System (scFAS), which is is a drug-device combination product containing a single-use buffered furosemide injection for subcutaneous infusion via patch pump for the treatment of edema associated with heart failure.

scPharmaceuticals plans to submit a 505(b)(2) NDA application relying on Hospira's furosemide (NDA 18667). scPharmaceuticals has had 3 pre-IND meetings and a WRO with the Division to discuss the development plan, which currently includes a comparative pharmacokinetic study, a clinical validation study, and a human factors studies.

scPharmaceuticals requested this meeting in preparation for a 505(b)(2) NDA submission planned for this year.

FDA sent Preliminary Comments to scPharmaceuticals on May 30, 2017.

## 2.0 DISCUSSION

[1] Via teleconference

scPharmaceuticals started the meeting by providing context for the intended use of the pump. The purpose is to provide an alternative to IV and oral furosemide in three settings:

1. Patients admitted for acute decompensated heart failure (ADHF) who are inadequately diuresed and thus unable to be considered for discharge. The pump could expedite hospital discharge perhaps by 2-3 days. .
2. Patients with milder exacerbations of HF presenting to the ER who would receive IV furosemide, and be discharged with the pump for outpatient use.
3. Patients with chronic heart failure unresponsive to oral diuretics, in the outpatient setting for whom the pump could be used as an alternative to hospitalization or emergency care.

scPharmaceuticals explained that the product is not intended for use in patients with severe/ highly symptomatic pulmonary edema or for patients naïve to furosemide injection. Patients treated with the pump will be instructed to alert their clinician and/or seek emergency care if there is absence of expected diuresis and/or persistent or worsening symptoms. Therefore, in the case of pump failure, which scPharmaceuticals believes will happen occasionally, patients will know what to do and should not be harmed. The Division asked if the pump would be effective for the other edema indications for which furosemide is approved. scPharmaceuticals explained that the true intention of the pump was for heart failure but agreed that the pump would be appropriate to use in other edematous patient populations for whom furosemide is indicated, including patients with renal disease and cirrhosis.

### 2.1 Regulatory/Medical Questions

Question 1 Based on the information provided in this meeting information package, will the Agency confirm that the 505(b)(2) regulatory pathway remains appropriate for submission of the SCP-101/sc2Wear Infusor combination product NDA?

**FDA response:** A 505(b)(2) application appears acceptable, at this time, based on the available information.

**Discussion during meeting**: No further discussion.

Question 2 Does the Agency agree that the proposed bridging strategy is adequate to support reliance on the Agency's findings of safety and efficacy for the LD, based on the comparative pharmacokinetic data (scP-01-002)?

**FDA response:** Yes. Study scP-01-002 provides PK and PD data that bridges SCP-101 administered as SC infusion to the LD administered as an IV injection. While Study scP-01-002 used an FDA cleared pump which ensured accurate delivery of the dose in this study, the performance of your to-be-marketed infusion device will need to be adequately evaluated.

**Discussion during meeting**: See discussion under Q4.

Question 3 Does the Division still agree that the Hospira Furosemide Injection product (NDA 18667) is an appropriate LD for reliance on the Agency's previous findings of

safety and efficacy, based on the comparative bioavailability demonstrated in the pharmacokinetic scientific bridging study?

**FDA response:** Yes.

**Discussion during meeting**: No further discussion.

Question 4 Does the Agency agree that the B. Braun pump (b) (4) (b) (4) demonstrates similar performance to the proposed sc2Wear Infusor, to substantiate use of the provided comparative PK data as the scientific bridge for reliance on the Agency's previous findings of safety and efficacy of the LD, Furosemide Injection (NDA 18667) for the SCP-101/sc2Wear combination product?

**FDA response:** While the PK data from the study using the B. Braun pump may be used to bridge to the sc2Wear Infusor, there are significant differences in pump design, administration and technology, including the alarms, fluid pathway and mechanics between the two devices, such that the overall safety and efficacy of the sc2Wear Infusor cannot be inferred from the PK study that utilized the B. Braun pump.

