CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	209988		
Applicant Name	scPharmaceuticals		
Drug Product Name	FUROSCIX (furosemide injection)		
Dosage Form.	Injection		
Proposed Strength(s)	80 mg per 10 mL		
Route of Administration	Subcutaneous		
Maximum Daily Dose	80 mg		
Rx/OTC Dispensed	Choose an item.		
Proposed Indication	Furoscix is a loop diuretic indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure.		
Drug Product Description	Furoscix is a sterile, clear to slightly yellow, non-pyrogenic liquid supplied in a single-dose prefilled cartridge for subcutaneous infusion co-packaged with the FUROSCIX On-body Infusor.		
Co-packaged product information	Furoscix is co-packaged with an on-body infusor device and sterile alcohol prep pad.		
Device information:	Description, performance attributes or N/A		
Storage Temperature/ Conditions	Store between 20°C and 25°C (68°F and 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. Do not refrigerate or freeze.		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Daniel Jansen ONDP/DNDAPI/NDB3	Zhengfu Wang ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Ali Mohamadi ONDP/DNDPIII/NDPB5	Theodore Carver ONDP/DNDPIII/NDPB5

	Manufacturing	Mark Johnson OPMA/DPMAIII/PMB7	Hang Guo OPMA/DPMAIII/PMB7
	Biopharmaceutics	Parnali Chatterjee	
	Microbiology	Jianli Xue OPMA/DMAI/MAB2	Nandini Bhattacharya OPMA/DMAI/MAB2
	Other (specify):	None.	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver ONDP/DNDPIII/NDPB5	
Consults	Consult review to CDRH for review of the Furoscix on-body infusor device: ICCR 00840255 — Primary: Jake Lindstrom — Secondary: Courtney Evans		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

An expiry dating period of 12 months is granted for the drug product when stored at 20°C to 25°C (68°F to 77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Summary of Recommendation.

The Office of Pharmaceutical Quality Review team has assessed NDA 209988 for Furoscix® (furosemide injection) with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it

purports the drug product to have. As such, OPQ recommends approval of this NDA from a quality perspective.

2.) Background.

scPharmaceuticals, Inc. has submitted a 505(b)(2) NDA 209988 for Furoscix®,(furosemide injection), a drug-device combination product consisting of a cartridge containing furosemide injection that is contained in a pre-programmed device that subcutaneously infuses furosemide over a period of five hours. The Applicant is relying on the Agency's finding of safety and efficacy for the Listed Drug (LD) Furosemide (Injection, USP, 10 mg/mL; NDA 18667; Hospira, Inc.), which is indicated for intravenous (IV) and intramuscular (IM) injection for the treatment of edema in adult patients with congestive heart failure (CHF), cirrhosis of the liver, and renal disease, including nephrotic syndrome. In the previous review cycle, deficiencies were identified for the manufacturing facilities and device, and these were communicated to the Applicant in a Complete Response letter. In addition to addressing the device and facilities deficiencies identified in the last review, the Applicant has submitted additional supporting information for the drug product in this NDA resubmission. These aspects are the subject of this integrated quality assessment.

3.) Review of the Applicant's responses to deficiencies identified in the previous complete response and new review issues identified in the current review cycle.

Manufacturing and Facilities - The Office of Product Manufacturing and Assessment (OPMA) facility review concluded in the previous review cycle that the (b) (4) facility, responsible for the manufacturing of the sterile disposable alcohol prep pads, was in an unacceptable state of compliance, resulting in a Withhold recommendation. This manufacturing facility has been withdrawn from the current submission and replaced with a new facility that has been approved in the current review cycle. Two other facilities, West Pharmaceuticals Services AZ, Inc. (FEI: 3001155023) and Sharp Corporation (FEI:3004161147), were unable to be inspected due to travel restrictions. CDRH requested a preapproval inspection for West Pharmaceuticals Services AZ, Inc. (FEI: 3001155023) because the firm is responsible for the manufacturing activities related to the device constituent part. This facility is recommended for approval based on the results of this inspection. The Sharp Corporation (FEI :3004161147) facility was withdrawn, and the current (b) (4) facility (b) (4)

(b) (4) was approved based on previous history. All other facilities are recommended for Approval based on previous history. The current review of the manufacturing process concluded that the process remains adequate. Therefore, there are no outstanding deficiencies from the manufacturing or facility perspective.

Drug Product – The review of the drug product concluded that it remains approvable, after the Applicant addressed several information requests relating to the acceptance criteria for impurities in the drug product specification and extractable/leachable studies for the drug product cartridge and the device fluid path. The latter responses were identified as device deficiencies in the previous Complete Response letter (12/3/2020). The Applicant provided satisfactory information to support risk assessments for potential for elemental impurities and (b) (4) impurities in the drug product. With regards to the stability and expiry dating period for the drug product, the stability of the combination product is limited by the shelf life of the co-packaged on-body infusor device, which has a shelf life of 12 months based on accelerated aging data (see CDRH review). The stability data for drug product in the cartridge (24 months), infusor (12 months), and alcohol pad (60 months) supports a shelf life of 12 months shelf life when the drug product is stored at 25°C/40% RH. There are no outstanding deficiencies with respect to information supporting the drug product. The quality labeling review was completed, and comments were addressed by the Applicant.

Device Aspects – The review of the single-use, disposable, on-body Furoscix® infusor device, which is separately packaged as part of the combination drug product kit and only used as part of this kit with the co-packaged furosemide cartridge, was conducted by Jake Lindstrom. A number of device-related deficiencies were identified in the last review cycle, and these were satisfactorily addressed in the NDA resubmission and subsequent responses to information requests. The Applicant addressed deficiencies (1) and (2) [Device] by providing information and supporting data for changes for the device that were made during the last review cycle. Information provided to address deficiencies (3), (4), and (5) [Biocompatibility] was reviewed and found to be adequate. The Applicant provided data for fluid path particulates obtained using Method 1, USP <788> The drug product reviewer reviewed extractables/leachables data submitted in the resubmission to address deficiencies (6), and (7) [Leachables] and the responses to information requests were found to be adequate (see also drug product review). The Applicant addressed deficiencies (8), (9), and (10) by providing additional information and revised labeling, including appropriate warnings. These deficiencies and the

response were jointly addressed by the CDER labeling and CDRH review teams, which concluded that, since the device is solely marketed as part of the drug-device combination product, a subset of the information provided for the device would be included in the IFU. In summary, the Applicant addressed all device-related deficiencies in the NDA resubmission and responses to information requests during the review cycle.

Microbiology – There were no significant changes to the device or drug product that affect the microbiological quality of the drug product; however, the Applicant submitted additional information regarding in-process controls and responded to information requests regarding this information, specifically, regarding bioburden testing. The review concluded that the microbiology information in the resubmission is adequate to support the microbiological quality of the drug product.

4.) Summary of reviews for other OPQ disciplines.

The drug substance review concluded that this NDA remains adequate, as there were no deficiencies with respect to this discipline and the information remains adequate. No biopharmaceutics review is included in the integrated quality assessment because there were no changes affecting the information required to support a scientific bridge to the listed drug, which was previously reviewed and found to be adequate.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations:

Established Conditions per ICH Q12: No

Comparability Protocols (PACMP): No

Additional Lifecycle Comments: None

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	Adequate per revision below: Furoscix® (furosemide injection) for subcutaneous use
Route(s) of administration	Adequate	(furosemide injection) for subcutaneous use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Adequate per revision below: Injection, 80 mg per 10 mL single-dose prefilled cartridge co-packaged with a single-use on-body infusor
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Adequate per revision below: single-dose prefilled cartridge co-packaged with a single-use on-body infusor
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets:	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	<u>Adequate per revision below:</u> Refer to the Instructions for Use (b) (4) FURSOCIX is intended for use in a setting where the patient can (b) (4) for the duration of administration. FURSOSIX is not compatible with use in an MRI setting. Load the prefilled cartridge of FUROSCIX into the on-body infusor and close the cartridge holder. Peel away the adhesive liner on the on-body infusor and apply onto the clean, dry area of the abdomen between the top of the beltline and the bottom of the ribcage that is not tender, bruised, red or indurated. The distance from the top of the beltline to the bottom of the ribcage should be at least 2 ½ inches. Do not remove until the injection is complete (signaled by the solid green status light, beeping sound, and the white plunger rod filling the cartridge window.

Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Inadequate	**Adequate per revision below (CMC comment):** (b) (4) inspect FUROSCIX prefilled cartridge prior to administration. FUROSCIX is a clear to slightly yellow solution. Do not use FUROSCIX if solution is discolored or cloudy
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Adequate per revision below: Injection
Strength(s) in metric system	Adequate	Adequate per revision below: 80 mg per 10 mL
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	single-dose prefilled cartridge for use only with (b) (4) single-use on-body infusor

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	FUROSCIX (furosemide injection 80 mg/10 mL)
Dosage form(s) and route(s) of administration	Inadequate	**Adequate per revision below (CMC comment):** FUROSCIX is a single-dose prefilled cartridge co-packaged with a single-use on-body infusor. The single-dose prefilled cartridge contains 80 mg per 10 mL sterile, clear to slightly yellow, and non-pyrogenic furosemide solution. The pH of FUROSCIX, 7.4, differs from that of Furosemide Injection USP.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	**Adequate per revision below (CMC comment):** Each 1 mL of FUROSCIX contains the following inactive ingredients: hydrochloric acid (pH adjustment, (b) (4), sodium chloride ((b) (4) 5.84 mg), sodium hydroxide (pH adjustment, (b) (4) tris HCl (b) (4) 7.88 mg), and water for injection (b) (4) quantity sufficient).
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	Sodium hydroxide and hydrochloric acid as needed to adjust the pH.

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	Sterile
Pharmacological/Therapeutic class	Adequate	Adequate per revision below: a loop diuretic
Chemical name, structural formula, molecular weight	Adequate	4-chloro-N-furfuryl-5-sulfamoylanthranilic acid Molecular Formula: $C_{12}H_{11}ClN_2O_5S$ Molecular Weight: 330.75 g/mol
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	pH 7.4

Section 11 (DESCRIPTION) Continued

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments** (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Adequate per revision below: subcutaneous infusion
Strength(s) in metric system	Adequate	80 mg/10 mL
Available units (e.g., bottles of 100 tablets)	Adequate	Single dose Single use
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Inadequate	**Adequate per revision below (CMC comment):** Do not use if the solution is discolored or cloudy.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single dose

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Inadequate	**Adequate per revision below (CMC comment):** Do not remove the cartridge from carton until it is ready for use. Protect the on-body infusor from water.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	**Adequate per revision below (CMC comment):** Store from 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature] Do not refrigerate or freeze.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured **by**: scPharmaceuticals, Inc., 2400 District Avenue, Suite 310, Burlington, MA 01803

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):
Clinical team decided (b) (4) because the Applicant included IFU.

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	N/A	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	N/A	

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

3.0 CONTAINER AND CARTON LABELING

(b) (4)

[redacted]

3.1 Container Labels

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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence)	Adequate	(b) (4) [redacted]
Strength(s) in metric system	Adequate	Cartridge: **80 mg/10 mL (8 mg/ mL)** Carton 80 mg/10 mL (8 mg/ mL)
Route(s) of administration	Adequate	Cartridge: For subcutaneous use only. Carton For subcutaneous use only.
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	N/A	
"Rx only" displayed on the principal display	Adequate	Rx only
NDC	Adequate	NDC 71767-100
Lot number and expiration date	Adequate	Carton (b) (4) [redacted]
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	**Adequate per revision below (CMC comment):** Store from 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Inadequate	**Adequate per revision below (CMC comment):** (b) (4) Adding "single-use" before "infusor"
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Inadequate	**Adequate per revision below (CMC comment):** (b) (4)
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	scPharmaceuticals I-855-SCPHARMA (I-855-727-4276)
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Inadequate	**Adequate per revision below (CMC comment):** Add the following comment in the cartridge and container label: The pH of FUROSCIX, 7.4, differs from that of Furosemide Injection USP.
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Inadequate*

Overall Assessment and Recommendation:

The labeling is adequate from CMC perspective if the Applicant resolves deficiencies stated in this review.

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 9/5/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Theodore Carver, 9/5/2022

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	209988
Assessment Cycle Number	MR03
Drug Product Name/ Strength	Furosemide Infusor/ 80 mg/10 ml
Route of Administration	Subcutaneous
Applicant Name	scPharmaceuticals Inc.
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DCN
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Resubmission	4/8/2022
IR response	8/9/2022

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: This resubmission provided response to CR letter sent on 9/3/2020. A new Type V DMF (b) (4) is submitted for Furoscix Infusor device constituent; a new kit co-packaging ((b) (4) site (b) (4) (b) (4) to replace Sharp Packaging Services. Microbiology review N209988MR02.pdf dated 11/9/2020 from previous submission was adequate.

Concise Description of Outstanding Issues: None

Supporting Documents: Microbiology review N209988MR02.pdf (adequate) dated 11/9/2020

The Furoscix Infusor is a drug-device combination product consisting of Furoscix (Furosemide Injection, 80 mg/10 ml) contained in a prefilled, Crystal Zenith® (CZ) cartridge, and a proprietary wearable, pre-programmed on-body subcutaneous delivery system (OBDS), the Infusor, based on the SmartDose 10 ml OBDS (West

Pharmaceuticals SmartDose 10mL). This resubmission has provided response to CR letter sent on 9/3/2020. Microbiology review N209988MR02.pdf dated 11/9/2020 from previous submiss is adequate. The reviewer notes that the in-process controls have been updated (p. 9/37 in reviewer-guide-sn0058.pdf). However, discrepancy has been noted for bioburden test for the (b) (4) drug solution: page 3-4 in 3.2.P.3.4 indicated that bioburden is tested (b) (4) (NMT (b) (4)); page 3 in 3.2.3.3 indicated that bioburden is tested (b) (4) : NMT (b) (4). Microbiology review N209988MR02.pdf (adequate) dated 11/9/2020 showed bioburden is tested (b) (4) (NMT (b) (4)). The clarification is requested below.
No additional microbiology quality related information is proposed in this submission.

Information Request: The following comment was conveyed to the applicant on 7/26/2022. The response was received on 8/9/2022.

1. *Discrepancy has been noted for bioburden testing for the (b) (4) drug solution: page 3-4 in Section 3.2.P.3.4 indicated that bioburden is tested (b) (4) (NMT (b) (4)); page 3 in Section 3.2.P.3.3 indicated that bioburden is tested (b) (4) (NMT (b) (4)). Please provide the following information for bioburden test for the (b) (4) drug solution and update the corresponding sections accordingly:*
   a. Confirm if the bioburden is tested (b) (4) and provide acceptance criterion.
   b. Clarify at which manufacturing step the bioburden sample is collected if bioburden is tested (b) (4)

   Response: The sponsor clarified that during manufacturing of Furoscix drug product (b) (4) bioburden samples are taken (b) (4) (b) (4) (b) (4). However, 3.2.P.3.4 has been updated to indicate bioburden is (b) (4) and the acceptance criterion is ≤ (b) (4). Since (b) (4) bioburden is tested for (b) (4) drug solution (b) (4) no additional clarification is requested.
   Section 3.2.3.3 has also been updated to indicate that bioburden is tested for (b) (4) drug solution (b) (4) (≤ (b) (4)).

