CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

OTHER ACTION LETTERS

NDA 209988

COMPLETE RESPONSE

scPharmaceuticals Services, Inc
Attention: Eric Kendig, PhD
Director, Regulatory Strategy
c/o: Camargo Pharmaceuticals Services, LLC
9825 Kenwood Road, Suite 203
Cincinnati, OH 45242

Dear Dr. Kendig:

Please refer to your new drug application (NDA) dated August 23, 2017, received August 23, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Furoscix™ (b) (4) (Furosemide), 80 mg/10 mL, Drug-device combination product.

We acknowledge receipt of your amendment dated June 30, 2020, which constituted a complete response to our June 11, 2018, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

Device

1. In SN0040, Section 1.12.4, you state, "*scPharmaceuticals and West have subsequently* [(i.e. since NDA 209988 resubmission in SN0034)] *explored a further modification* (b) (4) *and a corresponding software parameter adjustment*." You have made significant changes to the design of your to-be-marketed device during this review cycle without the FDA's prior knowledge. It is our expectation that you submit your to-be-marketed device and all finalized documentation to support your device functions safely and effectively when responding to a Complete Response or submitting a new application. In addition, changing your device during the review cycle raises additional questions regarding its safety and efficacy and the relevance of all the presented documentation. Therefore, we cannot determine whether the information presented in the original submission supports the safety and effectiveness of the to be marketed design. In responding to this Complete Response (CR) Letter, please make sure all submitted information is representative of your to-be-marketed device. Any testing performed on a previous

version of your device should be clearly stated and the relevance of said testing should be justified. Please note that due to the device changes, additional deficiencies may be identified once the final device design is submitted.

2. You reference Master Access File (MAF) (b) (4) for significant documentation to support the device constituent of your combination product. There are outstanding deficiencies, which have been separately communicated to the MAF Holder. We recommend: a) you work with MAF Holder to ensure adequate resolution of the identified deficiencies, and b) resubmit your NDA only once the deficiencies are all resolved and adequate documentation is present in the MAF.

Biocompatibility

3. In report "device-rpt-0352", you stated that there are differences between the biocompatibility test article and the final finished product. (b) (4) (b) (4) (b) (4). To ensure the final finished device has particulate matters within acceptable range, please provide particulates testing per USP <788> method 1 light obscuration method on the final finished device.

4. In report "device-rpt-0351" titled Furoscix Drug Compatibility and Particulates with Smart Dose Fluid Path, you provided particulates testing for fluid path, and stated that the testing was conducted per USP <788>. However, it is not clear whether method 1 *Light Obscuration Particle Count Test* or method 2 *Microscopic Particle Count Test* from USP <788> was performed. For devices intended to deliver infusion drugs, we recommend particulates testing using USP <788> method 1 light obscuration method. Please clarify which method was used. If method 2 was used, please provide particulates testing per USP <788> method 1 light obscuration method.

5. In report "3.2.R 1 P 3 – Device Summary", Table 7 Test Plan and Results Summary, ISO (b) (4) was used to address adhesive patch cytotoxicity endpoint; however, in report "device-rpt-0352," you provided a summary of Cytotoxicity Study Using the ISO Direct Contact Method for adhesive patch. Please clarify which method is used to evaluate cytotoxicity endpoint for adhesive patch.
    a. Please (b) (4) (b) (4) (b) (4) justification for this method.

Chemical Characterization

6. You provided the leachable report in the "Leachables Screening of scPharmaceuticals Inc.'s Furoscix® (Furosemide) Injection in Contact with SmartDose® Gen II 10 mL Fluid Path Assembly" document. In the sample preparation, the drug product was delivered through the fluid path using (b) (4) (b) (4) However, it is unclear if the extraction occurred under clinically relevant conditions. The sample preparation should be performed under clinically relevant conditions to represent the use of the device. Please discuss and clarify if the sample preparation and test extract method is clinically relevant. Alternatively, provide new testing under clinically relevant conditions.

7. You provided the leachable report in the "Leachables Screening of scPharmaceuticals Inc.' s Furoscix® (Furosemide) Injection in Contact with SmartDose® Gen II 10 mL Fluid Path Assembly" document. In the GC/MS direct injection results, you reported spike recoveries. However, (b) (4) (b) (4), it is unclear how you will ensure that the semi-volatile and volatile compounds of the sample are detected. Provide a rationale justifying that the methods are appropriate for detecting semi-volatile and volatile compounds or provide new testing using appropriate methods.

Electrical Safety and Electromagnetic Compatibility

8. Your labeling does not contain adequate electrical safety and electromagnetic compatibility, as recommended in the IEC 60601-1 series. Please address the following:
    a. Label-0063-ifu states, "*Do not use the on-body infusor within 12 inches of mobile phones, computers or wireless accessories (for example: TV remote control, Bluetooth computer keyboard or mouse)*." However, this warning does not include sufficient EMC information. As is recommended by clause 5.2.1.1.f of IEC 60601-1-2:2014, please revise this warning to "WARNING: Portable RF communications equipment (including peripherals such as antenna cables and external antennas) should be used no closer than 30 cm (12 inches) to any part of the FUROSCIX On-Body Infusor. Otherwise, degradation of the performance of this equipment could result."
    b. Label-0063-ifu does not include essential performance information. As is recommended by clause 5.2.1.1.b of IEC 60601-1-2:2014, please include your device's essential performance information in your Instructions for Use.
    c. Your device includes a battery. However, label-0063-ifu, label-0068, label-0069, label-0072, and label-0073 do not contain battery information (i.e. battery specifications including the type, RATED voltage, and power), as is recommended per IEC 60601-1. Please provide the battery information (battery specifications including the type, RATED voltage, and power) in your labeling.