**Discussion during meeting**: The Division asked why the sc2Wear Infusor pump was not used in the PK study and asked for an explanation why there was a trend for higher concentrations with the Infusor pump in the PDCV study vs the Braun pump used in Study scP-01-002. scPharmaceuticals explained that the proprietary Infusor pump was not ready at the time Study scP-01-002 was conducted. The Sponsor mentioned that they felt the need to conduct the relative BA study early in their development program to compare the PK and PD effects between s.c. and i.v. routes. Regarding the trend for higher concentration in the PDCV study with the Infusor pump (compared to the Braun pump), the Sponsor mentioned that these plasma concentrations were well within the clinical experience from the i.v. route such that there does not seem to be a safety concern. scPharmeceuticals asked if there is sufficient information in the briefing book or if another PK study would be needed. The Division stated that currently a PK bridging study does not need to be repeated with the Infusor pump, but the NDA should include a justification why a PK study does not need to be redone. While the current information appears to be adequate for filing, approvability will be a review issue.

Question 5 Does the Division agree that the annotated labeling content is complete, referencing appropriate information from Sponsor-conducted studies and information from the LD (Furosemide Injection, NDA 18667), upon which scPharmaceuticals plans to rely?

**FDA response:** Your proposed label is derived from the label for the listed drug upon which your proposed application relies. However if approved, the label for your product will need to conform the PLR Requirements for Prescribing Information. In your NDA submission, please submit a label with the Guidance Documents referenced in the Section below titled Prescribing Information. We encourage you to consider and support any additional revisions to labeling that may be appropriate based on the available literature and data.

**Discussion during meeting**: No further discussion.

Question 6 Does the Agency agree that the information included Sections 8.1 – (b) (4) f the draft annotated label, containing information from the approved label of the LD (Furosemide Injection, NDA 18667) and published literature, satisfies the requirements for the Pregnancy and Lactation Labeling Rule and no additional studies are required?

**FDA response:** We do not believe that additional clinical studies are required to support the requirement of the Pregnancy and Lactation Labeling Rule.

As noted below, your application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

**Discussion during meeting**: No further discussion.

Question 7 Does the Agency agree that, based on the information provided (regulatory history and planned elements of the NDA submission), the NDA submission would be considered acceptable for review?

**FDA response:** The content provided appears to be lacking several elements noted in the Infusion Pumps Total Life Cycle Guidance.

Within Appendix 5 -Table of Contents we were unable to locate the following requirement based on the Infusion Pumps Total Life Cycle Guidance:

- Engineering drawings (may be within device description)
- Environment of Use (may be within device description)
- Critical Performance Attributes (may be within device description)
- Alarms (may be within device description)
- Marketing Intent for the device (may be within device description)
- Safety Assurance Case
- Cybersecurity Plan (may be within the software documentation)
- Hazards Analysis documentation (FMEA, UFMEA, etc).
- Use Safety
- Mechanical Safety
- Shelf life
- Drug/biological product stability and compatibility

- Human Factors studies

The Safety Assurance Case should be provided as a standalone document with preferably active links to all referenced evidence (test reports, hazard analysis, etc).

A. Human Factors (HF):

Based on the information provided in the HF summary included in this meeting package, it is unclear where the product is with regard to its development program and also with regard to the human factors component. For a HF validation study that is designed to evaluate the intend-to-market commercial product, we typically expect the intend-to-market product be tested in the study.
Furthermore, you stated you plan to conduct a new HF validation study (Protocol-0074). However, meeting package p. 91 of 127 also stated this study is an "initiated HF study"; therefore, it is unclear if you have already started this new HF validation study. We recommend that you hold off on conducting your human factors validation testing until you adequately address the design-related failure issues discussed in our response to question 17 below. Please ensure your HF validation study is conducted with users that are representative of all intended users (e.g., Patients/Caregivers and HCP).