Assessment: ***Adequate***

Primary Microbiology Assessor Name and Date:
Jianli Xue, Ph.D.
CDER/OPQ/OPMA/DMA I/BII
8/17/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Nandini Bhattacharya
CDER/OPQ/OPMA/DMA I/BII
8/17/2022

Jianli Xue

Digitally signed by Jianli Xue
Date: 8/17/2022 03:23:02PM
GUID: 584afcd70041453da94854122880ab0c

Nandini Bhattacharya

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Date: 8/17/2022 03:24:16PM
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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	9/28/2022		
To:	Brian Proctor		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	ORO/DROCHEN
From	Jake Lindstrom, Ph.D. OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	ICC2200340, ICCR 00840255 NDA209988, Furosemide Pump scPharmaceuticals		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 9/28/2022 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Jake K. Lindstrom -S Digitally signed by Jake K. Lindstrom -S Date: 2022.09.28 17:15:02 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2022.09.28 17:29:47 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA209988
Sponsor	scPharmaceuticals
Drug/Biologic	Furosemide
Indications for Use	Treatment of edema associated with congestive heart failure
Device Constituent	On-body injector
Related Files	ICC2000553

Review Team		
Lead Device Reviewer	*Jake Lindstrom, Ph.D.*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A		

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation				Deferred
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

scPharmaceuticals is requesting approval of Furosemide Pump. The device constituent of the combination product is a on-body injector.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

ScPharmaceuticals has resubmitted their NDA 209988 for the Furoscix Infusor (combination product), indicated for the treatment of edema associated with congestive heart failure.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device Performance, Biocompatibility, Risk Analysis, Facilities Review

This review will not cover the following review areas:

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

ICC2000553

3.3. Indications for Use

Combination Product	Indications for Use
Furosemide Pump	Treatment of edema associated with congestive heart failure
On-Body Injector	Delivery of the Drug Product

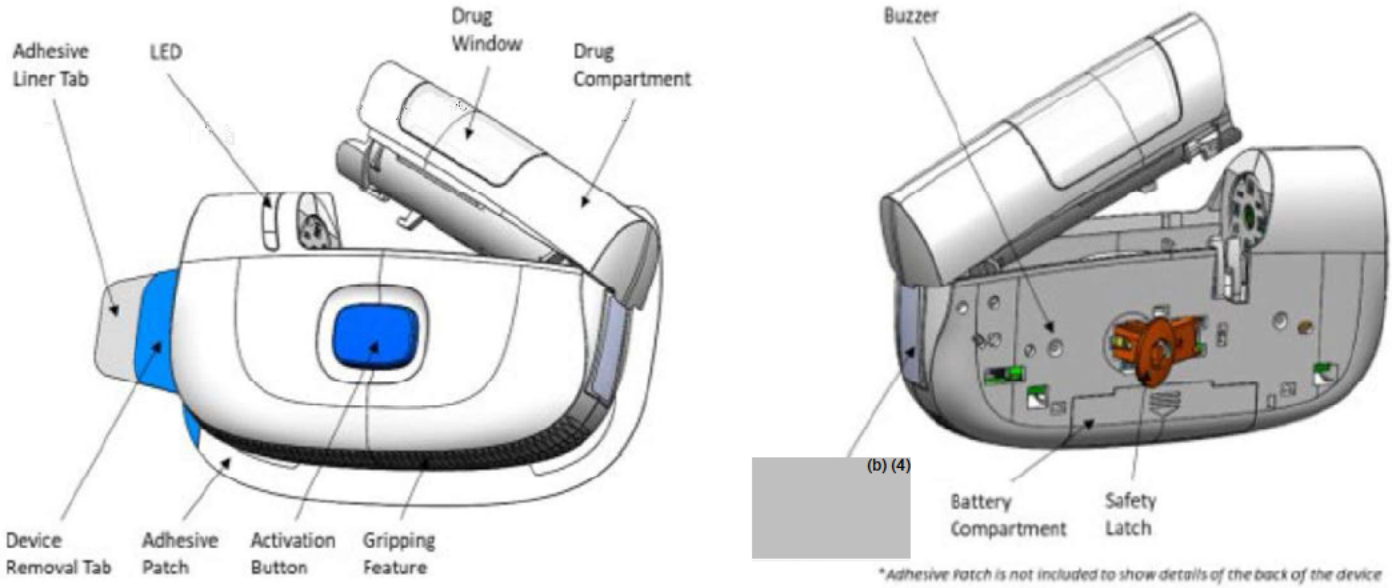
3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
NDA209988, Sequence 058	Documents cited in-text
DMF (b) (4) Sequence 001	Documents cited in-text

4. DEVICE DESCRIPTION

4.1. Device Description

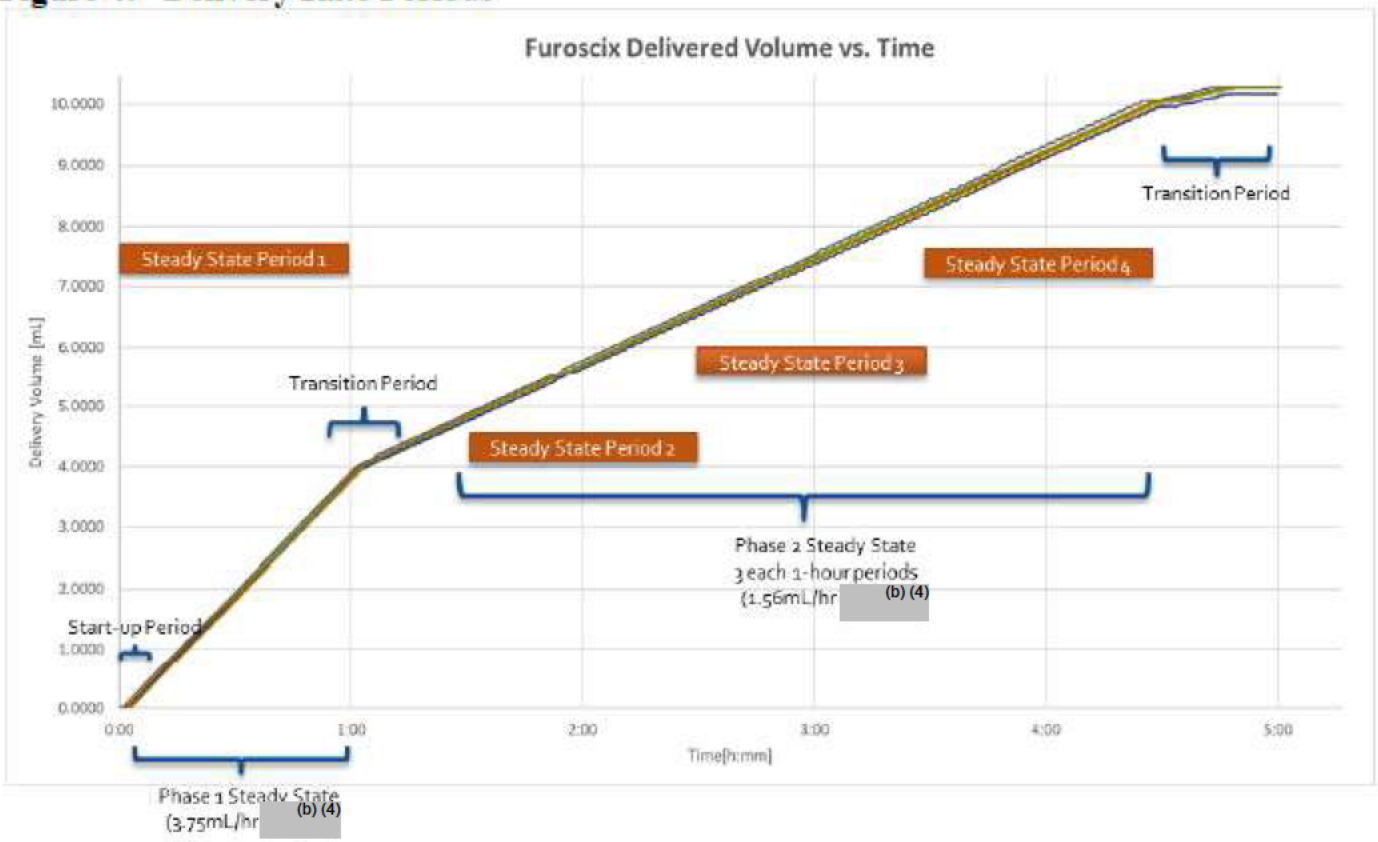
The device is an on-body injector, not an infusion pump. After cartridge insertion, the user adheres the device and presses the button. The user cannot program the device. The user can monitor progress via a "Drug Window." After completion, the user removes the injector, which includes a safety latch to protect against needle stick injuries.



Source: DD-0107

The device provides two flow rate regimes. The first acts likes a loading dose and the second provides the remaining portion of the dose. The delivered volume profile is shown below.

Figure 4: Delivery Rate Periods



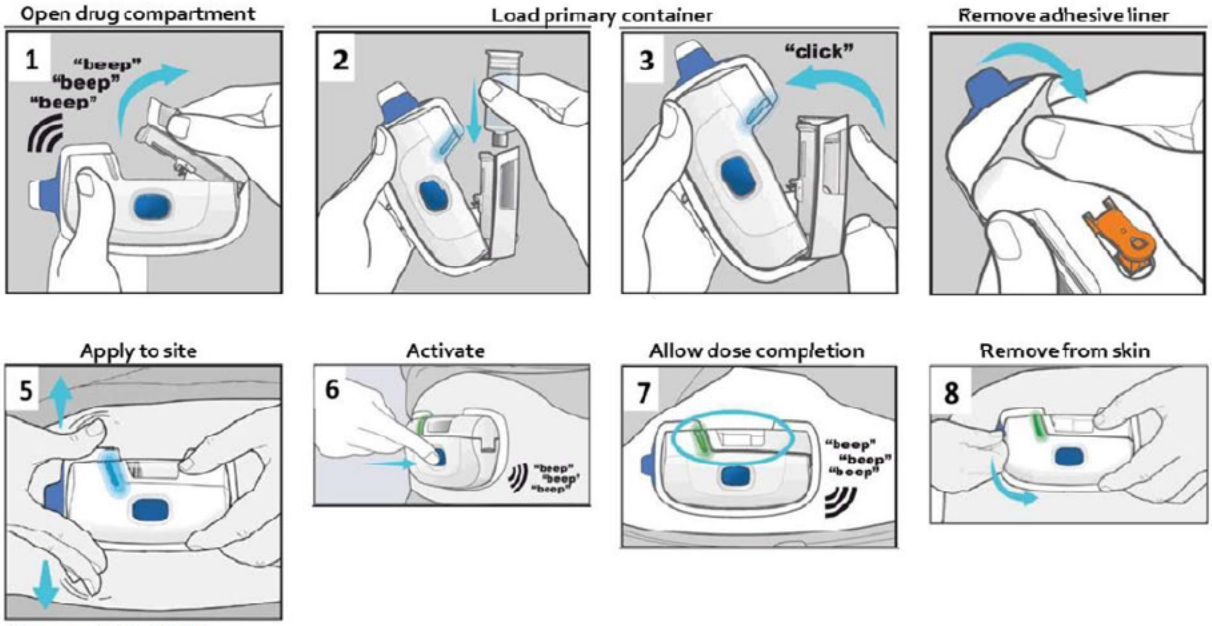
Source: scPharmaceuticals

4.2. Steps for Using the Device

From ICC2000553:

- Wash Hands
- Check expiration date
- Remove device from packaging, gather necessary equipment, and check for damage/compromised sterility/expiration.
- Load cartridge into the infusor by wiping the dispensing tip, opening cartridge holder in device, and inserting/closing.
- Prepare administration site and apply Infusor.
- Start infusion, deliver for 5 hours, remove device and dispose of properly.

For increased clarity, please see the graphical guide below.



Source: DD-0107.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

4.4. Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK

Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment
N/A

4.5. Filing Review Conclusion

FILING REVIEW CONCLUSION
Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A
Facilities Inspection Recommendation: ☑ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A **Site(s) needing inspection: West Pharmaceuticals AZ Inc. (FEI: 3001155023)**
Reviewer Comments See Facility Review in Section 11.
Refuse to File Deficiencies: ☐ Yes ☐ No ☑ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☑ N/A

Add Additional Information Request

5. LABELING

5.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, (b) (4) prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A

Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	Deferred		
Electrical Safety Labeling/Symbols	X		
EMC Labeling/Symbols	X		
Software Version Labeling	X		
MRI Labeling/Symbols	X		
RF/Wireless Labeling/Symbols	X		

Reviewer Comments
The sponsor provided additional information as requested in CR deficiencies 8, 9, and 10.

CR8 is about electromagnetic compatibility (EMC) information. The sponsor addressed the deficiency by adding the following information to the labeling (b) (4) (b) (4)

Note: While the sponsor adequately responded to this deficiency and CR9 and 10 as detailed subsequently, this labeling may change. This information is atypical for combination product labeling and may be changed after this review at the request of CDER.

CR9 requested specific information: Electrical Safety Labeling/Symbols, EMC Labeling/Symbols, Software version, Factors affecting accuracy, Residual/hold-up volume, Warnings/symbols regarding use in CT, ultrasound, and X-ray Environments, and Design Considerations for Devices Intended for Home Use The sponsor added the requested information except for the residual volume. The sponsor wrote, "*The residual or hold-up volume* (b) (4) *is accounted for* (b) (4)*; therefore, residual or hold-up volume is not relevant to the end user of the Furoscix Infusor because the full dose is intended to be administered for each combination product kit. Including residual or hold-up volume could be confusing because the user cannot account for this during use.*" This reasoning is acceptable, as the EPR is delivered volume.

CR10 requested either testing to demonstrate safe and effective use (b) (4) (b) (4) or labeling to warn (b) (4). The sponsor provided the warning, which is acceptable.

5.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

6. DESIGN CONTROL SUMMARY

6.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
N/A

6.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Volume	10mL ± 10% (1 mL)
Dose Delivery Time	5 hours (b) (4)
Flow Rate	First steady state: 3.75 ml/hr (b) (4) Second steady state: 1.56 mL/hr (b) (4)
Button Activation Force	(b) (4)
Deployed Needle Length	6.0 mm ± 1.0 mm
Adhesive Tack Force	(b) (4)
Time to Occlusion	

Reviewer Comments
The sponsor cites many other design inputs and outputs, but these are the most important for device functionality.

6.3. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION

Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	Final Deficiencies: ☐ Yes ☑ No ☐ N/A
Reviewer Comments N/A		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 8/29/2022	Date/Sequence Received: 8/31/2022
Information Request #2	In response to CR deficiency 19, you provided clinical justifications for your specifications; however, some of the specifications remain overly wide or long. You have also provided performance testing. For most of the specifications (e.g., flow rate, time to occlusion, dose volume) your product has substantially exceeded the specifications. As the specifications are broad, you should make the specifications tighter to better capture clinical needs. Tighten your specifications to better conform to user needs.	
Sponsor Response	The sponsor declined to change their EPRs and cited validation testing and previous interaction, such as Type A and C meetings.	
Reviewer Comments	The sponsor does not need to change their specifications, although preferable. However, as the Agency previously did not identify these areas and they do not appear to pose unacceptable risk, the specifications are acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

7. RISK ANALYSIS

7.1. Risk Management Plan

Per the sponsor in *device-ra0042.pdf*:

> *This Risk Management Plan describes the scope of the risk management activities for the Furoscix Infusor. It has been developed in accordance with scPharmaceuticals' Risk Management Procedure(SOP-0034) and ISO 14971:2019.*
> *The Risk Management Plan includes the following:*
> • *Scope of the risk management activities*
> • *Assignment of responsibilities*
> • *Identification and clear description of the product*
> • *Requirements for the review of risk management activities*
> • *Criteria for risk acceptability*
> • *Plan for Verification and Validation activities*
> • *Plan for activities related to collection and review of production and post-production information.*

Reviewer Comments
This overall approach is what we expect to identify and reduce risk.

7.2. Hazard Analysis and Risk Summary Report

The device constituent is not an infusion pump; however, CDRH policy previously considered on-body injectors as infusion pumps. They are not. They are electrically-powered injectors that can take several hours to deliver the drug product. As such, the device constituent risks are significantly lower than an infusion pump. Therefore, a Safety Assurance Case (SAC), as previously requested, and CR deficiencies issued about it are not necessary. An abbreviated review, however, is included below.

The sponsor's SAC structure is acceptable. The top level structure and then examples of claim-argument-structures and sub-structures are included below.