Labeling

9. We acknowledge your response in your SN0036 Section 1.11.1 response to IR #2c, d, e, 3f stating you will update your labeling. You have not; however, updated your labeling as requested. Your labeling needs to warn users against the hazards present in your system. Given the systemic issues in your submission, we recommend you revise your labeling and ensure that your labeling contains the following information, specifically, and follows the guidance in the listed FDA guidance documents:
    a. Electrical Safety Labeling/Symbols
    b. EMC Labeling/Symbols
    c. Software version
    d. Factors affecting accuracy
    e. Residual/hold-up volume
    f. Warnings/symbols regarding use in CT, ultrasound, and X-ray environments.
    g. *Design Considerations for Devices Intended for Home Use* from November 2014 (https://www.fda.gov/media/84830/download)
    h. *Infusion Pumps Total Product Life Cycle* from December 2014 (https://www.fda.gov/media/78369/download)

    Please provide the originally requested labeling updates sent on July 22, 2020 and ensure your labeling matches your proposed use-case.

10. In your SN0036 Section 1.11.1 response to IR #2a, you state, "*The Furoscix Infusor is intended to be applied to the patient in a clinic or a home setting and was validated in these environments.* (b) (4) (b) (4) You have provided insufficient evidence (b) (4) (b) (4) and your response to the IR #2a remains incomplete. Update your device's Instructions for Use (b) (4) (b) (4)

Human Factors

11. We note that you conducted a validation of adhesive effectiveness and local skin tolerability of the medical adhesive used to attach the on-body infusor to the patient, and that the study protocol lists the following exclusion criteria for the study participants [Clinical Protocol No. scP-00-003 - Appendix 16.1.1 Protocol and Protocol Amendments.pdf Section 4.2, page 24]:

    4.2. Exclusion Criteria -

    A Subject is not eligible for inclusion if any of the following criteria apply:

    1. *History of chronic skin conditions requiring medical therapy.*
    2. *History of allergy to medical adhesives.*
    3. *Received oral antihistamines (Benadryl, Allegra, Zyrtec, etc.) or systemic steroids (e.g. prednisone, dexamethasone, etc.) in past 7-days.*

4. *Used body lotions, oils or ointments on abdomen (adhesion area) within past 24 hours.*
5. *History of major abdominal surgery affecting the site of device placement.*
6. *Any local abdominal skin condition on the day of treatment i.e. sunburn, rash, eczema, etc.*
7. *Any surgical or medical condition which in the opinion of the Investigator may interfere with participation in the study or which may affect the outcome of the study.*

However, we note that your human factors/usability use-related risk analysis does not assess the risk of a patient applying the infusor if they have the characteristics listed in items 1 through 6 above. We further note that information about these characteristics does not appear in the proposed Instructions for Use (IFU) of your proposed subject device beyond the statement in Step 4: "Do not select a site where the skin is irritated or broken." This is important because a patient with these characteristics could experience skin injuries from the medical adhesive or that the device could fail to adhere to the skin over the time of treatment. Please submit an updated use-related risk analysis that assesses the risk to the patient of using the device if the patient has these characteristics. If you determine that the related tasks are critical tasks, please update the instructions for use with your proposed risk mitigations (e.g., contraindication statements, warnings), and submit supplemental human factors validation study data to demonstrate that the device can be used safely and effectively by the intended users for the intended use, or provide a justification for not conducting a supplemental human factors study. In addition, please add the appropriate contraindications to (b) (4) the Prescribing Information (PI) or provide a justification addressing why this information does not need to be provided to the intended prescribers of your proposed subject device.

12. 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 the HF validation study to be conducted with your to-be-marketed 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.

Software/Cybersecurity

13. We could not locate information regarding your alarms/errors in your Master File. The specific requests are communicated to the Master File Holder. As your device is a software medical controlled device, there remain items which you need to identify in your Safety Assurance Case to demonstrate you have adequately defined and verified your software. Please work with the Master file holder and update your Safety Assurance Case to contain the specific information the Master File is instructed to provide to you. This includes:
    a. Reliability specifications for your system level alarms/errors.
    b. Code coverage requirements for static testing in your reliability section.

Engineering/Performance/Risk Assessment

14. In your SN0036 Section 1.11.1 response to IR #2b, (b) (4) (b) (4) your justification for not requiring fluid ingress testing is not adequate for the following reasons:
    - You provide no evidence that your device design adequately mitigates against fluid ingress.
    - You refer to a component in your design (b) (4) which you have changed (See deficiency #1).

(b) (4)

- (b) (4)

Your device is an on-body infusion pump. There are several user-created routes of fluid and particulate ingress (e.g., washing hands following going to the bathroom). There are credible avenues for fluid and particulate ingress allowed because of your use-case. Furthermore, you have requirements for certain parts of your device to be protected from fluid/particulate ingress in order for the device to function safely and effectively. Provide ingress testing and labeling commensurate with your use-case.

15. Your response in SN0036 Section 1.11.1 to IR #4a is incomplete. You did not provide the trigger limits to your (b) (4) alarm function (b) (4) (b) (4)). As your response is incomplete, the original request remains. Please provide the trigger limits for all your alarms and ensure these are challenged at your boundary conditions through verification testing to ensure adequate function.

16. In your response in SN0036 Section 1.11.1 to IR #4b, you state, (b) (4) (b) (4) (b) (4). Please redesign your device to include error notification in a timely fashion so that a user does not unknowingly experience an underdose event for a significant period of time or provide scientifically (i.e., clinically) valid rationale for the selected (b) (4) error notification time.

Safety Assurance Case: Introduction

In SN0040 you declare a modification has been made to the device (See Deficiency #1). You have not updated your Safety Assurance Case (SAC) based on the modifications discussed. Therefore, your provided SAC contained in SN0034 device-ra0048 is considered irrelevant. A complete SAC is needed to demonstrate the device is safe for its intended use through (1) adequate verification and validation of design requirements, (2) adequate risk mitigations and (3) demonstration of adequate reliability. Therefore, provide a SAC containing all the elements described in the Agency Guidance Document “Infusion Pumps Total Product Life Cycle” (https://www.fda.gov/media/78369/download) for your to-be-marketed device and address the following high level structural deficiencies as well as those associated with each of the three sections of the safety assurance case:

Safety Assurance Case: Structural Deficiencies

17. All referenced evidence in the safety assurance case should be provided. You did not include references to all the evidence in your new safety assurance case. For example, citing MAF (b) (4) is an inadequate location for evidence. Citing a file

name is also inadequate, as you have continued to update your device and design; you should include the sequence and/or revision of the file with the file number as it is listed in your submission. Please provide complete reference information for your cited evidence in your SAC. We recommend you work with the MAF holder to gain all applicable reference document pointer information prior to submitting your updated SAC.