To ensure that your HF validation study methodology is acceptable, we strongly recommend that you submit the HF validation study protocol along with your use-related risk analysis for our review prior to conducting the study.

Please note that a 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 (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

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 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly.

The following items will facilitate an efficient review of your HF study protocol:

- A summary of preliminary analyses and evaluations, including formative studies;
  - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;
- Detailed HF validation study protocol to include the following elements:

- Description of intended product users, uses, use environments, and training (if applicable) for commercial product
- Graphical depiction and written description of product user interface
- Summary of known use problems with previous models or similar products
- User task selection, categorization (e.g., critical) and prioritization
- Validation testing details
    - Objective(s)
    - Type of testing (simulated or actual use)
    - Test environment and conditions of use
    - Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
    - Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
    - User tasks and use scenarios that will be studied
    - Description of data to be collected and methods for documenting observations and interview responses
    - Methods for root cause analysis of all use errors, difficulties, close calls
    - Definition of performance success and performance failure
    - Moderator transcript

- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
- Five intend-to-market samples of product that will be tested in the HF validation study

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

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

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

**Discussion during meeting**: See discussion under Q17.

Question 8 Does the Agency agree that the planned format and section organization for information pertaining to the sc2Wear Infusor is acceptable for NDA review?

**FDA response:** Please refer to the eCTD Technical Conformance Guide - Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" September, 2016: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf. In this guidance, Section 5 discusses Combination Products.

Specifically, regarding Device Engineering and Specifications - device-related material should be included in Module 3.2.P.7. Container Closure and referenced test reports and protocols can be located in Module 3.2.R. Additionally, a device specific reviewer's guide would be helpful provided in Module 1.2.

**Discussion during meeting**: No further discussion.

Question 9 Does the Agency agree that the AGREED iPSP for subcutaneous administration of the SCP-101 product with the sc2Wear Infusor is still acceptable and that the (b) (4) SCP-101 proposed indication does not trigger the requirements of PREA, based on the minimal formulation change for SCP-101 compared to the LD, Furosemide Injection (NDA 18667)?

**FDA response:** We are discussing this question with you as part of the iPSP process.

**Discussion during meeting**: No further discussion.

Question 10 Does the Agency agree that the format of the clinical study data provided in the Data Standardization Plan with the inclusion of the PD dataset and define file is acceptable for NDA submission and review?

**FDA response:** No. You will need to submit all safety and efficacy data for each clinical study, including imaging files. You should also submit CRFs for subjects who experienced SAEs and discontinued from the study for any reason.

**Discussion during meeting**: scPharmaceuticals stated they will comply with the requests in the preliminary responses and plan to hyperlink the images.

Question 11 Does the Agency agree that no ISE and ISS are required for the proposed SCP-101 product and that the Sponsor's plan for presenting the efficacy and safety data in Module 2 is sufficient for NDA submission and review?

**FDA response:** A review of the clinical safety and efficacy of the sc2Wear Infusor will be a review issue. You should include this analysis and supporting materials in Modules 2 and 5. Additionally, you should specifically identify all device related adverse events, including device malfunctions.

Further, you should include in the NDA submission an ISS that combines safety information derived from use of your product in the 3 studies you conducted, along with data from the control arms. You should provide separate analyses of safety findings from studies that included your product/placebo + sc2Wear Infusor and your product/placebo + Braun Infusor. In addition, the ISS should include a review of safety information from published literature regarding SC use of furosemide.

**Discussion during meeting**: scPharmaceuticals asked how the ISS should be submitted and if ISE needed to be submitted. The Division requested that the ISS should include overall safety, especially skin issues. The Division confirmed that an ISE is not needed.

Question 12 Does the Agency agree that the plan for providing FAERS database information is adequate for NDA submission and review?

**FDA response**: No, you not need to provide FAERS information because we do not believe the information will be useful in determining the safety of your product.