Figure 2: SAC Top Level Structure

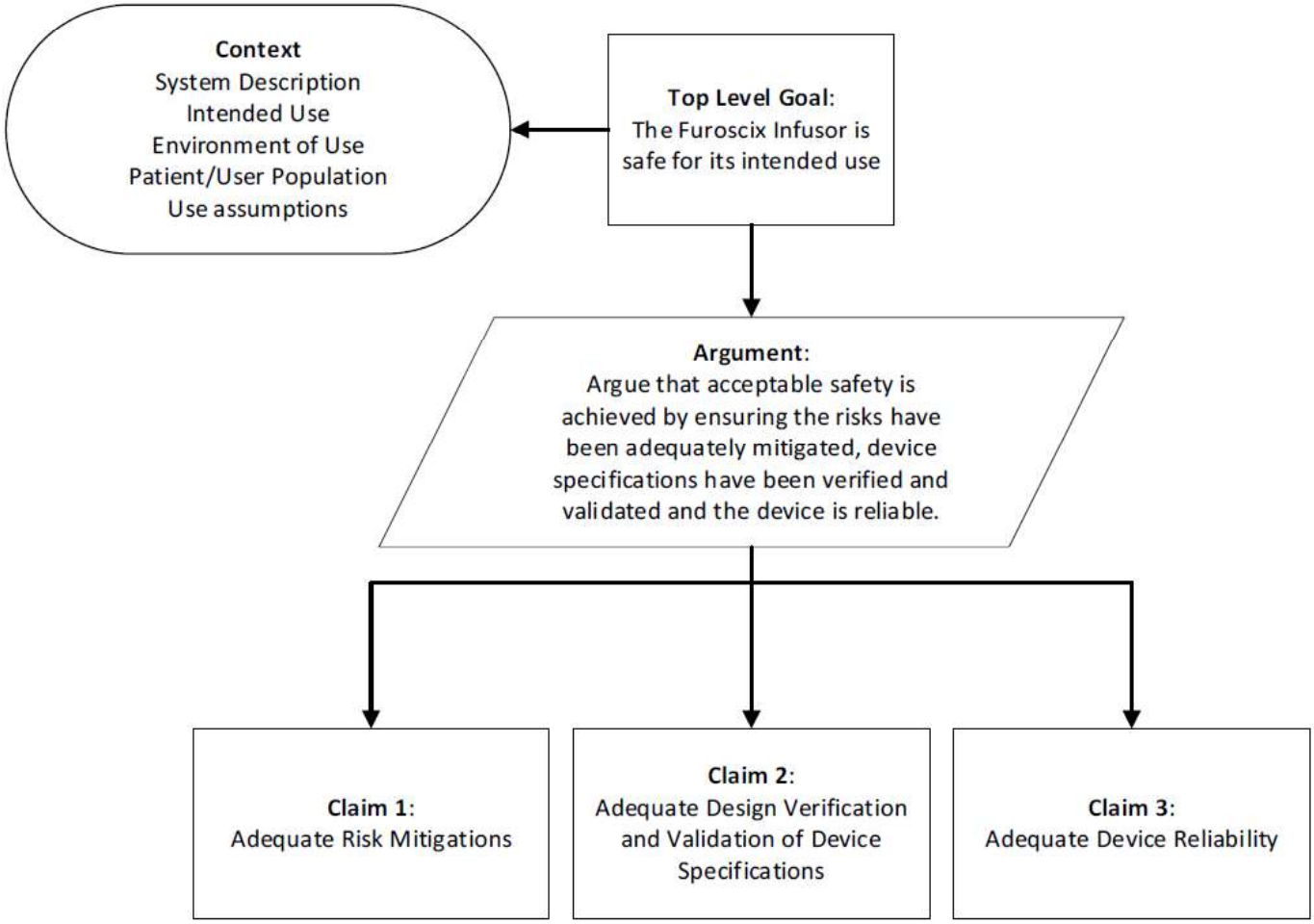


Figure 3: Claim 1 Argument Structure

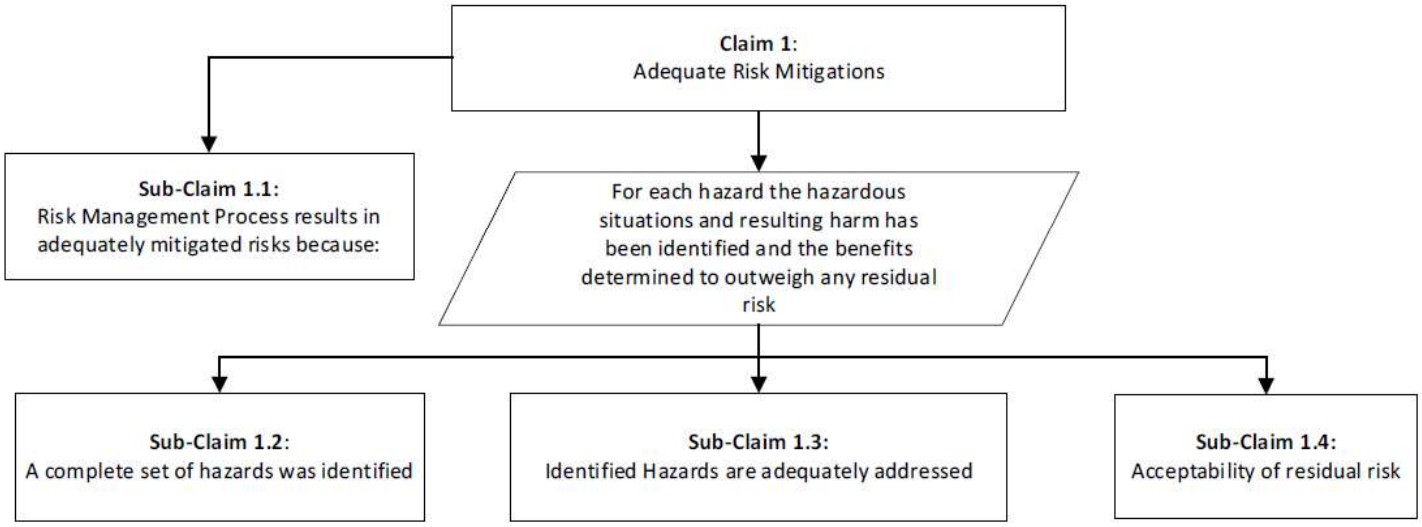
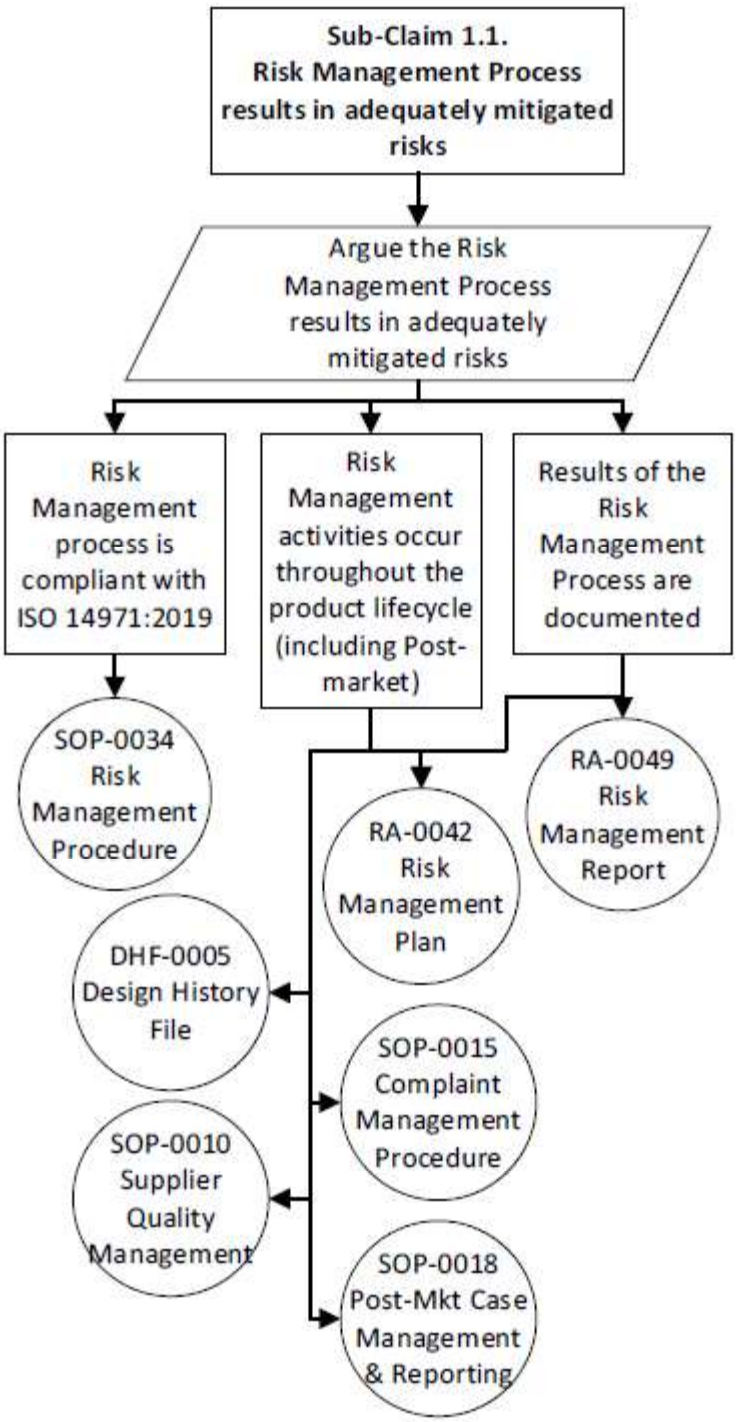


Figure 4: Sub-Claim 1.1 Structure



The sponsor has adequately linked goals, claims/sub-claims arguments to evidence to support them.

The sponsor also provided a Failure Mode and Effects Analysis (FMEA). The FMEA (example section below) notes the component involved, failure modes, effects on drug delivery or device operation, harm to user. It then details the risk control measures and residual risk estimation. The FMEA is appropriate and appears comprehensive.

RISK ASSESSMENT						RISK CONTROL						RESIDUAL RISK ESTIMATION					
ID #	Component, Subassembly	Potential Failure Mode (system/device hazard)	Potential Cause(s) / Mechanism(s) of Failure	Potential Effect on the Device	Potential Effect(s) of Failure (Harm to the patient/user)	Current Controls	Current Mitigation	Recommended Control and/or Mitigation	Requirements references (b) (4) (b) (4)	Actions taken or justification (referenced to their current revision)	Verification/ Confirmation of additional risk controls applied (referenced to their current revision)	Severity	P1 Probability [%]	P2 Probability [%]	(P1 x P2) [XX%]	Probability of Occurrence (O) [Score]	New Risk Priority Level
										P1 calculation method / Protocol (if applicable)							
(b) (4)																	

One hazard, fluid ingress, was specifically cited in a CR deficiency, CR14. See the discussion below.

CR deficiency #14	
Deficiency	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) 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.
Sponsor Response	The sponsor provided testing per IPX1 (ingress protection) and a rationale why IPX1 was sufficient, instead of IPX2. The testing report is in device-rpt-0440.pdf. The rationale was risk-based. Fluid ingress would, at worst, cause an incomplete dose to be administered. The risk of an incomplete dose is further mitigated by alarms and the viewing window, so the user would know the dose was incomplete, although not the infused volume. Additionally, given the intended patient population, mobility will be limited.
Reviewer Comments	Given the low risk of incomplete dose, and the mitigation of the viewing window, IPX1 is acceptable. While a greater ingress protection rating is preferable, the risks posed to patients by fluid ingress are sufficiently low, and the potential harm is reasonably mitigated.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

Reviewer Comments
N/A

7.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments N/A		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: **8/29/2022**	**Date/Sequence Received:** **8/31/2022**
Information Request #	In response to CR deficiencies 24 and 25, you refer to 32r-device-risk-management.pdf. Table 4 shows your risk acceptability levels. As noted in CR deficiency 24, you should ensure your risk levels are appropriate and, correspondingly as stated in CR deficiency 25, your hazard analysis should reflect these levels with appropriate mitigations. (b) (4) [redacted] Update your risk analysis table (i.e., Table 4) to adequately characterize risk acceptance levels. We recommend you use the rankings from Figure C.1 in AAMI TIR24971:2020 Medical devices— Guidance on the application of ISO 14971. Correspondingly, provide an updated hazard analysis and note any changes made necessitating additional mitigations or testing to higher confidence/reliability.	
Sponsor Response	The sponsor explained their risk management process and stated reclassification would be unnecessary. The sponsor provided a comparison of the severity levels in their analysis and the noted standard. The sponsor's levels do not align exactly, which means the risk levels also are not identical.	

Table 1 Side-by-side Comparison of Severity Level Definitions from Sponsor and TIR 24971 to Illustrate Differences in Definitions

Sponsor's Definitions (RA-0043)	TIR 24971 Definition
(5) Catastrophic Health Hazard: Immediate life-threatening condition or death	Catastrophic / Fatal: Result in death
(4) Severe Health Hazard: Permanent significant physical effects that require major medical intervention	Critical: Results in permanent impairment or irreversible injury.
(3) Moderate Health Hazard: Temporary but significant physical effects that may require minor medical treatment by health care professional	Serious/Major: Results in injury or impairment requiring medical or surgical intervention
(2) Limited Health Hazard: Temporary minor physical effects	Minor: Results in temporary injury or impairment not requiring medical or surgical intervention.
(1) No Health Hazard: No physical effect. May cause inconvenience or annoyance	Negligible: Results in inconvenience or temporary discomfort

Source: device-ra0043; TIR 24971, Figure C1

To end, the sponsor wrote, "The Sponsor reiterates that the Hazard/Risk Analysis has appropriate mitigations in place and all risks identified in the Hazard/Risk Analysis have risk controls established. To ensure the effectiveness of the Hazard/Risk Analysis throughout the product lifecycle, a new risk level will be created in the Sponsor's risk management procedures which will require investigation into establishing risk controls and creates alignment with TIR 24971."

Reviewer Comments	Given the overall risk of the product, the sponsor used different, lower harm levels, although they extend to the same highest severity (patient death). This approach was not clear before the IR. It is acceptable, as it accounts for risk and indicates when mitigations are necessary.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Volume	10mL (b) (4)	Y	Y	Y	Y
Dose Delivery Time	5 hours (b) (4)	Y	Y	Y	Y
Flow Rate	First steady state: 3.75 ml/hr (b) (4) (b) (4) Second steady state: 1.56 mL/hr (b) (4) (b) (4)	Y	Y	Y	Y
Button Activation Force	(b) (4)	Y	Y	Y	Y
Deployed Needle Length	6.0 mm (b) (4)	Y	Y	Y	Y
Time to Occlusion	(b) (4)	Y	Y	Y	Y

Reviewer Comment
Unaged and aged test reports included in *device-rpt-0424.pdf* and *device-rpt-0425.pdf*, respectively. The aging was, "(b) (4) *equivalent to 12 months real time aging. All essential performance requirements (EPRs) defined in DD-0092 were tested over shelf life.*" The sponsor calls design inputs EPRs, but what we consider to be the EPRs are included above. All are verified and validated adequately over the shelf life using accelerated aging.