18. (b) (4) (b) (4). It remains unclear how you link your performed testing back to the hazards in your system. Your SAC does not trace clearly from your system-level requirements to the performed testing to mitigate hazards, and the specific hazard present. While we note you provide DD-0094 for Design Inputs/Outputs and Hazard and Risk Analyses in RA-0043 and RA-0047, it remains unclear how you trace between your requirements and your hazards to ensure that your testing as mitigated your identified hazards. Please provide a Design Verification and Validation Plan that details your sampling plan, sampling justifications, aging approach, and verification output methods (i.e., specific reports) which traces between the hazards present in your system and your performed testing of your to-be-marketed device.

19. Your SAC does not include justification for the adequacy of your specifications for your intended use. (b) (4) (b) (4) (b) (4) Define and justify the adequacy of all your design requirements with scientifically valid rationale. If you determine a consensus recognized standard can be used to demonstrate adequacy of your requirements, please see the recommendations in Adequate Verification and Validation of Design Requirements.

Safety Assurance Case: Adequate Verification and Validation of Design Requirements

20. You provide a list of standards in 3.2.R.1.P.3.2 and state that evidence of conformity is contained in individual test reports. However, you did not provide adequate evidence for conformance with FDA recognized standards. Please address the following deficiencies:

    a. (b) (4) (b) (4) When utilizing FDA recognized standards, you should follow the recommendations for documenting such conformance in the Agency Guidance, "*Appropriate Use of Voluntary Consensus Standards in Premarket Submission for Medical Devices: Guidance for Industry and Food and Drug Administration Staff*" (https://www.fda.gov/media/71983/download). For FDA recognized standards you intend to claim conformity, you will need to provide the

information in the listed guidance. Alternatively, you can independently demonstrate the acceptability of the methods for evaluating design requirements.

b. In 3.2.R.1.P.3.2 you state, (b) (4) (b) (4) (b) (4). All allowances should be clearly stated, and their adequacy justified. Please see the aforementioned guidance document "*Appropriate Use of Voluntary Consensus Standards in Premarket Submission for Medical Devices: Guidance for Industry and Food and Drug Administration Staff*," and clearly state all allowances taken for consensus recognized standards.

c. (b) (4) (b) (4). If you are using a standard which is not recognized for your device-type (i.e., an infusion pump), you should justify the adequacy of the standard for your use-case. Please justify the use of standards which are not recognized for your device type. Alternatively, you can independently demonstrate the acceptability of the methods for evaluating design requirements.

d. You discuss your device's design control process in 3.2.R.1.P.3.1. You do not mention the word 'regulatory' in this document. You should complete your device development activities prior to seeking regulatory approval. Specifically, you should receive regulatory approval before completion of (b) (4) and commercialization of your product. We remind you that it is our expectation that you submit your to-be-marketed device for regulatory review and we note you have continued to make changes to your device (Deficiency #1). Therefore, we believe your approach to device design control is inadequate. Revise your approach to design controls to ensure your design is 'frozen' before seeking initial regulatory approval. Only submit your device for regulatory review once you have determined the design which you intend to market.

21. You provide device-ddp0038 as your Verification and Validation Plan. However, this document is inadequate for several reasons which are detailed. Without an adequate and complete Verification and Validation Plan, we are uncertain of the relevance of the documentation you present to demonstrate your design requirements have been adequately verified and validated. In order of us to ensure your device is safe and effective, please revise your device design verification and validation plan and evidence to address the following:

    a. You point to files within MAF (b) (4) for significant evidence of your verification and validation activities. We note the Master File documentation refers to different risk and sampling documentation than your submission. We do not know which documentation drives your design, including your

requirements, system risks, and sample sizing. Please work with the Master File holder and present unified documentation which contains all the necessary information to understand your design intent and testing design approach.

b. Your Verification and Validation Plan lacks significant detail expected in this document. Please revise your plan or provide specific pointers to the location of the following documentation locations within your Verification and Validation Plan:

   i. Sampling Plan

   ii. Statistical Methods/Approaches

   iii. Aging Plan

   iv. Description of the samples used for testing. We note you have changed your device during the review cycle (Deficiency #1). We specifically request that you state for EACH report if the to-be-marketed device is used as test samples. If the samples differ from the to-be-marketed device in ANY manner (form, fit, function, etc.), you should explain this clearly and justify why the modification to the samples does not impact the results of the testing

c. We note there are reports in MA (b) (4) which you do not refer to and contain the information you need. For example, the information in MAF (b) (4) (b) (4) does not verify your device (b) (4) shelf life (b) (4). You refer to MAF (b) (4) (b) (4) but there is no Report 'x.' Please work with the Master File Holder and refer to the correct documentation evidence in your SAC to support your argument.

d. We are unable to locate evidence which you refer to in device-ddp0038 (Verification and Validation Plan). For example, we are unable to locate Report-0332: This document is not referred to in your Reviewer Guide. We are unable to review evidence if we cannot locate the referenced information. Please ensure all necessary evidence is contained in your submission.

e. The evidence you are using to support the safety and efficacy of your device is known to have changed (Deficiency #1). For example, scP-00-004 in SN0040 is not referenced by device-rpt-0360. Provide a revised Verification and Validation Summary and SAC which references the current applicable documentation, including report revision, so we are certain of the evidence you are using to demonstrate your device is safe and effective.

f. You state several requirements do not require validation. We disagree this this assessment. You need to demonstrate that your device performs as designed (i.e., verification) and the design is adequate for your intended use (i.e., validation). Design Validation is part of 21 CFR 820.30 which is

required for combination products. Please provide validation evidence or an explanation of adequacy for the following requirements:

(b) (4)

g. You do not provide evidence for all the expected Essential Performance Requirements for an Infusion Pump, such as Flow Rate Accuracy. Without defining, verifying, and validating the requirements for your device, we are uncertain how you have determined your device is adequate for your intended use. Please identify all essential performance requirements and provide corresponding evidence to support the verification and validation for each requirement.

h. The data you provide to demonstrate your requirements are met are inadequate. These data are principally contained in the referenced MAF (b) (4) Please work with the Master File Holder to resolve the deficiencies in the Master File documentation.