**Discussion during meeting**: No further discussion.

## 2.2. Clinical Pharmacology/Biopharmaceutics Questions

Question 13 Does the Agency agree that referencing the clinical pharmacology information in the approved LD labeling, in conjunction with studies conducted by scPharmaceuticals and published literature, is sufficient to support the clinical pharmacology section of scPharmaceuticals' proposed 505(b)(2) NDA, and that no additional clinical pharmacology or pharmacokinetics studies are required?

**FDA response:** Yes, we agree.

**Discussion during meeting**: No further discussion.

Question 14 Based on the justification provided, does the Agency agree that a biowaiver for scPharmaceuticals' SCP-101 (b) (4) s justified under 21 CFR 320.22(b)(1)(i-ii) and (e) and acceptable for NDA submission and review?

**FDA response:** The only proposed route of administration that can be supported by your current data is subcutaneous. You do not need to submit a biowaiver for routes that will not be described in labeling.

**Discussion during meeting**: No further discussion.

Question 15 Does the Agency agree that the comparable extent of furosemide systemic exposure following subcutaneous administration of SCP-101 compared to iv injection of the agreed LD (NDA 18667, Hospira), demonstrated in the Sponsor-conducted Study scP-01-002, establishes a scientific bridge to rely on the Agency's previous findings of safety and efficacy for the LD, Furosemide Injection (NDA 18667) in support of the NDA submission and review?

**FDA response:** Please see response to question 2.

**Discussion during meeting**: See discussion under Q4

**2.3. Clinical Questions**

Question 16 Does the Agency agree that the overall clinical program conducted by scPharmaceuticals with SCP-101 for subcutaneous administration (PDCV study and PK study) with the sc2Wear Infusor (PDCV study and human factors studies) is acceptable for NDA submission and review, and that no additional clinical studies are required?

**FDA response:** No. See specific comments under Questions 17 and 18.

**Discussion during meeting**: See discussion under Q17.

Question 17 Does the Agency agree that the data generated in the PDCV study is adequate to support the safe and effective use of the sc2Wear Infusor for subcutaneous administration of SCP-101 for NDA submission and review?

**FDA response:** While the type of data collected in the PDCV study appears adequate, the actual data do not appear to support approval. In particular, the study did not achieve its prespecified aim, which was demonstrating that ≥ 95% of products were free of major system failure. You report 63/67 or 94% (95% CI; 85% - 98%) of products were free of major system failure. Additionally, you report several device-related adverse events, including skin irritation, as well as device-related malfunctions and failures in the PDCV study, including device dislodgement, under delivery, unintended alarms and software issues. Finally, we are uncertain that device failures can be adequately mitigated by IFU changes alone.

**Discussion during meeting**: scPharmaceuticals acknowledged that the PDCV study did not meet specified performance goals. They provided an overview; see attached slides. A total of 74 subjects initiated treatment with 63 completing infusion within the specifications that allowed them to be counted in the primary outcomes measures. Problems that were encountered in the

study included self-reported alarms, patient discomfort, and undetected fill errors. All patients who completed treatment reportedly achieved adequate plasma furosemide levels. Software changes have been made to address issues seen in the PDCV study that resulted in noncompletion or incomplete dosing and bench testing has been conducted to replicate errors seen in the study. Based on the errors, scPharmaceuticals has improved graphics and updated the IFU (b) (4) (b) (4) A simulated study has been conducted. The frequency of undetected errors was 0% in the simulated study compared to 30% in the PDCV study.

To address the Agency's concerns about the PDCV study statistical "failure", the sponsor summarized that they have rectified the device malfunctions that resulted in noncompletion in 11 subjects, provided evidence that all "completers" received therapeutic levels of furosemide, and provided a rationale why device failures would not result in clinically significant adverse events. scPharmaceuticals asked if this information was sufficient to alleviate the Division's concerns. The Division stated the NDA should include an assessment of all data, including safety data as well as a clinical assessment of worst case scenario of pump failure resulting in inadequate delivery of furosemide, but the proposed package seemed capable of supporting a review.