8.1.2. Evaluation of Test Methods

From *device-rpt-0424.pdf*

Title:	Dose volume accuracy [EPR]

Scope/Objective & Acceptance Criteria:	*The full delivered dose shall be 10.0 [mL] (b) (4) of drug product.*
Methods	The product is weighed before and after use to measure the expelled mass. That mass is then converted into volume by a density calculation. The apparatus is shown below. (b) (4) **Figure 3: Drug delivery during device operation** "*Based on a sample size of 126, CL and RL levels of 95.0 %/95.0 %, and Attribute test results, the predetermined acceptance criterion is accept on* (b) (4) *reject on* (b) (4)""
Results:	Numerically: **Min [mL]** 10.2 **Max [mL]** 10.3 **Average [mL]** 10.3 **STD [mL]** 0.02 **LSL [mL]** 9.0 **USL [mL]** 11.0 Graphically:

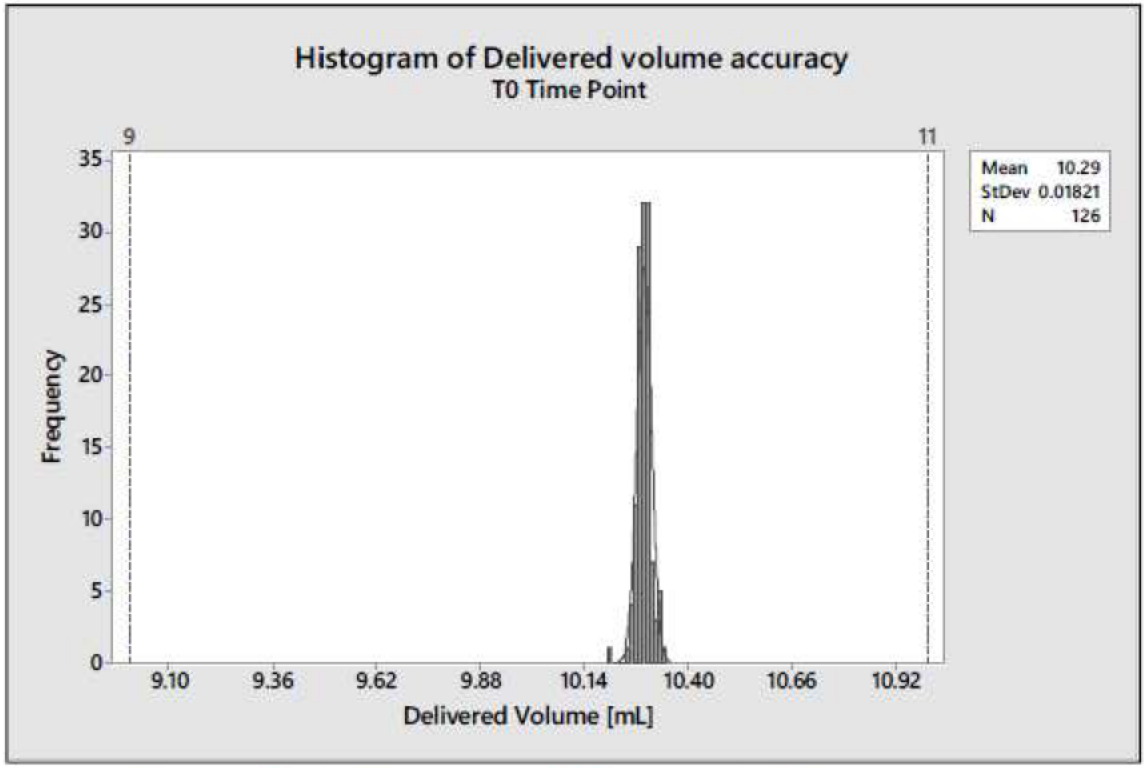


Figure 4. Histogram of delivered volume accuracy test results

Conclusions/ Reviewer Comments:	Testing adequately demonstrates the product meets the EPR specification.
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	Dose delivery time [EPR]

Scope/Objective & Acceptance Criteria:	*The operation time shall be 5 hours* (b) (4)
Methods	*"The total operation time is measured from activation button press until termination of operation (end of delivery or error)* (b) (4) (b) (4) (b) (4) *"Based on a sample size of 126, CL and RL levels of 95.0 %/95.0 %, and Attribute test results, the predetermined acceptance criterion is accept on* (b) (4) */ reject on* (b) (4) *."*
Results:	

Min [hr]	**4.9**
Max [hr]	**5.1**
Average [hr]	**5.0**
STD [hr]	**0.03**
LSL [hr]	**4.5**
USL [hr]	**5.5**

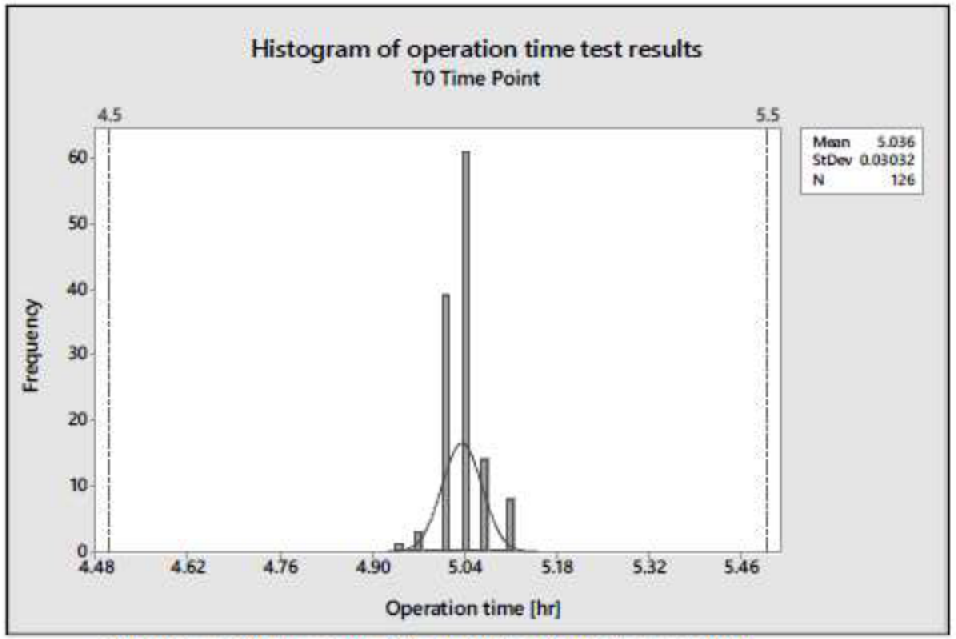


Figure 5. Histogram of operation time test results

Conclusions/ Reviewer Comments:	Testing adequately demonstrates the product meets the EPR specification.
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	Flow rate accuracy [EPR]
Scope/Objective & Acceptance Criteria:	Following activation, the system shall deliver 3.75 [mL] (b) (4) in the first hour and 1.56 mL/hr (b) (4) for the subsequent 4 hrs.
Methods	*The test method for the flow rate requirement measures the drug product flow rate during the device operation for the duration of the delivery period. Flow rate is determined by measuring the mass of fluid dispensed from the device over time on an electronic scale as the device delivers the drug product. The time is recorded by the Labview program.*
Results:	Numerically:

Min [mL/h]	3.82	1.72	1.72	1.46
Max [mL/h]	3.98	1.77	1.75	1.72
Average [mL/h]	3.93	1.75	1.74	1.60
STD [mL/h]	0.03	0.01	0.01	0.04
LSL [mL/h]	2.81	1.17	1.17	1.17
USL [mL/h]	4.69	1.95	1.95	1.95

Graphically:

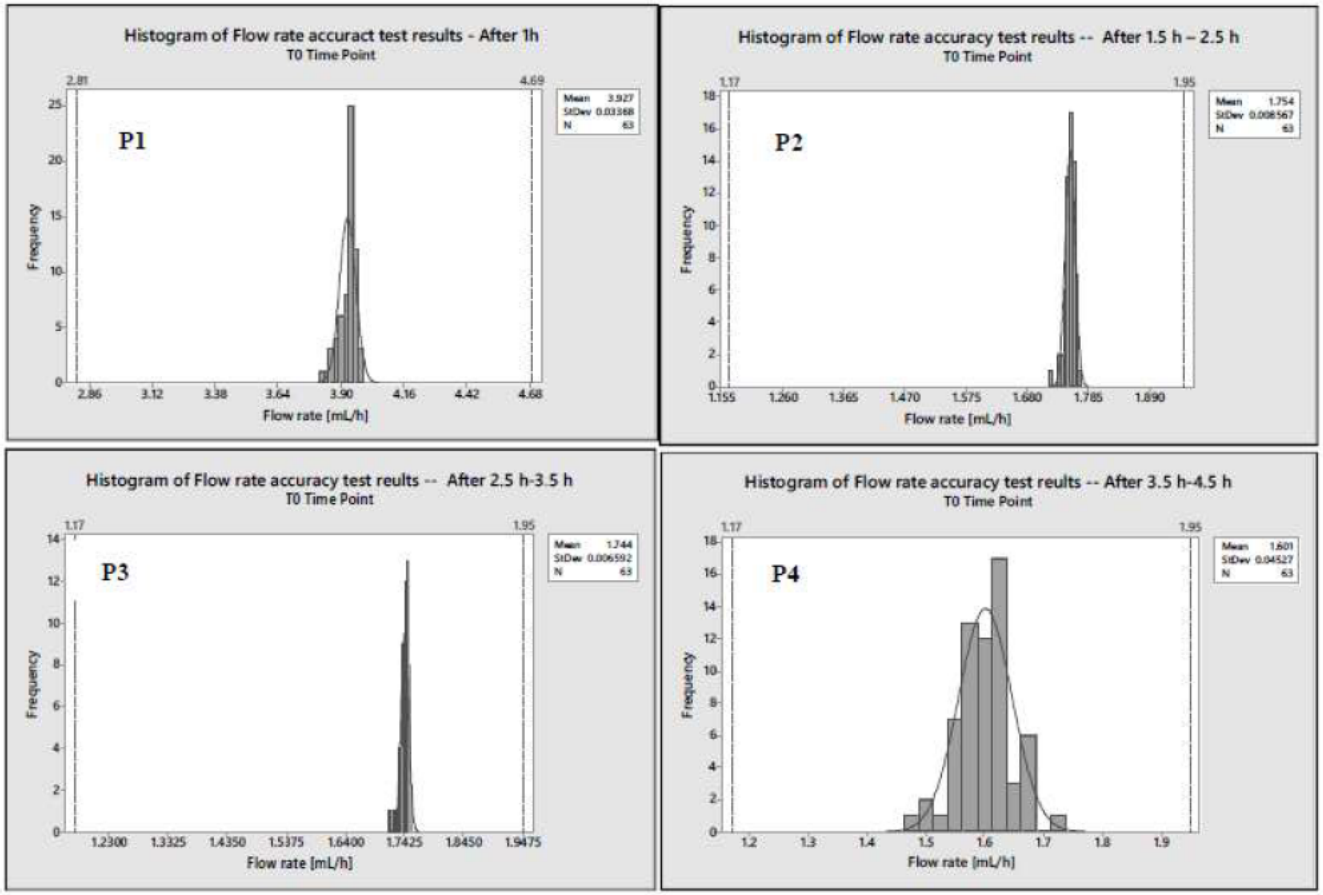


Figure 7. Histogram of flow rate accuracy test results

Conclusions/ Reviewer Comments:	Testing adequately demonstrates the product meets the EPR specification.
Acceptable:	☒Yes ☐No

Reviewer Comment

Title:	Deployed needle length [EPR]
Scope/Objective & Acceptance Criteria:	The device shall have a patient needle with deployment length of 6.0[mm] (b) (4) as measured from the back of the device to the distal end of the needle.
Methods	*Patient needle deployment length is measured by an optical inspection system to inspect the needle length from the back surface of the device (without adhesive patch applied) to the tip of the patient needle.* Apparatus shown below. (b) (4) **Figure 9: Optical inspection system for needle length** "*Based on a sample size of 60, CL and RL levels of 95.0 %/95.0 %, and Attribute test results, the predetermined acceptance criterion is accept on* (b) (4) */ reject on* (b) (4)"

Results:	<table><tr><td>**Min [mm]**</td><td>5.4</td></tr><tr><td>**Max [mm]**</td><td>6.6</td></tr><tr><td>**LSL [mm]**</td><td>5.0</td></tr><tr><td>**USL [mm]**</td><td>7.0</td></tr></table>
Conclusions/ Reviewer Comments:	Testing adequately demonstrates the product meets the EPR specification.
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Title:	Button activation force [EPR]
Scope/Objective & Acceptance Criteria:	*The force required to press the activation button when the loaded System is applied to the injection site shall be in the range of* (b) (4) (b) (4)
Methods	*The button force test method* (b) (4) (b) (4) *to measure the force required to press the button over a fixed distance. A set distance for the button travel has been determined to ensure the button reaches its final position.* The apparatus is shown below.

Figure 16: Button press testing configuration

Results:

Min [N]	**9**
Max [N]	**14**
Average [N]	**11**
STD [N]	**1.17**
LSL [N]	**4**
USL [N]	**30**

Conclusions/ Reviewer Comments:

Testing adequately demonstrates the product meets the EPR specification.

Acceptable: ☒Yes ☐No

Reviewer Comment
N/A

Title:	Representative Fault Condition Notification – (b) (4) Alarm [EPR]
Scope/Objective & Acceptance Criteria:	*The system shall detect* (b) (4) *) and provide a fault condition notification*
Methods	(b) (4)

(b) (4)

Results:

Min [hr]	0.5
Max [hr]	0.7
Average [hr]	0.6
STD [hr]	0.03
USL [hr]	1.5

	One failure also occurred, where the root cause analysis determined an occlusion was not formed.
Conclusions/ Reviewer Comments:	Testing adequately demonstrates the product meets the EPR specification.
Acceptable:	☒Yes ☐No

Reviewer Comment
N/A

Biocompatibility

See ICC2000553 for additional biocompatibility review.

In the previous CR, deficiencies 3-5 relate to biocompatibility of the device constituent.

CR3 and CR4 relate to particulates in the fluid path. Namely, they request testing per the USP <788> Method 1 light obscuration method and clarity on which method was used, respectively. In response, the sponsor clarified Method 1 was used and provided adequate results. See below. This response resolves these deficiencies.

Table 6: Drug-Device Fluid Path Particulates Test Results

Description	**Specification**	**Results** **Commercial Device BOM #:** **Lot #: SC00012328**
Particle Class I ≥ 10um	NMT 6000 particles/container	(b)(4) Particles/ Container
Particle Class II ≥ 25um	NMT 600 particles/container	Particle/ Container

Source: Report-0351 (device-rpt-0351), provided in Section 3.2.R

CR5 request clarification on cytotoxicity testing methodology. The sponsor clarified the "*adhesive patch cytotoxicity testing was performed using the ISO Direct Contact Method,* (b) (4)." This response resolves the deficiency.

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments N/A		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent: 8/29/2022	**Date/Sequence Received:** 8/31/2022
Information Request #3	The device constituent has a sharps injury prevention feature; however, it does not appear to have been adequately tested. FDA guidance "Medical Devices with Sharps Injury Prevention Features" (available at https://www.fda.gov/files/medical%20devices/published/Medical-Devices-with-Sharps-Injury-Prevention-Features---Guidance-for-Industry-and-FDA-Staff-(PDF).pdf) outlines suitable sharps injury prevention feature testing, including simulated use testing. Provide testing of the sharps injury protection features as indicated by this guidance, a sample size of 500 with zero failures in a simulated use study.	
Sponsor Response	The sponsor explains their approach but does not provide the requested testing. Their approach involved testing with a simulated finger, not simulated use. The testing they provided n=300 without aging (but with preconditioning), extremes of the environmental conditions (n=240), and after 1 year of accelerated aging (n=60) all passed this test.	
Reviewer Comments	While this test is different that the simulated use, it is acceptable. We also agreed in a Type A meeting that this testing would be acceptable.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.	

8.3. Discipline Specific Sub-Consulted Review Summary

☐ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

Discipline-Specific Design Verification / Validation adequately addressed						
Discipline	**Consult needed**			**Comment**	**Section**	**Adequately Addressed (Y/N/NA)**
	Yes	**No**	**N/A**			
Engineering (Materials, Mechanical, General)		X				Y
Biocompatibility		X				Y
Sterility			X	No sterility CR deficiencies		Y
Software / Cybersecurity		X				Y
Electrical Safety / EMC		X				Y
Human Factors			N/A	Deferred	11	N/A
Clinical			X			N/A

CDRH sent Deficiencies or Interactive Review Questions to the Sponsor	☑ **Yes** ☐ **No**

CR deficiency #15	
Deficiency	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) 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.
Sponsor Response	Sponsor provided further information about the trigger limits, including the "Criteria that result in a Fault Condition." The limits are tabulated in *Furoscix Infusor Fault condition notification Requirements* (device-dd0096.pdf). See example below.

Table 1 – Fault condition notification function requirements and criteria for fault conditions

scP Functional Requirement (DIR-0017)	Rationale	Criteria that result in a Fault Condition	Error code Group	West Error code #
(b) (4)				

The sponsor also provides a table including all Design Verification Testing, including alarms. See the example below which includes the two referenced alarm limits in the example above.