22. In summary, to support the adequate verification of your design requirements, you should provide evidence in the form of test reports which contain clear objectives and quantitative scientific evidence that your design functions to its specification. The test reports you cited lacked all the elements described in the FDA Guidance Document "*Recommended Content and Format of Non-Clinical Bench Performance Testing Information in Premarket Submissions*" (https://www.fda.gov/media/113230/download) from December 2019. Therefore, please provide test reports which contain clearly defined, objectives, acceptance criteria (including sample sizing based on the associated risks with statistically valid rationale), verifiable objective evidence, analysis, and conclusions so that we can determine whether the evidence supports the device meets the specifications. Please be aware it remains our expectation that you demonstrate your device functions at its labeled boundary conditions. Please provide design verification which evaluates all design requirements at the appropriate boundary conditions of use and demonstrate that your requirements are adequate for your intended use.

Safety Assurance Case: Adequate Risk Mitigations

23. Your SAC should be driven by the risks in your system, as properly acknowledging and addressing the risks associated with your device is essential to understanding your design methodology and verification activities. Your SAC lacks clear tracing between risks and mitigations. Please update your SAC to include proper reference to your risk documentation. Determination of the acceptability of your risk mitigations is contingent upon successful testing. Please see our comments regarding verification and validation evidence and on your risk documentation.

24. You define your severity ratings in SOP-0034. (b) (4) (b) (4) (b) (4). Please provide adequate mitigations for all severities rated (b) (4) OR revise your definitions of severity rating (b) (4) based on the need to require medical intervention. If you choose to revise your severity ratings, please ensure your severity assignments are adequate and relate to the risks associated with the stated hazard. Additionally, ensure that your hazard assignments and sampling approaches align to the methods used by the Master File Holder.

25. Your Hazard and Risk Analyses contained in RA-0043 and device-ra0047 and RCM analysis in device-ra0049 does not clearly illustrate how you mitigate each of your risks. Please update your Hazard Analysis and other referenced risk documentation to specifically illustrate how you mitigate the known risks in your system and ensure that this argument is included in your safety assurance case.

    In addition to the overall strategy of the document needing clarification and update, please address the following specifically:

    a. (b) (4)

       Provide mitigations to all hazards requiring medical intervention.

    b. Your hazards do not clearly align to the stated risks. (b) (4) (b) (4) (b) (4) Please update your risk documentation to ensure your hazards and risks align.

    c. There are several hazards which do not align to your device design. We believe these are related to a previous version of your device. Please update your hazard analysis to be specific to your device design. This includes the risks associated with charge errors, AC supply errors, battery

over/under charge, key de-bounce prevention, alarm priority being set incorrectly, incorrect drug library loaded, inadequate device cleaning.

d. We recommend that all hazards, including software only related hazards, are classified by severity [redacted] For software specifically, it is not possible to predict [redacted] software only hazards. You may use a probability of harm if the software hazard occurs.

Safety Assurance Case: Demonstration of Adequate Reliability

26. You have changed your device during this review cycle. Therefore, your provided reliability argument should be revised to be specific to your to-be-marketed device and your proposed use case. The relevance of your documentation is unknown. Please provide updated reliability documentation to support the reliability of the to be marketed device.

27. While we acknowledge your submission of device-memo-0079 Rev 02 containing your reliability analysis, this document does not appear to be governed by a reliability protocol to define your testing. In addition, there are issues with the identified MAF reports in this memo which are communicated to the MAF holder. Your reliability analysis should clearly illustrate, based on prospective testing and analysis, how you achieve the reliability requirements commensurate with your system hazards. Please define a reliability requirement and provide an evidence-based argument for your to-be-marketed device to demonstrate the device's ability to meet this requirement.

28. We note you do not link your reliability argument to the clinical risks associated with your device. [redacted] Your device is outside the FDA recognized scope [redacted] Please see our recommendations under Adequate Verification and Validation of Design Requirements and ensure that your reliability arguments align to the clinical use-case of your device.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances. Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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 in the PI on 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.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[5]

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[1] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

Please refer to correspondence dated, September 9, 2020, which addresses the proposed proprietary name, Furoscix. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

FACILITY INSPECTIONS

Facilities Not Found Acceptable
During a recent inspection of the (b) (4) manufacturing facility for this application (b) (4) our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Comments about Facility Inspection Not Completed Due to Travel Restrictions:

1. An inspection of the Sharp Corporation (FEI # 3004161147, Allentown, PA) facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID-19. These guidances can be found at: https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

2. An inspection of (b) (4) facility is required before this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to conduct an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are

assessed. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors. For more information, please see the FDA guidances related to COVID-19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. We have provided comments below and recommend that you implement them prior to resubmission of this NDA.

Identified Issues and Recommendations			
	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 (b) (4) 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. (b) (4)	(b) (4)	

	[redacted] (b) (4) We acknowledge that you have revised [redacted] (b) (4) to minimize confusion. However, we have identified additional labeling mitigations to address this error.		
3.	Your IFU can be improved to better illustrate one infusor is to be applied per dose. [redacted] (b) (4)	We are concerned that users may misinterpret the shapes used [redacted] (b) (4)	Revise [redacted] (b) (4)

PREA

We have completed our review of your revised Pediatric Study Plan (PSP) submitted August 22, 2019 and agree with your proposal. We have no further comments at this time.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting,

submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
12/03/2020 02:43:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209988

COMPLETE RESPONSE

scPharmaceuticals, Inc.
Attention: Sanjay Sehgal, PhD
Senior Vice President
Regulatory Affairs, QA & Compliance
2400 District Ave, Suite 310
Burlington, MA 01803

Dear Dr. Sehgal:

Please refer to your New Drug Application (NDA) dated and received August 23, 2017, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Furoscix™ (b) (4) Furosemide), 80 mg/10 mL, Drug-device combination product.