The Division also requested that a high level safety assurance case (SAC) be submitted before the NDA submission. An initial SAC is rarely acceptable, and required revisions can delay review of the NDA.

Question 18 If the additional human factors study demonstrates acceptable use of the TBM equivalent combination product, does the Agency agree that the overall human factors studies conducted with the sc2Wear Infusor adequately support safe and effective use of the sc2Wear Infusor by the intended users in the intended use environments for NDA submission and review?

**FDA response:** As noted above in Response 17, we are concerned that device malfunctions and failures observed in the studies may not be adequately mitigated by simply changing the IFU and conducting additional Human Factor studies.

The following should be submitted at the time of NDA submission:

- A summary of preliminary analyses and evaluations, including formative studies;
  - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis
- An updated risk analysis for your product;
- Detailed HF validation study report. See Appendix A of Guidance *Applying Human Factors and Usability Engineering to Medical Devices,* available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf for a description of elements to include in the HF validation study report.

- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed)
- Five intend-to-market samples of product
- Summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the human factors validation study, including a description of how the changes were validated;
    - If changes to Instructions for Use (IFU) were made, a side-by-side comparison that points out the differences between the tested version and the intend-to-market version should be included

Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

**Discussion during meeting**: See discussion under Q17.

Question 19 Does the Agency agree that the clinical program conducted by scPharmaceuticals (PDCV study, human factors studies, and PK study) demonstrates safe and effective use of the SCP-101/sc2Wear Infusor combination product for all intended use environments, including home use, by both healthcare professionals and patients or caregivers to achieve a patient/caregiver home-use labeling claim?

**FDA response:** No, see FDA response to Q18.

**Discussion during meeting**: See discussion under Q17.

## 2.4. Nonclinical Questions

Question 20 Does the Agency agree that the proposed supporting nonclinical information provided in Section 7.4 is adequate for NDA submission and review, and that no additional nonclinical studies are required?

**FDA response:** The information provided is consistent with our previous discussions about nonclinical testing.

The nonclinical studies on local tolerance testing, and information on furosemide and the adhesive patch are adequate for the evaluation of subcutaneous patch infusion delivery of furosemide injection solution.

**Discussion during meeting**: No further discussion.

## 2.5. Chemistry, Manufacturing, and Controls Questions

Question 21 Does the Agency agree that the release and stability specifications for SCP-101 are acceptable for NDA acceptance for review?

**FDA response:** The test attributes for the release and stability specification appear appropriate. The actual acceptance criteria depend on the data. Provide justification for not testing the osmolality in the release specification (b) (4). We recommend the following revisions to the appearance test attribute and acceptance criteria:

Appearance - Solution
Acceptance criteria: Clear, colorless to slightly yellow solution. Free from visible particles in solution

Appearance – Container closure
Acceptance criteria: Free from visible defects – cracked glass and missing components

You did not provide release criteria for the device. You will need to include this information in your NDA.

**Discussion during meeting**: No further discussion.

Question 22 Does the Agency agree that the stability data for scPharmaceuticals' SCP-101 formulation is adequate for NDA acceptance for review?

**FDA response:** The stated amount of stability data and storage conditions appear adequate for the NDA filing. In order to evaluate the effects of the container closure on the drug product stability, we recommend storing stability samples in both the upright and inverted positions.

**Discussion during meeting**: No further discussion.

## 3.0 OTHER IMPORTANT INFORMATION

**Additional Device Comment**

You have not submitted a draft of the Safety Assurance Case for the sc2Wear Infusor. While the verification plan was previously submitted there are comments from prior Agency Feedback sent in February 2016 and August 2016 that you have not adequately addressed. The Agency recommends that you submit for our review responses to the outstanding comments and a draft of the Safety Assurance Case prior to submitting your NDA.