Design Inputs		Design Outputs	Verification Evidence			Notes
Ref.	Requirement Description	Reference / Description	Report Reference	Data Summary	Result (Pass/Fail)	
(b) (4)					Pass	None
					Pass 95%/95% Confidence/ Reliability	None
					Pass	None

Reviewer Comments	This response is adequate. They have identified their trigger limits and traced them to their performance testing of those specifications.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

CR deficiency #16	
Deficiency	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.
Sponsor Response	"The Sponsor has provided expanded rationale for the selection of, and specifications for EPRs and critical Safety Performance specifications in Section 3.2.P.5.6-device. The clinical justification (b) (4) is provided in Section 3.2.P.5.6.4.1-device. Relevant system-level verification testing for error notifications, including occlusion testing, is summarized in Section 32r-deviceverification, Table 14." The clinical justification states, in part, "Justification for this specification relies on the half-life of the drug product being approximately (b) (4) and an average serum concentration of Furosemide of (b) (4) compared to a therapeutic threshold concentration of (b) (4) and therefore, a (b) (4) pause in drug delivery would be clinically insignificant."
Reviewer Comments	The sponsor's response is adequate. (b) (4) (b) (4). However, the risks for delay in therapy do not demand further mitigation; the sponsor provided a scientifically valid rationale for the specification. The time (b) (4) is acceptable as the risks of a delay in therapy or incomplete dose are relatively low for this drug product used in this manner.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

CR deficiency #13	
Deficiency	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.
Sponsor Response	The sponsor primarily cited DMF (b) (4) The sponsor linked to both specifications and code coverage information. See the two examples below respectively.

	(b) (4)
Reviewer Comments	The sponsor provided adequate information about the noted areas. This response is acceptable.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Firm Name:	West Pharmaceuticals AZ Inc.
Address:	14677 N 74th St Scottsdale AZ 85260-2403 United States
FEI:	3001155023
Responsibilities:	Manufactures Infusor On Body Device. Manufactures sterile cartridges and distributes stoppers for drug product primary container

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product
Inspection Recommendation: ☐ A pre-approval inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm has not been performed. ☑ An inspection is not required because the manufacturing site does not require an inspection at this time given the risk of the combination product.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History An analysis of the firm's inspection history over the past 2 years: ☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item.. ☑ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected. ☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product
Inspection Recommendation: ☐ A pre-approval inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm has not been performed. ☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☑ Yes	☐ No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☑
CDRH Quality Systems Documentation Review was not conducted	☐

11.2.1. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission: Yes, all information described in *32r-device-quality-system.pdf*.

What Quality System did the Sponsor choose:
☐ Device QSR-based
☑ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): scPharmaceuticals	**Reviewer Discussion –** "periodic management review meetings (b) (4) (b) (4) in accordance with SOP-0021, Management Review"
21 CFR 820.30 Summary of Design Controls	Firm(s): scPharmaceuticals	**Reviewer Discussion –** Reviewed in detail in Section 7
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): scPharmaceuticals	**Reviewer Discussion –** "controls the purchase of goods and services by complying with SOP-0011, Purchasing Controls (device-sop-0011) and SOP-0010 Supplier Quality Management."
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): scPharmaceuticals	**Reviewer Discussion –** "Corrective and Preventive Actions (CAPA) at scPharmaceuticals are defined by SOP-0036, Corrective and Preventative Actions (CAPA; device-sop-0036). Corrective Action Investigations apply to identified product, process, system nonconformities and problematic performance with respect to internal quality, manufacturing and discrepancies cited during internal and external audits."
Subpart G – Production and Process Controls	Firm(s): West Pharmaceuticals	**Reviewer Discussion –** Reviewed in Section 11.3
Subpart H – Acceptance Activities	Firm(s): scPharmaceuticals	**Reviewer Discussion –** "Quality Assurance is responsible for performing technical reviews and approvals of the Device Master Records (DMR) and Master Batch Records (MBR), which ensures the documentation meets the technical requirement for cGMP production of the product. Product requirement documents detail the specifications, procedures and methods to be performed for each finished product"
Subpart I – Nonconforming Product	Firm(s): West Pharmaceuticals	**Reviewer Discussion –** "The process steps for non-conforming materials involve identification of the material, documentation of the non-conformity, segregation of the material, disposition of the material, and investigation into the cause of the non-conformity."

Reviewer Comments
N/A

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product* (b) (4)

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
Dose Volume	Release testing	Y
Dose Delivery Time	Release testing	Y
Flow Rate	Release testing	Y
Button Activation Force	Release testing	Y
Deployed Needle Length	Release testing	Y
Time to Occlusion	Release testing	Y

Reviewer Comments

Release testing the EPRs is acceptable. The sponsor will use (b) (4) a surrogate for the drug product during release testing. (b) (4), this is acceptable.

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

Theodore Carver

Digitally signed by Theodore Carver
Date: 9/30/2022 05:10:16PM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

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/

THEODORE E CARVER
09/30/2022 05:24:28 PM

NDA 209988-SN0034: Furoscix® (Furosemide) Injection

Integrated Quality Review

Recommendation: Complete Response

Drug Name/Dosage Form	Furoscix® (furosemide) Injection
Strength	8 mg per mL
Route of Administration	Subcutaneous administration via Furoscix Infusor
Indication	Treatment of edema in adult patients with worsening New York Heart Association (NYHA) Class II and Class III heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization
Rx/OTC Dispensed	Rx
Applicant	ScPharmaceuticals. Inc.
Submissions (s) Reviewed	NDA 209988-SN-0034, CMC amendments, and supporting documents

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Daniel Jansen	OPQ/ONDP/DNDAPI/NDB3
Drug Product	Ali Mohamadi	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Mark Johnson	OPQ/OPMA/DPMAIII/PMB7
Biopharmaceutics	Parnali Chatterjee	OPQ/ONDP/DB/BB3
Microbiology	Jesse Wells	OPQ/OPMA/DMAI/MAB1
Device	Max Lerman	CDRH/OPEQ/OHTIII/DHTIIIC
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

RBPM: Grafton Adams (OPQ/OPRO/DRBPMI/RBPMB2)

RELATED/SUPPORTING DOCUMENTS

Document	Application Number	Description
DMF	(b) (4)	Type II DMF
Master Access File (MAF)		Cross-referenced for SmartDose Gen II 10mL OBDS information

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209988-SN0034; Furoscix® (Furosemide) Injection is **not** recommended for approval because per Official Action Indicated (OAI) status, the [redacted] facility is considered to be in an unacceptable state of compliance with regards to current good manufacturing practice (CGMP). Additionally, due to unresolved device-related deficiencies, the device constituent parts of the combination product are not approvable. Satisfactory resolution of these device-related deficiencies as well as outstanding deficiencies concerning the [redacted] facility is required before this application can be approved. Pre-approval inspections of Sharp Corporation (FEI # 3004161147), and [redacted] facilities could not be conducted due to Covid-19 pandemic-related travel restrictions. An inspection of each of these facilities, to assess the ability of the facility to conduct the listed manufacturing operations in compliance with CGMP, is required before this application can be approved.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

II. Quality Assessment Summary

A. Background

Based on review of the original NDA 209988 (SN0001), the Agency issued a Complete Response Letter dated June-11-2018. The current resubmission (NDA 209988-SN0034) is aimed to address the deficiencies listed in the Complete Response Letter. The proposed product Furoscix® (Furosemide) Injection is a drug-device combination product. The Applicant discontinued the development of the original device constituent and has incorporated an improved device constituent. Information about the improved device constituent is cross-referenced to Master Access File (West Pharmaceutical Services, Incorporation's MAF [redacted] For this 505(b)(2) NDA resubmission, scPharmaceuticals is relying on the Agency's finding of safety and efficacy for the Listed Drug (LD) Furosemide (Injection, USP, 10 mg/mL; NDA 18667; Hospira, Inc.), which is indicated for intravenous (IV) and intramuscular (IM) injection for the treatment of edema in adult patients with congestive heart failure (CHF), cirrhosis of the liver, and renal disease, including nephrotic syndrome. There are other approved furosemide injectable products including the LD, but their basic pH (8.0-9.3) makes them not most optimal for subcutaneous administration.

B. Drug Substance (Furosemide USP)

The drug substance, a light-sensitive crystalline powder, is practically insoluble in water. The Applicant has referenced all CMC information concerning the drug substance, including structural characterization, manufacturing, batch analysis, control strategies and stability to DMF [redacted]

which has been previously reviewed (Review #26, January 2020) and found adequate. The Furosemide drug substance specification complies with the USP monograph. Based on review of information provided in the NDA, the critical quality attributes (CQAs) of the drug substance are monitored on release per specification. The drug substance stability data support a retest period of (b) (4) under storage conditions (b) (4)

C. Drug Product Furoscix® (Furosemide) Injection

C1. Formulation Design, Composition and Specification: Furoscix® (furosemide) injection; 8 mg/mL is a clear liquid in a 10 mL cartridge closed with a (b) (4) piston and septum. Specifically, the proposed drug-device combination product consists of two components i.e., the cartridge and infusor. The cartridge is a (b) (4) polyolefin container that contains 10 mL of formulation at one strength, 8o mg/10 mL. All inactive ingredients are compendial (USP-NF) and their levels are below the maximum listed amount in the FDA Inactive Ingredient Database (IID) for subcutaneous administration, except for Tris HCl. Tris HCl is not listed in the inactive ingredient database; however, its neutral form, tromethamine (Tris base, Tris, or Tham; CAS 77-86-1 or 83147-39-1) is USP compendial and listed in the IID. Also, Tris base is approved as a Tham solution (tromethamine injection; NDA 013025, Hospira; 3.6 g/100 mL). The drug product specification meets the requirements of USP-NF monograph. The product critical quality attributes (CQAs) such as appearance, identification, pH, volume in the container, assay, related substances, weight loss, osmolality, particulate matter, (b) (4), container closure integrity, endotoxin, sterility, and break loose and glide force are tested on release. Regarding the specified impurities, Compound A is controlled at identification threshold per ICH Q3B (calculated per the maximum daily dose of 80 mg). The acceptance limit (1.0%) for compound B is consistent with furosemide USP-NF monograph. The toxicological qualification data for (b) (4) are deemed adequate by the Pharmacology/Toxicology review team. The pH acceptance limit per furosemide USP-NF monograph i.e., 8.0-9.3 differs from the Applicant's proposed pH acceptance limit of (b) (4) In the original submission, the OPQ recommended that the Applicant contact the USP to request a revision to the monograph, or alternatively include the following statement: "FDA-approved pH specification differs from the USP". The Applicant agreed to the latter and, therefore, the pH acceptance limit is acceptable. The Applicant has provided an elemental risk assessment; showing elemental impurities remains within thresholds of ICH Q3D. The (b) (4) levels are markedly lower than the WHO "acceptable safe range" of (b) (4) mg/day intake for adults.

C2. Volume in the Container: Per USP <1151>, for a 10-mL labeled volume, the allowable excess volume is 0.5 mL. The proposed acceptance criterion for volume in the container, (b) (4) mL, exceeds the afore-mentioned limit. However, the Applicant claims that the device tightly controls the administered volume at 10.0 mL (b) (4) The validity of this device performance-related claim remains to be confirmed given a series of device-related deficiencies, identified by the CDRH review team.

C3. Product Stability: The stability data indicate that the drug product is stable at long-term storage conditions (25°C/40% RH) up to 9-month (commercial batches) and up to 6 months at accelerated storage conditions (40°C, NMT 25% RH). The photostability study results indicate that the commercial pack protects the drug product from light.

C4. Manufacturing: The manufacturing process for commercial production of Furoscix utilizes typical pharmaceutical unit operations associated with the small volume parenterals profile class (b) (4) (b) (4). Each manufacturing unit operation has been evaluated for its potential impact on product quality. The unit operations have been found to have a low level of risk on both intermediate and final drug product quality attributes. Satisfactory execution of manufacturing instructions within the Master Batch Records, in conjunction with favorable results from both in-process checks and from release testing of registration batches, suggest that the unit operations mentioned above were properly controlled during manufacture of the registration batches that support this resubmission. The overall control strategy sufficiently supports consistent production of finished product capable of meeting predetermined acceptance criteria.

C5. Microbiological Aspects: Based on review of the original NDA submission, the container closure integrity testing and (b) (4) bioburden testing were deemed inadequate. However, these deficiencies are not currently relevant because the Applicant has proposed a new manufacturing site and a new container closure system in the NDA resubmission. (b) (4) (b) (4) (b) (4) The submitted information regarding the microbiological aspects such as container closure integrity testing and sterilization validation is adequate. The drug product release specification includes testing for bacterial endotoxins (USP <85>) and sterility testing (USP <71>).

C6. Biopharmaceutics Aspects: Per the original submission, the current NDA relied upon the FDA's findings of safety and efficacy for the LD. The bridge between the proposed drug product and the LD was established by a two-way crossover bioequivalence study. Hence, no biowaiver has been requested in the resubmission. This NDA resubmission does not include any biopharmaceutics data/information to be assessed by the biopharmaceutics review team.

D. Device Evaluation

The device components of the proposed combination product consisting of Crystal Zenith® (CZ) cartridge, and a proprietary wearable, pre-programmed on-body delivery system, the Infusor, which is based on the SmartDose® Gen II 10 mL design. The Infusor is a pre-programmed device that administers a fixed dose of cartridge solution into the subcutaneous tissue of the abdomen. It can be administered by patients, caregivers, or a health care professional at home or in a clinic setting. The Infusor has an integrated adhesive patch, which attaches the device to the skin for dose administration. The device is loaded with a prefilled primary container assembly by the user prior to use. The system delivery parameters are to be pre-programmed (b) (4) to deliver 10 mL of Furoscix over 5 hours using a biphasic delivery profile, which results in dosing 30 mg furosemide over the first hour followed by 12.5 mg furosemide per hour for the subsequent 4 hours (total dose of 80 mg furosemide).

The user interface consists of one activation button, a drug compartment, LED lights, auditory signal (beep), and viewing window for viewing the dose delivery. User interface with the program

controller is limited to the activation button; operation parameters are inaccessible to the user. The device is pre-programmed by West and does not allow the user to alter program settings.

Based on CDRH review, the device constituent of the combination product is not approvable. The principal concern is that the Applicant has made significant changes to the design of to-be-marketed device during this review cycle without the FDA's prior knowledge. Changing the device during the review cycles raises additional questions regarding its safety and efficacy and the relevance of all the presented documentation. Hence, the Agency cannot determine whether the information presented in the original submission actually supports the safety and effectiveness of the to-be-marketed device design. In addition, the Master Access File (MAF) (b) (4) cross-referenced for significant documentation to support the device constituent of your combination product, is inadequate. The Device Improvement Report submitted on September 29, 2020 indicates that the Applicant's proposed device has been modified subsequent to the completion of the human factors (HF) study. It is unclear whether the device modifications affect critical tasks associated with the safe and effective use of the device or whether changes to Instructions for Use (IFU) are warranted. Additionally, the information regarding device performance, and biocompatibility evaluation is inadequate. A series of identified device-related deficiencies, to be communicated to the Applicant, are listed in Section H. List (page 6-17).

E. Assessment of Manufacturing Facilities

The drug substance, drug product, and device-related manufacturing facilities have been assessed by the Office of Product Manufacturing and Assessment (OPMA) and CDRH teams (where needed). Several facilities related to device manufacture and kit packaging are recommended for pre-approval inspection (PAI) by the CDRH review team as per ICC2000553. ORA has concurred. Per Official Action Indicated (OAI) status, the (b) (4) facility is considered to be in an unacceptable state of compliance with regards to current good manufacturing practice (CGMP). So, the manufacturing inspection recommendation (OMIR) is 'Withhold'. All other supporting facilities are acceptable based on inspectional history and demonstrated manufacturing, packaging, and testing capability. The outstanding deficiencies and facility inspection-related comments, to be communicated to the Applicant, are listed in Section H. List (page 6-17).

F. Environmental Assessment

The Applicant's claimed categorical exclusion from the requirement of an environmental assessment per 21 CFR 25.31 (b) is acceptable.

G. Product Quality Labeling Recommendations: Because the NDA is not recommended for an approval, a detailed labeling evaluation for the proposed drug-device combination product has not been carried out.

H. List of Outstanding Deficiencies:

Device

Overall

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) (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 cycles 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 [redacted] 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 [redacted] provide a 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 [redacted]. 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, [redacted] 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. You 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. You labeling needs to adequately 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) and your response to the IR #2a remains incomplete. Please 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 (e.g. 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 your HF validation study to be conducted with your intend-to-market device. Furthermore, it is unclear whether the device modifications affect critical tasks associated with the safe and effective use of the device or require changes to your Instructions for Use (IFU). Thus, additional information is necessary to determine whether the modified device can be used safely and effectively.