We have completed our review of this application and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CDRH/DEVICE

1. As part of the device description, we were unable to locate the following alarms consistent with the FDA Guidance, Infusion Pumps Total Product Life Cycle within your submission for the Furoscix Infusor:
   - Occlusion detection alarm
   - Low or empty reservoir alarm
   - Undocking alarm
   - Key pressed alarm
   - Tone test failure alarm

   The Agency believes these alarms are critical to the safe operation of the device. Make appropriate changes to the device, provide a justification for why these alarms are not necessary, or provide alternative mitigations.

2. In the study, CP-00001 Product Design Clinical Validation, you defined the volume accuracy endpoint as "Delivery 80mg ±10% = minimal 9mL dispensed from device." This is inconsistent with the device specifications which state dose accuracy as volume to be delivered: (b) (4). Therefore, according to the device specifications the delivery volume should be between (b) (4) mL. It is unclear how dose

accuracy was measured in this pivotal study. Since dose accuracy is a critical endpoint this discrepancy needs to be resolved. Please describe how you measured dose accuracy in the study and how the study validates the design specifications for the device.

3. According to the results from the CP-00001, Product Design Clinical Validation study you did not meet the predefined endpoints. Please address how the improvements since the study was completed result in a device that can meet the pre-defined endpoints for this particular study and provide evidence to validate that these changes are likely to address the errors or provide a new clinical validation study. (Please see the Clinical comments for additional information regarding study CP-00001).

4. You provided several documents outlining the Risk Management process for the Furoscix Infusor in Sequence 0001/3.2R. The risk assessment criteria and risk acceptability as outlined in RA-0002, scPharmaceuticals Risk Management Plan, Appendix I, defines the severity, occurrence and detection ratings in accordance with ISO 14971. Additionally, you have defined the risk threshold for the intended use of the Furoscix Infusor on p.7-8 as:

(b) (4)

The resulting risk and hazard analyses do not follow the definitions as defined in RA-0002.pdf. From a high-level perspective, the Agency disagrees with the severity ratings assigned in the Use Error Analysis (DD-0001.pdf), scPharmaceuticals Risk Management Report (RA-0023.pdf), scFAS Risk Analysis Report (RA-0010.pdf) and scPharmaceuticals Hazard Analysis (RA-0007.pdf) to the hazards of underdosing, infection and over-diuresis for the following reasons:

   a. Hazard – Underdosing: Device failures resulting in underdosing, especially undetected, can lead to decompensation in patients with congestive heart failure which requires medical intervention or hospitalization. Revise your risk analysis document to make all hazards with harm of underdosing, a severity of 4.
   b. Hazard – Infection: Harm causing local or systemic infection in patients with congestive heart failure requires medical intervention. Revise your risk analysis document to make all hazards with harm of infection, a severity of 4.
   c. Hazard – Over-Diuresis: Over-Diuresis in patients with congestive heart failure can lead to electrolyte imbalances which require hospitalization to stabilize. Revise your risk analysis document to make all hazards with harm of over-diuresis a severity of 4.

You will need to update your risk management documentation to reflect these new severity ratings and then recalculate the Risk Level (Risk Analysis and FMEA) and Risk Priority Numbers (Process FMEA and Design FMEA). Based on the revised risk

analysis you will need to update your design verification/validation documents, Human Factors documentation (See Human Factors section, request for updated use-related risk analysis) and Risk Analysis documents (including the Safety Assurance case) to reflect the new evaluation of the risk for each hazard. You should use these new evaluations to drive the mitigation measures as appropriate for each hazard.

Revise your risk documentation to reflect the new severity ratings including any new mitigations that are resulting from the higher risk categorization. Provide evidence to support the new mitigations including any additional testing to support design or labeling changes.

5. When revisiting the risk analysis, the Agency has the following comments that need to be addressed for specific aspects of the submission including the risk management, design verification/validation and human factors sections (See Human Factors section, request for updated use-related risk analysis).
   a. (b) (4) (b) (4) You will need to update you risk documentation to use consistent definitions of limited, moderate, severe and catastrophic health hazards.
   b. You have provided multiple severity ratings for individual hazards. Each hazard should have a single severity rating. You will need to revise the risk documentation to be consistent in defining the severity rating for each hazard.
   c. In the Use Error Analysis (which we refer to as the use-related risk analysis), we note a discrepancy, please refer to Human Factors section, request for updated use-related risk analysis.

6. In your safety assurance case, you have not provided evidence to support the following claims:
   - (b) (4)
   -

- (b) (4)

Without evidence to support the claims, the safety assurance case is incomplete and does not support the top level goal of safety. Therefore you will need to provide arguments supported by evidence for all claims in the safety assurance case.

7. In your safety assurance case under the risk mitigations for under-dosing (S#10375) you have not considered any use errors or environmental factors which may contribute to an under-dosing event. Therefore, the safety assurance case is not complete. You will need to update your assurance case and any supporting evidence to consider environmental factors and user errors which might contribute to under dosing.

8. Because of the deficient reports, the evidence does not support that acceptable mitigations have been implemented and verified to support the top-level goal of safety. Therefore, the deficient reports will need to be resolved before the safety assurance case can be deemed complete and acceptable.

9. You provided several reports to support the verification and validation of the performance criteria of your device. However, the Agency identified several deficiencies in the reports. You will need to resolve the following deficiencies associated with the reports:
   a. Report-0154 – (b) (4)
      i. All test reports should have clearly stated objectives, acceptance criteria, methods, results (including raw data) and a conclusion that states how the results met the user requirement. Report-0154 does not contain this information and it is not clear which requirements are being supported by this report. For that reason, the report is deficient. Provide a test report (b) (4) that provides all the required elements to support design verification.
      ii. Report-0154, (b) (4) was performed with an earlier version of the software. Provide a justification for why the updates to the software since the testing do not impact the results of the verification testing or repeat the testing with the current version of the software.
   b. Report-0167 – (b) (4); Report-0173 – (b) (4); Report-0170 – (b) (4); Report-0172 – (b) (4); Report-0186 – (b) (4)

i. Reports -0167, -0170, -0172, -0173 and -0186 are audits of the actual verification tests. While you state the tests were conducted and passed, you do not provide the specific test methods, specifications, or results. Therefore, the Agency cannot determine whether the reports support the user requirements. Provide a test report that contains the objective, acceptance criteria, methods, results (including raw data) and a conclusion that states how each test satisfies the user requirements.