**Combination Product Comments:**

The furosemide formulation (SCP-101) for subcutaneous administration that is to be delivered via the sc2Wear Furosemide Infusor is a drug-device combination product per 21 CFR Part 3. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR Part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach.

If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in Part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR Part 4, see *Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products* (Jan. 2017), available at: http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm.

Information to include in NDA Form 356h: List the manufacturing facilities for the combination product and its constituent parts and identify what activities occur at each site (e.g., assembly, design, filling, sterilization, packaging) involving which constituents parts (e.g., drug only, device only, both drug and device). For facilities that have manufacturing activities for both drug and device constituent parts, you should identify which CGMP operating system is being used at the site for the combination product (streamlined or non-streamlined) and if it is a streamlined system, whether it is a drug-CGMP-based or QS-regulation-based system.

Information to include in your NDA Application: If you are using a drug-CGMP-based operating system, you must demonstrate compliance with the provisions from the QS regulation addressed below. Please provide the information indicated for each requirement unless you are otherwise informed by FDA. Please ensure that the information describes how your firm has applied each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and references to the types of protocols used by your firm for each activity. Using the eCTD format, this information should be provided in Section 3.2.P.3 (for further information, see sec. 5 of eCTD Technical Conformance Guide (Sept. 2016), available at https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

- **Management Responsibility (21 CFR 820.20)**

Provide a summary of how your firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4). Also, provide a description of the functions and responsibilities of each facility involved in the manufacturing of the combination product and its constituent parts.

- **Design Control, General (21 CFR 820.30)**

Explain how you utilized the design control process to develop the combination product under review and provide a description of your design control procedures. Please address how requirements for design and development planning, design input, design output, design review, design verification, design validation, design transfer, design changes, and design history file are being satisfied. Provide a copy or a summary of the plan used to design the combination product.

- **Purchasing Controls (21 CFR 820.50)**

Provide a summary of the procedure(s) for purchasing controls. The summary should:

a. Describe your supplier evaluation process and describe how it will determine the type and extent of control you will exercise over suppliers.
b. Explain how you maintain records of acceptable suppliers and how you address the purchasing data approval process.
c. Explain how you will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.

Explain how the procedure(s) will ensure that changes made by contractors/suppliers will not affect the final combination product. Provide a description of how you apply the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreements).

- **Corrective and Preventive Action (21 CFR 820.100)**

Summarize the procedure(s) for your corrective and preventive action (CAPA) system. The CAPA system should require:

a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
b. Investigation of nonconformities and their causes;
c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and
d. Verification or validation of the actions taken.

- **Installation (21 CFR 820.170) and Servicing (21 CFR 820.200)**

If installation and service requirements apply based on the type of device constituent part included in your combination product, the following information should be provided:
*Installation*. A summary of how your firm has established installation, inspection instructions, and test procedures for the installation of the combination product.
*Servicing*. A summary of how your firm established and maintains instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements for these activities.

## PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below.

The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

**PRESCRIBING INFORMATION**

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

## SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

## MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

**505(b)(2) REGULATORY PATHWAY**

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon

(see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

| **List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature** | |
|---|---|
| **Source of information (e.g., published literature, name of listed drug)** | **Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)** |
| *1. Example: Published literature* | *Nonclinical toxicology* |
| *2. Example: NDA XXXXXX "TRADENAME"* | *Previous finding of effectiveness for indication A* |
| *3. Example: NDA YYYYYY "TRADENAME"* | *Previous finding of safety for Carcinogenicity, labeling section B* |
| *4.* | |

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were

approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

**4.0 ISSUES REQUIRING FURTHER DISCUSSION**

None

**5.0 ACTION ITEMS**

None

**6.0 ATTACHMENTS AND HANDOUTS**

Slides entitled "Pre-NDA Meeting"

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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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NORMAN L STOCKBRIDGE
06/20/2017