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

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

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

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

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)

    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 design 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 which 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) 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) 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 (e.g. 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 MAF (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 are known to have changed (Deficiency #1). For example, scP-00-004 in SN0040; this document is not referred to 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)

[redacted]

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) 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 (b) (4) For software specifically, it is not possible to accurately predict (b) (4) 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. (b) (4) (b) (4) (b) (4) Your device is outside the FDA recognized scope (b) (4) (b) (4). 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.

Facility Inspection:

29. During a recent inspection of the (b) (4) manufacturing facility for this application (FEI: (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 with regard to your application. 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 the [redacted] (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 with regard to your application. 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

III. Life Cycle Knowledge Information

(Please see the next page)

Final Risk Assessment

NDA 209988-SN0034: Furoscix® (Furosemide) Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation/Enhancement**	**Final Risk Evaluation**	**Comments**
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment / Site	Low	(b) (4)	Acceptable	
Solid state - Polymorphic form)	Formulation Raw materials Process parameters Scale/equipment/ site	Moderate		Acceptable	
Particulate matter	Formulation Raw Materials Process Parameters Scale/equipment/ site	**Low**		Acceptable	
pH	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	**Low**		Acceptable	
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	**Low**		Acceptable	
Manufacturing Facilities	Manufacturing Site Status cGMP	**High**		**Unacceptable**	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation/Enhancement**	**Final Risk Evaluation**	**Comments**
Device attributes	Device Design Device performance Device specification Compatibility	**High**	(b) (4)	**Unacceptable**	
Microbial limits	• Formulation • Raw materials • Process parameters Scale/equipment/site	Low		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209988-SN0034; Furoscix® (Furosemide) Injection is not recommended for approval because per Official Action Indicated (OAI) status, the (b) (4) facility is considered to be in an unacceptable state of compliance with regards to current good manufacturing practice (CGMP). Additionally, due to unresolved device-related deficiencies, the device constituent parts of the combination product are not approvable. Satisfactory resolution of these device-related deficiencies as well as outstanding deficiencies concerning the (b) (4) facility is required before this application can be approved. Pre-approval inspections of Sharp Corporation (FEI # 3004161147), and (b) (4) facilities could not be conducted due to Covid-19 pandemic-related travel restrictions. An inspection of each of these facilities, to assess the ability of the facility to conduct the listed manufacturing operations in compliance with CGMP, is required before this application can be approved.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead; Division of Cardiology and Nephrology
Member, Emerging Technology Team (ETT)
Office of Pharmaceutical Quality; CDER/ FDA

Mohan K. Sapru -S

Digitally signed by Mohan K. Sapru -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohan K. Sapru -S, 0.9.2342.19200300.100.1.1=2000589315
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CHAPTER VII: BIOPHARMACEUTICS

NDA: 209988-ORIG 01/RESUB-34 following Complete Response Letter (dated 06/11/2018)
Drug Product Name / Strength: Furoscix™ (furosemide injection), 80 mg/10 mL
Route of Administration: Subcutaneous Injection via the infusor
Applicant Name: scPharmaceuticals, Inc.
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Poonam Delvadia, Ph.D.

Background:

This NDA 209988-ORIG-1 (dated 06/30/2020/SN 0034) is a resubmission in response to a Complete Response Letter that was issued on 06/11/2018. scPharmaceuticals, Inc. submitted the original NDA 209988 on 08/23/2017 to seek approval for Furoscix® (furosemide injection), 80 mg/10 mL for the treatment of edema associated with congestive heart failure *via* the 505 (b)(2) regulatory pathway. The listed drug (LD) is Furosemide Injection, USP, 10 mg/mL which was approved under NDA 018667 on 05/28/1982.

REVIEW SUMMARY:

The proposed drug-device combination product contains 8 mg/mL furosemide solution, pH (b) (4) that will be provided in a sterile, single-use prefilled Crystal Zenith® (CZ) cartridge assembly with a target fill volume of (b) (4) mL and optimized to deliver Furoscix® subcutaneously with the help of a wearable, pre-programmed on-body Infusor based on SmartDose® Gen II 10 mL delivery system. The Infusor will be pre-programmed to deliver 10 mL Furoscix® over a period of 5 hours with 30 mg furosemide to be delivered over the first hour, followed by 12.5 mg furosemide per hour for the next 4 hours for a total dose of 80 mg furosemide using a biphasic delivery profile.

Following the issuance of the Complete Response Letter (dated 06/11/2018) and to address the deficiencies in the Complete Response Letter, the Applicant discontinued the development of the B. Braun Perfusor Space Infusion Pump device (pre-change) from the original submission and introduced an improved pre-programmed Infusor device that is based on SmartDose® Gen II 10 mL delivery system (post-change).

In the original submission, the current NDA relied upon the FDA's findings of safety and efficacy for the LD. The bridge between the proposed drug product and the LD was established by a two-way crossover bioequivalence study. No biowaiver was requested in the submission. The drug product is a clear and sterile solution for subcutaneous injection that does not contain any rate limiting excipients, therefore an in vitro drug release testing was not applicable for batch release or stability testing of the originally proposed drug-device combination product. The To-

Be-Marketed/registration batch (Lot 006E14) was used in the pivotal bioavailability/bioequivalence studies (ScP-01-001, 002, 003 and CP-00001). Therefore, there was no need for formulation bridging.

In the current resubmission, the formulation for Furoscix® is unchanged. However, as the Applicant introduced a new Infusor device in the current resubmission, there is a need for bridging the pre-change and post-change drug-device combination product that will be assessed by the CDRH Reviewers.

OVERALL REVIEW RECOMMENDATION:

There is no biopharmaceutics information contained in the submission, and therefore a Biopharmaceutics review is not needed for this NDA.

Parnali Chatterjee

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Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 9/14/2020 09:07:59AM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	209988
Assessment Cycle Number	MR02
Drug Product Name/ Strength	Furosemide Infusor/ 80 mg/10mL
Route of Administration	Subcutaneous
Applicant Name	scPharmaceuticals Inc.
Therapeutic Classification/ OND Division	OCHEN/DCN
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Resubmission	06/30/2020
Response to IR	07/23/2020
Response to IR	08/03/2020
Response to IR	09/16/2020
Response to IR	10/21/2020
Response to IR	11/06/2020

List Submissions being assessed (table):

Highlight Key Issues from Last Cycle and Their Resolution: CCIT inadequate; (b) (4) bioburden testing inadequate. Deficiencies from last cycle are not reviewed because the sponsor proposes a new manufacturing site and a new container closure system in the resubmission dated 06/30/2020.

Remarks: NDA209988 was originally submitted on 08/23/2017. The original submission was reviewed and found inadequate on 03/12/2018. CR letter was issued on 06/11/2018. Resubmission was provided on 06/30/2020, which proposes changes in the product manufacturing site and the container closure system. The product composition remains unchanged. Submission dated 07/23/2020 and 08/03/2020 were provided in response to the Agency's information request dated 07/21/2020. Submission dated 09/16/2020 was provided in response to the Agency's information request dated 08/19/2020. Submission dated 10/21/2020 was provided in response to the Agency's

information request dated 10/06/2020. Submission dated 11/06/2020 was provided in response to the Agency's information request dated 10/27/2020.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): N/A

Supporting Documents:
DMF (b) (4) was reviewed and found adequate (b) (4) on 09/15/2020.
DMF (b) (4) was reviewed and found adequate (b) (4) on 09/15/2020.
DMF (b) (4) was reviewed and found adequate (b) (4) on 09/24/2020.

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product—

The product Furoscix® is a clear liquid in a 10 mL cartridge closed with a (b) (4) piston and septum. Each cartridge has a fill volume of (b) (4) mL and contains a single-dose of 80 mg furosemide. It is intended for subcutaneous

administration and will be administered via Furoscix Infusor, a single-use subcutaneous delivery system.

Drug product composition—no change.

Ingredients	Quantity	Function	Quality Standard
Active Substances(s)			
Furosemide	8.00 mg	Active ingredient	USP/Ph. Eur.
Excipients			
Tris HCl	7.88 mg	(b) (4)	(b) (4)
Sodium Chloride	5.84 mg		USP/NF, Ph. Eur.
Hydrochloric Acid	qs to pH 7.4	pH adjustment	USP/NF, Ph. Eur.
Sodium Hydroxide	qs to pH 7.4	pH adjustment	USP/NF, Ph. Eur.
Water for Injection	qs to 1 mL	(b) (4)	USP/NF, Ph. Eur.

NF = National Formulary; Ph. Eur. = European Pharmacopoeia; qs =quantity sufficient; USP = United States Pharmacopeia

(Table reproduced from the submission).

Description of container closure system

Component	Description	Supplier
Crystal Zenith (CZ) SmartDose Cartridge assembly 10 mL	Ready to use, polyolefin plastic cartridges with (b) (4) rubber septa and plastic tip caps	West Pharmaceuticals
SD2 10 mL Piston (b) (4)	Ready to use, (b) (4) rubber piston	Daikyo

Assessment: Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

[redacted]

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MICROBIOLOGY LIST OF DEFICIENCIES

N/A

Primary Microbiology Assessor Name and Date: Yan Zheng, Ph.D. 11/09/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Jesse Wells, Ph.D., SPQA. 11/09/2020

Jesse Wells

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Date: 11/09/2020 12:00:29PM
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Yan Zheng

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Date: 11/09/2020 12:00:39PM
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OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	11/13/2020		
To:	Brian Proctor and Carol Holquist		
Requesting Center/Office:	CDER/OND and CDER/OSE	**Clinical Review Division:**	DROCHEN and DMEPA
From	Max J. Lerman, PhD OPEQ/OHT3/DHT3C		
Through (Team)	Carolyn Dorgan, MS, Acting Assistant Director, Infusion Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Acting Director OPEQ/OHT3/DHT3C		
Subject	NDA209988 , Furosemide Pump (Furoscix Infusor) ICC2000553 ICCR00022595 and ICCR00022793		
Recommendation	**Filing Recommendation Date: 7/22/2020** ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing ☑ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 4 for Deficiencies		
	Mid-Cycle Recommendation Date: Click or tap to enter a date. ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A		
	Final Recommendation Date: 11/13/2020 ☐ Device Constituent Parts of the Combination Product are Approvable ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2 3 ☑ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2 2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

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1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA209988
Sponsor	scPharmaceuticals
Drug/Biologic	Furosemide Pump (Furoscix Infusor)
Indications for Use	Treatment of edema associated with congestive heart failure
Device Constituent	Infusion Pump
Related Files	ICC1800677 and ICC1700691

Review Team		
Lead Device Reviewer/Engineering	Max J. Lerman, PhD	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
Biocompatibility	Rong Guo (CDRH/OHT3/DHT3C)	CON2017344
Sterility	David Wolloscheck (CDRH/OHT3/DHT3C)	CON2017345
Human Factors	Janine Purcell (CDRH/OHT3/DHT3C)	CON2017347
Chemical Characterization	Berk Oktem (CDRH/OSEL/DBCMS)	CON2017433
Toxicological Risk Assesssment	Caroline Pinto (CDRH/OSEL/DBCMS)	CON2017440
Electrical Safety	Ethan Cohen (CDRH/OSEL/DBP)	CON2017343
Electromagnetic Compatibility	Bonhye Koo (CDRH/OHT3/DHT3B)	CON2017342
Software	Marc Neubauer (CDRH/OHT3/DHT3C) **Reviewer note**: Device is stated as having no connectivity functionality. Therefore, cybersecurity is not considerd a relevant discipline for this review.	CON2017346

Important Dates	
Discipline-Specific Review Memos Due	9/15/20
Final Lead Device Review Memo Due	12/8/20
Interim Due Dates	**Meeting/Due Date**
Filing	7/22/20
74-Day Letter	7/22/20
Mid-Cycle	9/30/20 **Reviewer note**: No MidCycle review memo was provided as it was determined this file would be receiving a second CR.
Primary Review	12/8/20
Internal Meeting(s)	11/17/20
Sponsor Meeting(s)	N/A

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☑ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description		X		
Labeling		X		
Design Controls		X		
Risk Analysis		X		
Design Verification		X		
Consultant Discipline Reviews		X		
Clinical Validation			X	Deferred to Next Review Cycle. Not completed at this time.
Human Factors Validation		X		
Facilities & Quality Systems			X	Deferred to CR response. Not completed at this time.

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #1: The principal concern is the device was modified by the Sponsor during the review cycle. This jepordizes the submission as the Lead Reviewer is unable to definitively determine the adequacy of the provided information – changing the device impacts nearly all review areas. The Sponsor and the MAF holder are advised of this. The Sponsor should:

1) Freeze their design (as is required per their approach to design controls)
2) Submit their device design for review.

Given the changes and the reququested information, clinical validation and QS/Facility review is deferred to the next review cycle.

Comment #2: The Lead Review division should provide comments to the Sponsor and to the MAF holder. These are separated to maintain the requested confidentiality between the parties. Please submit CR deficiencies in 2.2.1 to the **NDA Sponsor** (scPharmaceuticals). Please submit CR deficiencies in 2.2.2 to the **MAF holder** (West).

2.2. Complete Response Deficiencies

☐ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☑ CDRH is providing the following 'letter-ready' Deficiencies written so they can be directly communicated to the NDA Sponsor and MAF Holder:

2.2.1. NDA Sponsor Deficiencies

Introduction

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 cycles raises additional questions regarding its safety and efficacy and the relevance of all presented documentation. Therefore we cannot determine if the information presented in the original submission supports the safety and effectiveness of the to be marketed design. In responding to this 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 MAF (b) (4) for significant documentation to support the device constituent of your combination product is safe and effective. There are outstanding deficiencies with the Master File. Please work with the Master File Holder to ensure adequate resolution of the identified deficiencies. Then resubmit your NDA only once the deficiencies are all resolved and documentation is present in the Master File.

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, ISC (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) provide a 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). 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 Compatability

8. You labeling does not contain adequate electrical safety and electropmagnetic 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 updated your labeling. You have not; however, updated your labeling as requested. You labeling needs to adequately 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 Intened 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) You have provided insufficient evidence to support (b) (4) and your response to the IR #2a remains incomplete. Please 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 (e.g. 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.

Software/Cybersecurity

12. 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 deivce, 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 Assurnace 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

13. 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 mitiates against fluid ingress.
    - You refer to a component in your design (b) (4) which you have changed (See deficiency #1).

    (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.

14. 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). As your response is incomplete, the original request remains. rms and ensure these are challenged at your boundary conditions through verification testing to ensure adequate function.

15. In your response in SN0036 Section 1.11.1 to IR #4b, you state, (b) (4)

    (b) (4)

    (b) (4) Please redesign your device design 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

Commented [LM1]: Reviewer note: CDER/RPM should confirm cross-reference of highlighted deficiencies before issuing CR letter. The cross-reference is correct in this memo. These are highlighted throughout memo.

Commented [DC2]: Double check cross reference before issuing CR Letter

16. 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.

17. (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 which 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.

18. Your SAC does not include justification for the adequacy of your specifications for your intended use. (b) (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

19. 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) 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). 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) (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.

20. 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 (e.g. 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 MAF (b) (4) which you do not refer to and contain the information you need. For example, the information in MAF (b) (4) does not verify your device (b) (4) (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 are known to have changed (Deficiency #1). For example, scP-00-004 in SN0040;this document is not referred to device-rpt-0360.

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Provide a revised Verification and Vaidation 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.

21. 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

22. 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.

23. You define your severity ratings in SOP-0034. (b) (4) (b) (4) (b) (4) Please provide adequate mitigations for all severities (b) (4) OR revise your definitions of severity rating to distinguish (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.

24. 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 (b) (4) For software specifically, it is not possible to accurately predict (b) (4) software only hazards. You may use a probability of harm if the software hazard occurs.

Safety Assurance Case: Demonstration of Adequate Reliability

25. 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.

26. 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-markeded device to demonstrate the device's ability to meet this requirement.

27. We note you do not link your reliability argument to the clinical risks assopcaited with your device. (b) (4) (b) (4) (D) (4) Your device is outside the FDA recognized scope (b) (4) (b) (4). 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..