c. Report-0178 – UL Test Report (IEC 60601-1) Medical electrical equipment
   i. It is unclear what system-level performance verification was performed to verify the system-level performance requirements at the intended environmental conditions and at reasonable challenged environmental conditions. It is unclear how this report supports the user requirements. Provide a test report that explicitly states the objective, acceptance criteria, methods, results (including raw data) and a conclusion that states how the test satisfies the user requirements.

d. Report-0185 – (b) (4)
   i. In Report-0185, (b) (4), did not provide the scope/objective or methods. It is not clear which requirements are being supported by this report. Provide a test report that contains the objective, acceptance criteria, methods, results (including raw data) and a conclusion that states how each test satisfies the user requirements.
   ii. This testing was performed with an earlier version of the software. Provide a justification for why the updates to the software since the testing do not impact the results of the verification testing or repeat the testing with the current version of the software.
   iii. Per the sample size requirements in Report-0185 more than 30 samples are needed to establish a 95/95 confidence interval for the acceptance criteria. Provide a justification for why only 30 samples were used or repeat the testing with a sample size large enough to establish a 95/95 confidence interval as described in the acceptance criteria.

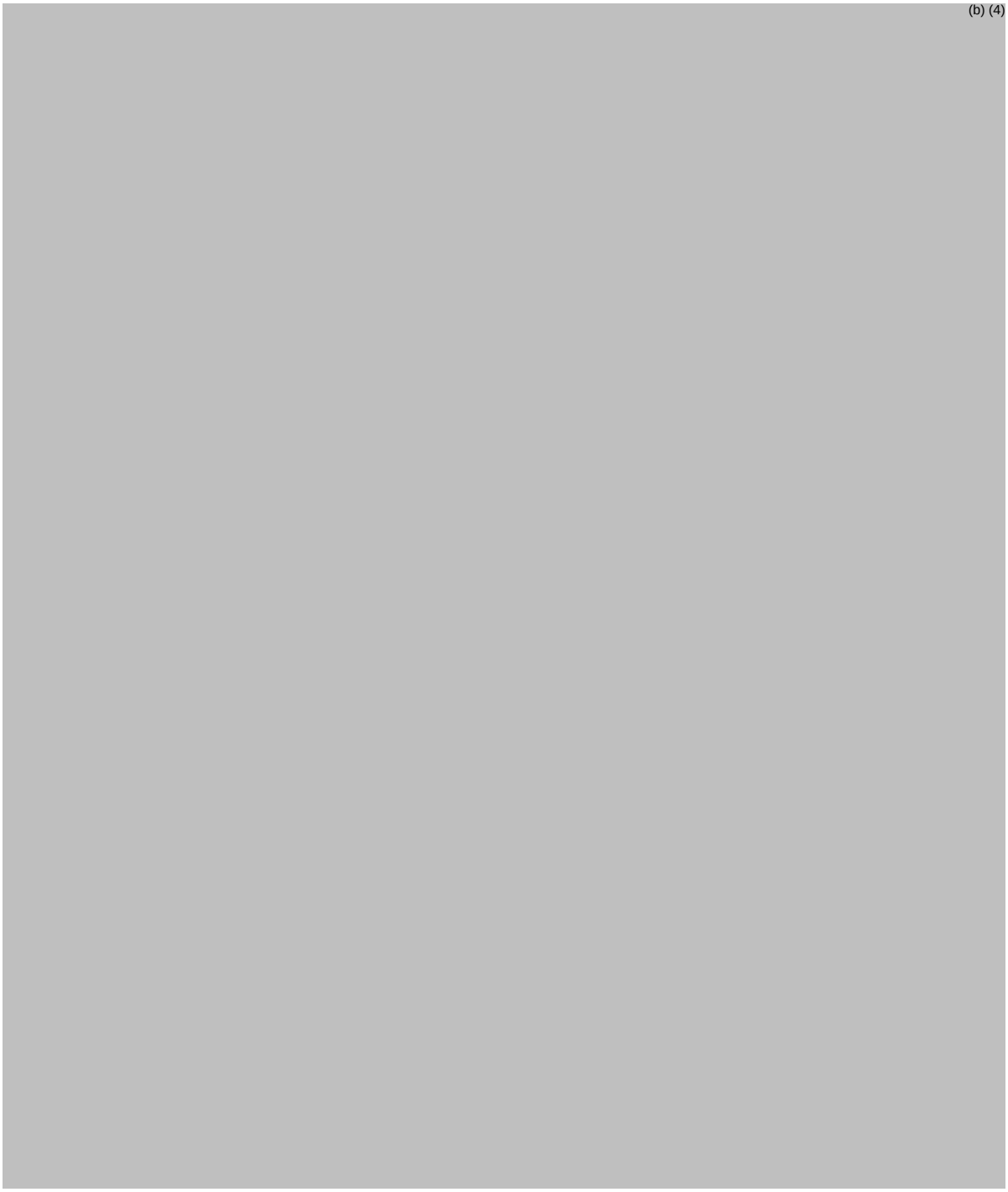
e. Report-0190 – (b) (4)
   i. Within Report-0190, (b) (4), you have not provided evidence that the device can continue to perform essential functions (b) (4) (b) (4). You will need to provide evidence (b) (4) (b) (4).

f. Report-0151 Summative Human Factors Report
   i. This report is insufficient (See Human Factors section). You will need to provide validation of the design requirements. This may require resolution of the deficiencies associated with the Human Factors Summative Report, additional testing, or new methods for validation.

10. You provided scP-00-02 Adhesion Study as validation for the effectiveness of the adhesive for your device. However, the study design was not designed to validate the adhesive, (b) (4) (b) (4). You did not define the requirements and specifications (b) (4). You did not provide evidence to verify the device meets the specifications or validate the

requirements. The adhesive is part of the essential performance for the device and therefore should be defined, verified and validated. You will need to develop design controls and corresponding evidence for the adhesive.

11 (b) (4)



12 (b) (4)

(b) (4)

(b) (4) Address the following deficiencies:

a. Provide your justification and/or testing (b) (4)

b. (b) (4)

c. Because a software alarm is used to prevent a hazard we deem to have a severity of 3, you need to make the additional revisions to your document, (b) (4) (b) (4).

   i. For the hazards associated with this alarm not triggering due to a software defect or the audio or visual components of this alarm fail to trigger, change the severity to a 4 and reassess if your risk mitigation strategy is appropriate for these hazards. If not, provide the revised SRS, SDS, risk and verification documentation.