2.2.2. MAF Holder Deficiencies

Introduction

1. The NDA holder has informed the Agency that you, "…*explored a further modification* (b) (4) (b) (4) *and a corresponding software parameter adjustment.*" We are uncertain as to the relevance of the testing you have submitted, as you continue to make modifications to the device and submit new data. It is our expectation that you finalize the device design and then submit your to-be-marketed device, and its supporting information, for review. This includes, but is not limited to, your design verification, sterility, and software testing. Please finalize your design and the submit complete documetantation for Agency review.

2. We note that you continue to make changes to your device during the review cycle and your documentation details recommended device redesigns to address failing device attributes. Given these two items, we remind you that it is our expectation that your testing is performed on your to-be-marketed device. Please:
   a. State for each reference report, the device version used in your testing.
   b. If you use a previous version of your device for any verification evidence, you should clearly state the differences between the to-be-marketed device and the version which testing was performed on and justifiy the relevance of the testing.

3. The structure of your MAF (b) (4) continues to make it extremely difficult to determine (1) the relevance of repeated information (i.e Sterilization) and (2) the location of specific reports/documents/information (i.e. within the Design Verification Test Reports). We acknowledge you have submitted data in Ammendments 3, 4, and 5. A unified table of contents which contains only the relevant information for review would allow us to rapidly determine the location of evidence in your submission. Please provide a unified table of contents which references only the information pertitnent to your to-be-marketed device and identifies the location of all current, relevant, referenced documents within the Master File in response to updates to the Master File.

Sterility

4. We have determined that your submitted sterilization information is sufficient to support a 1 year shelf-life. We could not locate data to support your (b) (4) shelf-life. We understand you are seeking a (b) (4) shelf-life; therefore, you should provide data to support your intended shelf-life. Provide data which demonstrates your device's sterile barrier is maintained at expiry, at worst-case, reasonably-conceivable, conditions (e.g. following (b) (4) sterilization and shipping simulation, sequentially) for (b) (4) or modify the labeling to recommend a shelf-life commerserate with your testing.

5. You stated in 3.2.R.1.P.3 Section 7.1 that the device constituent is delivered non-pyrogenic. However, we were unable to locate information regarding bacterial endotoxin testing of the device constituent parts of your proposed combination product. This information is needed to ensure that your device is safe for its intended use. Provide preliminary endotoxin testing demonstrating that the device meets the appropriate limits for endotoxin for a direct or indirect blood contacting device. For further guidance on this issue please refer to ANSI/AAMI ST 72 Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing and Guidance for

Industry Pyrogen and Endotoxins Testing: Questions and Answers.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm

a) Please provide endotoxin unit (EU) limits, test methodology to determine EUs (extraction volume, limit of detection with the given volume, inhibition/enhancement testing), and test reports for bacterial endotoxin demonstrating acceptable EU limits.
b) Please specifically address the number of devices tested per lot, and lot size.
c) Please indicate whether batch testing or an alternative sampling plan will be utilized.

Software/Cybersecurity

6. In Amendment 3, you provide additional information regarding your alarms/errors into your description document; however, you did not update your software requirements specification document or software design specification document. In addition, you did not provide quantitative triggering definitions including all appropriate ranges, tolerances and units for all alarms/errors where applicable, provide SRS specifications that define your algorithms (b) (4) and their performance requirements (i.e. specificity/sensitivity) to ensure unnecessary false alarms do not occur, trace these requirements to their risk hazards and verification testing, provide verification testing that ensures the boundary conditions are tested where applicable, and for system level alarms/errors that include software and hardware components, test a representative sample of pumps per your defined reliability specification. This information is important to determine if your errors/alarms are adequately defined for their intended use and will trigger reliably in the field. Please provide the following information:
    a. In your SRS document, please provide quantitative definitions with ranges, tolerances and units, where applicable, for your software alarms/errors.
    b. Please define the sound pressure level for your alarms and provide a justification for this specification.
    c. Please clarify the number of software algorithms used in your firmware (b) (4) (b) (4) and provide SRS requirements that describe how these algorithms work and performance requirements (i.e. sensitivity/specificity, etc.) to ensure the algorithms work appropriately (i.e. do not have too many false alarms).
    d. For all SRS requirements, including those that define errors/alarms, provide a traceability table that traces the SRS requirement to its risk hazard, if appropriate, and verification testing.
    e. Provide system level verification protocols (i e. test steps, acceptance criteria) and reports (i.e. raw data and conclusion) for all applicable errors/alarms which should include:
        i. Testing at the boundary conditions for each SRS, where applicable.
        ii. System level testing with an adequate sample size that meets the definition of your reliability specifications, where appropriate.
        iii. Please provide this testing in one document or groups these documents in one section for ease of review.
    f. Please provide the NDA holder with reliability information for your system level alarms/errors as this information is needed to ensure reliability aligned with the intended use..

7. In your document, SmartDose Gen II 10 ml SW Code Review, you provide your static code analysis and state it is for a full code coverage of SW Revision SW0025.02.03. This does not provide us adequate assurance that you have rigorously conducted your unit testing since you have not defined code coverage requirements (i.e. statement coverage, branch coverage) and provided evidence that you have met your requirements.
    a. Please provide a list of software modules with a short description of the functionality, the IEC 62304 safety classification and your predefined code coverage requirements taking a risk based approach.
    b. Provide a summary report that demonstrates you met your code coverage requirements for each module. If you do not meet the requirements for some modules then provide a risk based justification.
    c. Please provide the NDA holder with code coverage information for static testing as this is needed to support the NDA application per the intended use.

8. Please address the following concerns regarding your software development environment and software defects:

   a. You state your software configuration and defect handling procedure is included in [redacted] Software Life Cycle Procedure but you did not provide this procedure. For Major Level of Concern software, this documentation is required. Please provide [redacted] Software Life Cycle Procedure. In addition, ensure your software defect procedure includes the requirements that open defects include a risk severity and a risk based justification for not addressing the defect in the current software release.

   b. You provide in Amendment 003, [redacted] Attachment A: Unresolved SW Anomalies. Your list of open software defects should discuss the potential harm and severity score associated with each unresolved defect and the clinical justification for why you do not have to address this defect in the software version you intend to release to the market.

   Without this information, we are unable to assess the safety and efficacy of your software. Please provide the requested information.

9. You provided a document titled SmartDose® Gen II 10 [redacted] SW Cybersecurity Risk Assessment. This document discusses your assets, threats and controls; however this document is not complete and additional information is needed for us to analyze the controls you have in place. Please address the following deficiencies:

   a. We recommend you provide a threat model that describes for each unique asset/vulnerability combination, you include a description of the attack vector, the severity score and description of the associated harm, the chain of events to carry out attack, the level of skill required for the attacker to compromise the asset/vulnerability, your control measures, NIST core function classification of the control (i.e. protect, detect, etc.), reference any requirement (i.e. SRS), and provide link to FMEA.
   b. This document does not discuss if there is any off-the-shelf (OTS) software used in your pump. It is important to list the OTS software and discuss if there are any known vulnerabilities. Please state if you incorporate any OTS software. If you do then update the assets on your risk document and for each OTS asset, list any known vulnerabilities and how you plan to address them.
   c. It does not appear your cybersecurity includes the hazardous situation of malicious programming that may lead to a higher programmed rate than acceptable per your specifications. An unauthorized user may be able to program a higher rate and which may lead to harm of overinfusion. Please add this harm and reassess if you need additional controls. For example, if a higher rate may lead to serious harm then you should consider stronger controls [redacted].
   d. You state the controls you have in place at manufacturing [redacted] however you do not provide the specification/requirements for these controls or provide your manufacturing procedure that controls this process. It also appears you do not assume you may have a rogue employee. Please provide the specifications/requirements for your controls, provide your manufacturing procedure, and discuss how you may mitigate against a rogue employee. Please ensure your passwords are not documented in your SOP.

Electrical Safety

10. You did not provide your electrical safety evaluation checklist performed by your testing house. Your device should conform to the FDA recognized standard AAMI/ANSI ES60601-1-1:(2005) R2012 Part 1 *Medical Electrical Equipment General requirements for basic safety and essential performance* to ensure your device is electrically safe. Please supply the missing testing house checklist to assure patient safety.

11. You did not provide your home healthcare electrical safety evaluation checklist performed by your testing house. Please be aware that your device should conform to the standard IEC 60601-1-11 *Medical electrical equipment – Part 1-11 General requirements for basic safety and essential performance – Collateral Standard Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment*. Please supply the missing testing house checklist to assure patient home healthcare safety with the combination product.

12. You did not provide a water ingress (IPX) rating for your deivce. Your device is body worn and has the potential to come incontact with liquids while in use. Without an IPX rating, and accompanying testing, we are unsure your device is electrically safe for your proposed use-case. Please supply an IPX rating for your device to assure patient safety on either the product labeling or patient instructions for use and testing to support your rating.

13. You did not provide your risk management document (b) (4) to show conformance to ISO 14971. We recommend you build your risk documentation following one of the FDA recognized versions of ISO 14971 (e.g. 2007 or 2019). In order to assure adequate patient safety and adequate risk mitigation, please supply the missing design failure mode and effects analysis document and any other risk management documents.

14. You provide testing in (b) (4) Rev 1.0/Attachment 9-4 in Amendment 003 for your alarms. The method contained from your testing house states (b) (4). Your approach to assuring alarm adequacy is unjustified and you have not provided evidence that your device meets the alarm requiments detailed in the FDA recognized standard IEC 60601-1-8: 2012 *Medical electrical equipment –Part 1-8 General requirements for basic safety and essential performance –Collateral standard General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems*. Please demonstrate your device is in conformance with IEC 60601-1-8:2012 or provide a justification for why your alarms are appropriate for your intended use and meet the elements of IEC 60601-1-8:2012 using alternative methods.

Electromagnetic Compatibiltiy

15. You provide EMC testing in Attachment 9-5 in Ammendment 003. You use (b) (4) (b) (4) for your requirements and justification for several EMC tests, (b) (4) (b) (4) While the FDA recognizes these standards, these are recognized for injection devices. Your device is an infusion device; therefore, the relevance of these standards is unknown. We are unable to evaluate the adeaucy of your EMC testing without a scientifically valid justification for your requirements and testing design rationale. Please provide a valid scientific justification for your EMC testing design or provide new testing which demonstrate your device functions in the relevance challenge conditions.

16. According to the EMC test report contained in Attachment 9-5 in Ammendment 003, the battery specification is (b) (4) However, you did not provide the manufacturer, the type, and the power of the battery. This information is recommended by IEC 60601-1 and necessary to ensure your battery is adequate for your use-case. Please provide the manufacturer, the type, and the power of the battery.

17. On page 7 of Attachment 9-5, you state, "*All tests were performed on SmartDose® Gen II 10 mL* (b) (4) (b) (4) *Rev.A.02, with Bi-phasic delivery of 10.0 [mL]* (b) (4) *drug in 5* (b) (4) *hours,* (b) (4) ou did not state if the tests were conducted with the to-be-marketed version of the device. We understand that you have changed your device during the review cycle (i.e. Deficiency #1); therefore, we believe you did not perform this testing on the final version of your device. All tests should be conducted with the final version of the device. Alternatively, your may provide a valid justification explaining the adequacy and relevance

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for the performed testing. Please state which version of the device your EMC testing was conducted with (e.g. the to-be-marketed version) or provide a justification as to why device changes do not affect the test results.

18. In the EMC test report, you did not clarify if there are device modifications. This information is needed to ensure that the tests were adequately conducted. Please clarify if there were device modifications/test allowances from the to-be-marketed device. If there was, please justify why the modifications do not affect the validity of the test results.

Engineering/Performance/Risk Assessment

19. 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 contained in you Master File are incomplete. All test reports should contain 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 are below and for examples where your test reports lack the elements described in the guidance:
    a. You fail to provide complete explanation of your methods and justification for apporaches. Without knowing how you collect data, we are unable to review the adequacy of the data. Provide all your relevant methods so we can ascertain the adequacy of your data collection approaches and the data generated. These include:
        i. (b) (4)
        ii.
        iii.
        iv.
        v.
        vi.
        vii.
        viii.
        ix.
        x.
        xi.
        xii.
        xiii.
        xiv. In (b) (4) Rev 1.0 Attachment 9-11 in Amendment 003, you appear to state the intent is to perform a documentation review, but then present data from other documentation locations. Please make it clear in your reports if you are verifying a design requirement is present in the design (e.g. the device contains an LED) or if the report is verifying the design requirement is adequate (e.g. LED illuminates).
    b. You refer to data/explanation as being located in files which you do not provide. We are unable to review data if you do not provide a clear location to all necessary information. Please review your submission and ensure it is complete. Specifically, please address the following:
        i. You refer to 15.1.8.1.1 and 15.1.8.1.2 in Attachment 11-7 Part 1 of Amendment 004 for containing data on out of specification devices. These sections could not be located. Provide all referenced data locations

ii. You refer to Appendices V-BB in Attachment 11-7 Part 1 of Amendment 004 for containing data. The highest attachment letter provided is V. Your file is incomplete. Provide all referenced data locations.

c. We are unable to determine the information contained in your reports due to a lack of clarity. Please address the following:
   i. Portions of your submission are difficult to read due to poor scan quality (Attachment 11-7 Part 1 Amendment 004, Attachment 9-11 Amendment 003, Attachment 11-8 Amendment 004). We are unable to assess the adequacy of data we cannot interpret.
   ii. You use inconsistent dating convention in your submission. For example, Page 128 of Part 1 Attachment 11-7 uses, what is believed to be the dating convention Month/Day/Year. Page 1 of Part 2 Attachment 11-7 uses, what is believed to be the dating convention Day/Month/Year. We are unable to assess the adequacy of data we cannot interpret.
   iii. Portions of your submission are not in English (e.g. pages 241-328 of Part 2 of Attachment 11-7 Amendment 004, pages 76, 205, 206 in Attachment 9-11 Amendment 003). We are unable to interpret data which is not in English. Revise your submission so all submitted information is in English or contains an adequate translation.
   iv. Your data in Amendment 003 and 004 appears to be on a previous version of your device (b) (4) (b) (4) in Attachment 9-12 of Amendment 003 regarding the (b) (4) Design Change of the (b) (4) configuration, in (b) (4) Attachment 11-2 Amendment 004/T5 timepoint in Attachment 11-8 and Attachment L for out of specification devices, (b) (4) for force to detach adhesive from the device and concealment of the patient needle, etc., (b) (4) for force to activate the button if the safety latch is open, Appendix 1 and 2 in (b) (4) in Attachment 9-10 Amendment 003). In addition, the NDA Sponsor has discussed changing your device. Please revise your submission to contain data for the to-be-marketed device only. If a report is being used to support your submission from a previous version of this device, you should justify the adequacy of the data contained (i.e. why the design changes do not impact the results).
   v. You refer to two different Appendix #2 in (b) (4) Attachment 9-9 in Amendment 003. We are uncertain as to which evidence you are referring to due to your chosen, overlapping, naming convention. It is important that we are able to rapidly identify the evidence you are using to support your submission in order to be able to evaluate its adequacy. Revise your submission to have clear, district, pointers to all necessary information.

d. You fail to justify and explain your approaches for adequacy. We are unable to determine the adequacy of your approach if you fail to provide your testing rationale. For example, please explain the following or revise your test method.
   i. Provide test method validations (e.g. TMV Report #3967-R, #3966-R, #4214-R, etc.), if you are relying on this evidence to demonstrate your test method is adequate.
   ii. You refer to many ISO standards which are not relevant your device, (b) (4) (b) (4). Your device is an infusion pump. If you are using an ISO standard to justify your testing, please ensure that the consensus recognized standard is recognized by the FDA for your device type. If it is not recognized, pleaes justify the use of the standard in building your test method.
   iii. While you refer to ASTM D4169-16 schedules (e.g. Attachment C of Attachment 11-7), you do not define an overarching distribution cycle or assurance level for your testing nor do you justify the adequacy of these choices for your device. We note you use the same approach for all ship-testing challenged. When referring you standardized testing with multiple methods to complete the testing, it is important that your clearly define your chosen method and justify your selection. Please define your methods and justify their adequacy. In addition, specifically, define and justify your shipping challenge method or provide testing for a stated distribution cycle.
   iv. While you state the use of IEC 60601-1-8 in defining your Alarm testing, your testing and test method do not follow this standard. Specifically, we note that your test lab's report in (b) (4) Attachment 9-4 Amendment 003 states (b) (4). You should

accurately present the data in your submission so we are certain of your approaches and can evaluate your methods. Provide testing which demonstrates conformity to IEC 60601-1-8: 2012 Ed 2.1

v. We note you reference IEC 60601-1 3.1 Edition for defining your free fall drop testing (b) (4) (b) (4) Attachment 9-9 in Amendment 003. This standard specifies distance of 1 m. Your testing does not align to the requirements of the standard. Provide testing which aligns to all referenced recognized consensus standards.