Page 65 discusses your justification for classifying your software as Safety Class (b) (4) per IEC 62304. Since we consider the alarm (b) (4) an alarm that could prevent potential death or serious injury, change your classification to Safety Class C. With this change, describe the additional measures you need to take to comply with Safety Class C and provide the evidence.

13. (b) (4)

a. It does not appear you provided a software design specification document. (b) (4) document, (b) (4) does not provide any traces from the SRS requirements to the SDS requirement. Provide an SDS specification document and revise your trace document to trace the SRS requirements to their SDS documents.
b. For any SRS that defines internal checking performed by your software outside of the POST testing, include the frequency at which this testing is performed. This frequency is not defined in your SRS requirements. This should include how often device status messages are relayed to the module that monitors it (i.e. battery level checking, etc.).
c. The following SRS requirements define errors but you did not define how they are triggered (voltage values, etc.). In the SRS requirement provide how the error triggers including a boundary range if applicable (b) (4) (b) (4)

(b) (4)
(b) (4) Note: some of these requirements reference the ELDD (Electronic Design Description) but this document does not appear to have been provided. It is preferred if you provide these values directly in the SRS requirement.

d. It is not clear what software modules are included in some of your POST testing. Describe where in the software architecture, the error code mechanisms in SRSs: (b) (4) and (b) (4) look for faults. Indicate if there are any software units these mechanisms do not test and justify why they do not.
e. It is not clear from your requirements how the pump checks to determine if its system time is correct and is not affected by a software defect or data corruption. Since your five-hour delivery profile has two phases, a defect to the system time can affect the length of each phase thus causing potential over- or under-delivery. Provide the SRS and SDS specifications that describe how your pump ensures the integrity of its time data and if there are any errors that triggered if this information is corrupted. If you do not have an error code for this situation, devise and provide the SRS, SDS, risk and verification documentation.
f. There are no requirements for the maximum load (data usage and error messages) the memory can handle or how the system may purge information so this maximum load is not met. Correct this deficiency by 1) explaining how the data generated from 100 use cycles cannot affect the memory of the system or 2) providing the SRS requirements defining maximum load and/or purge, and the verification testing, and stress testing to verify these requirements.

The FDA guidance document, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued on May 11, 2005, recommends a SDS document be provided for software with a Major Level of Concern, and the traceability document to trace the SRS to the SDS.
https://www.fda.gov/RegulatoryInformation/Guidances/ucm089543.htm

The FDA guidance document, General Principles of Software Validation, issued on January 11, 2002, recommends SRS and SDS requirements are complete.
https://www.fda.gov/MedicalDevices/ucm085281.htm

14. Your document, (b) (4) , you describe two unresolved defects #325 and #368. Provide the following additional information for these defects:
    a. Is defect #325 and #368 the only unresolved defects you have (b) (4) (b) (4) ? If not, provide a list of all unresolved defects with adequate description of the problem and impact of the defect.
    b. Defect #325 (b) (4) Explain (b) (4) how this defect can impact delivery (b) (4) .

c. Defect #368, [redacted] (b) (4)

Your description of the impact is inadequate because you did not provide enough detail on the problem to determine if your occurrence rate is correct. Provide answers to the following questions:

i. [redacted] (b) (4)

ii.

iii.

If this is a software defect, then you need to correct this issue before releasing to the market because you cannot predict software defect occurrence rates regardless of how much testing you perform. IEC 62304 recommends performing software risk analysis based on severity alone because if there is a defect it will always present when you understand the actual user actions that causes the defect. Answer our questions above to determine if it is a software defect [redacted] (b) (4). If it is a software defect, correct it and provide the verification to show it was adequately corrected and the correction did not inadvertently affect your device.

The FDA guidance document, Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices, issued on May 11, 2005, recommends unresolved software defects be explain with adequate detail.
https://www.fda.gov/RegulatoryInformation/Guidances/ucm089543.htm

15. Your document, Software Unit and Integration Test Plan, Project SCIP, Version 1.0, states [redacted] (b) (4) tests must reach statement coverage goals only. The test goal in percent will be defined in each code review. Correct the following omissions:
    a. We could not find your statement coverage goals in the documentation you provided. Provide your statement coverage goals.
    b. Your Software Unit and Integration Test Plan does not provide any detail how you will perform white-box testing outside of code coverage. Please describes your white-box testing strategy including what programs you use to perform your static analysis.

    The FDA guidance document, General Principles of Software Validation, issued on January 11, 2002, recommends unit testing is performed per a protocol with adequate description including the code coverage.
    https://www.fda.gov/MedicalDevices/ucm085281.htm

16. You have provided cytotoxicity testing on the "scFAS (sub-cutaneous Furosemide Administration System) Cartridge", [redacted] (b) (4) (b) (4)

a. Please clarify if the adhesive was the only component included in this testing, or if other components were included. If other components were included, please clarify the components included in this test.
b. Please provide a rationale for why the cytotoxic component(s) will not result in an adverse biological response or expose the patient to toxic compounds. This rationale should include an identification of the cause of the cytotoxicity.
c. If the adhesive has been used in a previously cleared device or approved combination product (with no modifications to manufacturing/processing and similar intended use/duration of contact), please provide the submission number or masterfile (with letter of authorization).

17. You have provided cytotoxicity testing on the "scFAS (subcutaneous Furosemide Administration System), Skin-Contacting Components", (b) (4) (device-rpt-0039).
    a. (b) (4)
    In order (b) (4) to support the biocompatibility of a component:
        i. Please provide a justification (b) (4) Additionally, please include a description of the manufacturing process, including any manufacturing/processing agents in your rationale. Please also include the amount of the compounds to which the patient will be exposed (i.e., the formulation).
        ii. (b) (4)
        Please provide clarification on the test article preparation (b) (4) (b) (4).

18. Under section 1.7.2. in RA-0016; revision 02, you state that (b) (4) " You have provided a comparison of the extractable/leachable chemicals from the to-be marketed pump and the original version of the pump included in the biocompatibility studies. This information can be used to evaluate if there is an increased toxicological risk for systemic endpoints; however, you have not provided an evaluation of how any new compounds or increased amounts of compounds

would impact the following endpoints: cytotoxicity, irritation, sensitization, hemolysis, and pyrogenicity. Provide a discussion on why each new compounds or compounds with increased amounts would not impact the biocompatibility of the device, for each of the following endpoints: cytotoxicity, irritation, sensitization, hemolysis, and pyrogenicity.

19. The test reports identified the test article name as 1) scFAS (sub-cutaneous Furosemide Administration System) Cartridge; 2) scFAS (sub-cutaneous Furosemide Administration System) Cartridge and Vial Adapter; or 3) sc2Wear Cartridge Fluid Path with (b) (4) Pump. (b) (4) (b) (4). Please update the Table 15- summary of Biocompatibility and Toxicology Studies Conducted (located in SN 0001, 3.2.R.1.P.3 – Device Summary) to include a list of the components included in each test. (b) (4) (b) (4)

20. You have included two test reports for a number of endpoints both of which appear to be conducted on the fluid path of the device. (b) (4) (b) (4)

    a. For each of the endpoints, please clarify which test was conducted on the fluid path on the final, finished, to-be marketed device.
    b. Please confirm that all fluid path components were included (including the needle) and clarify if any skin-contacting components were included.
    c. Please clarify the difference between the test articles in the two reports.

    Additionally, there are endpoints that are supported by only one test report (b) (4), (b) (4) (b) (4). Please clarify that these tests were performed on the fluid path on the final, finished, to-be marketed device.

21. You have not included an evaluation of the particulates that are present within the device fluid-contacting components of the device. Particulates within the device fluid path will be transferred to the drug; therefore, the Agency recommends that the particulate size and amount are in line with the USP <788> . Per the guidance, "*Infusion Pumps Total Product Life Cycle*", for device related particulate evaluation, you should follow current USP <788> Particulate Matter in Injections Please perform an evaluation of the particulates of the fluid path according to USP <788> particulate matter in injections (Method 1).

22. You have provided a list of the components and materials used in the cartridge (Table 3; (located in SN 0001, 3.2.R.1.P.3 – Device Summary). However, the Agency recommends

that you include the following information for each of the patient contacting components (indirect and direct contacting): Material class (e.g., "polypropylene," "high density polypropylene – HDPE"); General material characteristic (e.g., "thermostable plastic", "cross linking agent"); Material supplier; and Trade name or common name. You have not included the Material class; General material characteristic; and Material supplier within the list of materials/components. Please provide the above information on the patient contacting materials. This list of materials should include any colorants or additives, used in the construction of the proposed device.

DRUG PRODUCT QUALITY

23. The container closure integrity validation results using the microbial ingress method and the dye ingress method provided in section 3.2.P.2.5 micro-attributes and 3.2.R device-rpt-0147, respectively, are acknowledged. It is noted that acceptable results from only one method are needed to validate the integrity of the proposed container closure systems. Please address the following:
    a. Provide the result of microbial ingress test (b) (4) (b) (4).
    b. Provide the following information for the dye ingress test: 1) description of any positive and negative controls and the actual results of the controls; 2) description of the result readout method; 3) limit of detection. Please note that the dye ingress test should be shown to be capable of detecting ingression of a small amount of liquid (b) (4).

24. You commit to establish the specification for (b) (4) bioburden; however, this specification is necessary for review of your application. Provide the specification for (b) (4) bioburden, noting that our recommended (b) (4) bioburden limit is NMT (b) (4) cfu/mL. Refer to (b) (4) (b) (4) guidance on (b) (4) bioburden.

CLINICAL

25. The Furoscix Infusor Product Design Clinical Validation Study (PDCV), Study CP-00001 did not meet its primary endpoint, "Absence of Major Product Failure." Success for this endpoint was based on a success rate for "freedom from major system related failures leading to under-infusion." The trial was to be deemed successful if the lower limit of the 95% confidence interval of the success rate was ≥95%. Even when the 7 patients who did not complete the 5-hour infusion period are excluded, the success rate was 63 of 67, or 94%.

    Of the 4 device failures among the 67 completers, 3 were dispensing failures related to inadequate preparation of the device coupled with a device design flaw. In each of these cases, (b) (4) the device failed to

alert [redacted]. The other dispensing failure resulted from [redacted] No alarm indicated this failure, either. You should re-engineer your device to include an alarm [redacted].

26. In CP-00001, the devices were prepared, attached to the patient and then removed at the end of the 5-hour treatment period by trained study staff. We think it is likely that if patients or lay caregivers had been given responsibility for these tasks in CP-00001, the failure rate in the study might have been higher than it was. Thus, the results from study CP-00001 may overstate the reliability of the studied device. However, we believe that if this product is approved, it will not be uncommon for patients or lay caregivers to set up, attach, and remove the device. Accordingly, if you conduct another study to validate the performance of a re-engineered version of your device, you should require only suitably trained patients or lay care-givers to set up, attach, and remove the device. If the training is performed using a video presentation, the video should be a component of the proposed labeling. The study should include persons with a range of educational backgrounds.

HUMAN FACTORS

27. 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. You state that [redacted] would not cause serious harm to the patient [redacted] However, we disagree because delayed, partial, or omitted treatment may require medical intervention and potential hospitalization.

28. 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 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.

29. We recommend you consider the following as you update your use-related risk analysis and design your HF protocol methodology:
    a) Use errors that can cause potential serious harm (including compromised medical treatment, contamination, and infection) should be evaluated as critical tasks[1].
    b) 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 communicate hazardous situations to the users, and ensure your use-related risk analysis and HF protocol evaluate such hazards and associated mitigations accordingly.
    c) 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.
    d) 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).
    e) 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) 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 (final instructional material) in the intended user populations.
    f) 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.

30. Our review of the proposed product's labels, labeling and video 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, and Video)

(b) (4)

[1] 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

7 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please call Brian Proctor, Regulatory Project Manager, at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

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

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

/s/

NORMAN L STOCKBRIDGE
06/11/2018