vi. In (b) (4) Attachment 9-10 Amendment 003 you provide a mechanical analysis in Attachment A to demonstrate a lack of influence of device orientation on dose delivery. Your analysis is limited to break loose/glide force (b) (4) (b) (4). Your justifications should clearly account for your device design and your intended use-case. Please justify your methods to adequately explain your approaches for your device and consider how your device will be used by the patient.

vii. We note you use a surrogate test liquid, not the proposed drug product in the cross-referenced NDA (e.g. (b) (4) Attachment 9-10 Amendment 003). You should justify the use of a surrogate test fluid so we can evaluate the adequacy of the presented data. Provide justification for the use of any test fluid surrogate or state the use of the drug-product of interest in your reports.

viii. We note the use of variable data analysis in your submission (e.g. (b) (4) Attachment 9-10 Amendment 003). While we acknowledge and agree with your demonstration of data normality and the use of goodness of fit testing to determine non-normal data models, your explanation of non-normal data should relate to your device and/or data collection methods. Without this explanation, we are unable to determine the adequacy of the presented data analysis. Please ensure you explain data non-normality for processes which are anticipated to be normal.

e. You fail to adequately justify protocol failures. Without an adequate explanation of protocol failures, we are unable to agree that your device is safe and effective. Please consider the following and explain why protocol failures still demonstrate your device adequately meets its intended use or redesign your device to correct the failures and repeat testing.

i. (b) (4)

ii.

iii.

iv.

v.

vi (b) (4)

20. We are unable to locate significant documentation which you refer to in your Master File for defining your risks, verification master plan, product requirements, test methods, data, etc. Please ensure your Master file is complete and contains necessary driving input documentation so that we understand your design intent and the inputs into your testing design. This includes the following or the applicable replacement documentation. Please ensure this documentation aligns to the NDA holder's understanding of your device and ensure consistency in your requirements and hazard assignments. Specifically, please provide:
    a. (b) (4) Design Verification Master Plan
    b. Product Requirements
    c. Design Input/Output
    d. dFMEA
    e. (b) (4)
    f. (b) (4) Design input requirements
    g.
    h. We note (b) (4) is in your submission, however, in (b) (4) Attachment 9-10 Amendment 003 your point to (b) (4)
    i. (b) (4)
    j.
    k. Attachment B of (b) (4)
    l. (b) (4)
    m.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

TABLE OF CONTENTS

Update Table of Contents

Formatting Guide – Interpreting this Memo:

The following pertains to the comments entered by the Lead Reviewer.

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Plain text indicates commenting and paraphrasing of reviewed submission documents
Italics indicate direct quotes from the sponsor
All Screenshots are direct quotes from the sponsor
Reviewer notes: provide context to remaining entered test. This includes relevant analysis to Sponsor summaries.
Underline is a subheading within a section, document, or review
Items in red are noted as deficient in context and analysis.
Items highlighted in red indicated deficiencies referred to in other sections for greater detail
Items highlighted in yellow are to draw attention. These potentially relate to other items in the submission but may not be explicitly deficient.

3. PURPOSE/BACKGROUND

3.1. Scope

scPharmaceuticals is requesting approval of Furosemide Pump (Furoscix Infusor). The device constituent of the combination product is an Infusion Pump.

CDER/OND has requested the following consult for review of the device constituent of the combination product:

ScPharmaceuticals has resubmitted their NDA 209988 for the Furoscix Infusor (combination product), indicated for the treatment of edema associated with congestive heart failure

CDER/OSE has requested the following consult for review of the device constituent of the combination product:

We request a review of the HF Validation Study report of results from the CDRH HF team perspective. NDA 209988 was resubmitted following CR and Type C meetings on June 30, 2020. The cover letter states that "In January 2019, following two meetings with the FDA to identify a path forward for continued development of the initial device constituent of the Furoscix® Infusor, scPharmaceuticals, Inc. (the Sponsor) discontinued the development of the original device constituent (pre-change device) and has incorporated an improved device constituent (postchange device), based on the SmartDose® Gen II 10 mL (West Pharmaceutical Services), for the combination product that addresses issues identified by the Agency in the CRL." CDRH provided recommendations on the HF Validation Protocol on 8/6/2019 under IND 118919 (ICC 1900582). DARRTS Link: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8050ba35&_afrRedirect=905941346941035 Additionally, CDRH provided comments to Questions 1-8 for a Type C Meeting Request for the Furoscix Infusion NDA 209988 (ICC 1800904 and ICCR2018-03895) DARRTS Link: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af804cd838&_afrRedirect=903189666505126 The applicant states validation studies commenced on Oct 29, 2019 and that they incorporated the Agency Advice in the revised protocol. We request you review the HF validation study results and provide a review back to DMEPA. CDRH's review should include CDRH HF's recommendation on whether the proposed HF results are acceptable or not, and any recommendations for labels and labeling modifications. Link to Reviewers Guide: \\cdsesub1\evsprod\nda209988\0034\m1\us\12-cover-letter\reviewer-guide-sn0034.pdf Module 5.3.5.4 contains links to the HF studies:

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device specific discipines of biocompatibility (including chemical characterization and toxicological risk assessment), sterility, human factors, electrical safety, electromagnetic capatibility, software, engineering/performance, labeling, and facilities/quality systems.

This review will not cover the following review areas:

Drug product, primary drug container, and the clinical acceptablitity of specifications/validaitons, including dosing regiment.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

There has been significant interaction with the Sponsor prior to this reivew. The Team Lead identified ICCs 1800677 and 1700691 as the most pertinent files. The original NDA submission received a CR decision June 11, 2018. In response to the original CR, the Sponsor, scPharamcueticals changed to a completely new device platform. This change necessitated a complete new review of the device information as none of the information for the device in the original NDA could be leveraged.

3.2.1. Related Files

The following files are noted to be relevant: ICC1800677, ICC1700691, ICC1700765, ICC1700766, ICC1700768, ICC1700796, ICC1700767, ICC1700769, ICC1700773, ICC1800037

3.2.2. Sponsor Identified Key Interactions between FDA and the Sponsor

Reviewer Note: Table (Table 2) is copied from 3.2.R 1 P.3-device-summary. References/hyperlinks function in that document and point to the specific referenced document.

Interaction	Submission/ Meeting Date	Agency Response	Reference
Pre-IND Type B Meeting	September 18, 2013	October 7, 2013 (Minutes)	3185472
Pre-IND Type B Meeting	July 30, 2014	August 28, 2014 (Minutes)	3618057
Email communication from Alexis Childers –Information Request-Protocol	January 14, 2015	February 9, 2015	20150210
Advice/Information Request-Non Clinical Hold Comment	January 14, 2015	February 19, 2015	3704113
Email communication to Alexis Childers – Listed Drug	February 6, 2015	February 23, 2015	20150223
Pre-IND Type B Meeting	April 27, 2015	May 19, 2015 (Minutes)	3759198
Advice/Information Request – Human Factors Validation Protocol and Product Design Clinical Validation Protocol	June 4, 2015	August 20, 2015	3808195
Type C Meeting	July 28, 2015 and July 31, 2015	October 8, 2015 (Written Response Only)	20151008
Agreed Initial Pediatric Study Plan – Agreement	October 29, 2015	November 19, 2015	3849446
Proprietary Name Request	December 1, 2015	April 22, 2016	3921012
Advice/Information Request – Device/Labeling	January 8, 2016 January 19, 2016	March 3, 2016	3896596
Email communication from Alexis Childers –Information Request-Device	January 5, 2015	February 11, 2016	20160211
Advice/Information Request – Training Video	June 21, 2016	September 9, 2016	3983571
Advice/Information Request – Instructions for Use and Quick Reference Guide	June 21, 2016	September 9, 2016	3983567
Email communication from Alexis Childers –Information Request-Device	June 9, 2016	July 22, 2016	20160722

Interaction	Submission/ Meeting Date	Agency Response	Reference
Email communication from Alexis Childers –Information Request-Device	July 25, 2016	August 11, 2016	20150811
Advice/Information Request – Device	August 18, 2016	September 15, 2016	3986122
Email communication from Alexis Childers –Advice	October 19, 2016 November 23, 2016	January 11, 2017	20170111
Agreed Amended Initial Pediatric Study Plan – No Agreement	March 23, 2017	June 26, 2017	4118577
Pre-NDA Type B Meeting	June 1, 2017	June 20, 2017 (Minutes)	4113729
Email correspondence – Indication	June 28, 2017	June 29, 2017	20170629-a
Email correspondence - iPSP	June 28, 2017	June 29, 2017	20170629-b
NDA Acknowledgment	August 23, 2017	September 14, 2017	4151885
NDA Filing Communication - No Filing Review Issues Identified	August 23, 2017	October 27, 2017	4173623
Complete Response Letter	n/a	June 11, 2018	4275803
Type A Meeting	September 24, 2018	October 16, 2018 (Minutes)	4335753
Type C Teleconference	January 9-10, 2019	February 1, 2019 (Minutes)	4384986
General Advice (Extension for CRL Response)	May 22, 2019	June 3, 2019	4442346
Type C Meeting	June 18, 2019	July 7, 2019 (Minutes)	4460535
HF Protocol Advice	July 2, 2019	August 29, 2019	4483989
HF Advice/information Request	September 27, 2019	December 20, 2019	4537570

3.3. Indications for Use

Combination Product	Indications for Use
Furosemide Pump (Furoscix Infusor)	**Reviewer note**: From Label-0071 (prescribing information): *FUROSCIX is* (b) (4) *indicated for the treatment of congestion due to fluid overload in adults with NYHA Class II/III heart failure who display reduced responsiveness to oral diuretics and do not require hospitalization.* (b) (4) *FUROSCIX is not indicated for emergency situations or in patients with acute pulmonary edema.*
Infusion Pump	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
034	1.2, 1.14.13, 3.2.R
036	1.11.1, 3.2.R
037	1.11.1

Reviewer note: Specific file names are noted throughout the review.

4. DEVICE DESCRIPTION

4.1. Device Description

Reviewer note: From 3.2.R.1.P.3-device-summary. Items marked'^'are from MAF (b) (4) Section 1 Description.

The device is an on-body infusion pump for the administration of subcutaneous Furosemide (loop diuretic, LD) to treat edema associated with congestive heart failure. "*The Furoscix Infusor offers an alternative outpatient route of administration of furosemide for heart failure patients to alleviate the signs and symptoms associated with congestion when responsiveness to oral diuretics is reduced and hospitalization is not indicated. Patients with heart failure could receive Furoscix at the initial worsening signs and symptoms of congestion when the response to oral diuretics is not adequate*"

The casing provides the structural integrity to contain the internal components and a viewing window to view the dose delivery.^

(b) (4)

[redacted]

(b) (4)

Primary Drug Container

Reviewer Note: Review of the adequacy of the Primary Drug Container is deferred to CDER.

The device using a Crystal Zenish cartridge, (b) (4) septum, and (b) (4) piston. (b) (4)
(b) (4)

The MAF holder states a separate Drug Master Filecontains the primary container information. This cross reference is not explicitly provided in the Description file of MAF (b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer Note: Labeling is reviewed in Section 6 Labeling.

Drug Product

Reviewer Note: Drug Product review is deferred to CDER. Information here is intended to inform the review and the risks associated with the drug and its delivery.

(b) (4)

[redacted]

The device itself, developed by West Pharmaceutricals, is intended to allow for self-administration of drug products with larger volume (i.e. 10 mL).

Infusion is designed to deliver a single 80 mg dose at a concentration of 8 mg/mL over 5 hours via pre-programmed delivery.

(b) (4)

Reviewer note: It is not immediately clear why the number of years of exposure decreases in the second presented exposure estimation. The primary reason understood by the Lead Review is the dosing regiment no longer becomes effective/patient dies. Regardless, the exposures estimated and the use-case have impacts on the biocompatibility review.

Reviewer note: items marked '*' are considered essential. items marked '^' were located in MAF (b) (4)

Characteristic		Stated Quality of Device	Lead Reviewer Comments
Operating characteristics	Operating Environment*	Out-patient (i.e. hospital) or home-use setting Adult, single use, only. Prescription only. Adhered directly to body via adhesive. (b) (4)	EMC requirements should be met for more stringent condition for total use condition (e.g. immunity) Risk assosciate with failure for device function will be assumed to be at home environment (i.e. not direct clinician supervision). Device not recommended to be used during transit, (b) (4) (b) (4) and discouragement of use during transit should be clearly stated in the device's labeling. It is not in the Instructions for Use. Deficient.
	Ingress protection*	Not provided.	Device includes warning against getting device wet. (b) (4) (b) (4) (b) (4) This requires clarification, as the device is intended to be used on a patient population likely to be in poor health, predisposed to sweat, and for use in flexible evironments (up to 40 C). While the labeling may provide some mitigation against voluntary fluid exposure, it provides no mitigation against involuntary fluid exposure. This is an electrical safety issue. Deficient.
Flow Characteristics	Delivery Modes/Infusion Options*	5 hour biphasic subcutaneous delivery Non-acute and non-emergency use. Placement: on abdomen between bottom of ribcage and belt-line.	No Bolus function.
	Flow accuracy specifications*	(b) (4) 10 mL	No flow accuracy is described, only dose delivery accuracy. Deficient.
	Flow rates & Volume to be infused (including Bolus or KVO Flow Rates/Volumes)	5 hour biphasic subcutaneous delivery: 3.75 mL/first hour and 6.25/next four hours Non-acute and non-emergency use.	No Bolus function. Delviery accuracy appears to be stated in hours; therefore, verification testing should challenge this directly.

	Units of delivery*	mL	N/A
	Maximum Rate*	N/A	device has a single pre-set programmed biphasic flow rate and cannot be programmed for other flow rates.
	Minimum Rate*	N/A	device has a single pre-set programmed biphasic flow rate and cannot be programmed for other flow rates.
	Delivery Limits	Not Described	Not Described
	Dose limit / Bolus limit exceeded alarms	N/A	Device is prepogrammed without bolus function.
	Lock Out features	None	Device is pre-proprogammed, therefore functionality cannot be changed. MAF Holder declares in description that the button remains depressed following activation, thereby preventing reuse. Acceptable..
	Infusion Complete Notification*	Indicator light turns green, audible feedback, and plunger is fully across the window	Description is pulled from the Instructions for Use
((b) (4) Sensors/Alarms	(b) (4)	See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		(b) (4)	(b) (4)
			(b) (4) Greater detail on this alarm/the functionality/predefined thresholds is likely necessary. Verfication of alarm functionality is contained in SAC/V&V review.

[redacted]	[redacted]	Deficient. [redacted]	
	[redacted]	[redacted] This requires explanation.	
		See Alarm Summary Below.	See Alarm Summary Below.
		N/A	Device is pre-programmed. Therefore, it is understood that the user should have no ability to change these settings.
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		N/A	Activation key becomes locked after activation. User input is disabled upon activation
		N/A	Sponsor states the device contains no communication capability.
		N/A	Sponsor states the device contains no communication capability.
		N/A	Sponsor states the device contains no communication capability.

Device Description		Stated Quality of Device	Lead Reviewer Comments
Operating Characteristics	Storage Environment*	Room temperature storage.	Testing is stated to have been performed [redacted] MAH [redacted] is referenced for further detail.
	Dimensions*	65 mm x 120 mm x 33 mm	N/A
	Weight*	10 g w/o drug product	N/A
Power	Power Supply (including battery)*	[redacted] Battery^:	Loading of drug component activates electrical connection

		(b) (4)	
(b) (4)			
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		Visual indicator – Piston window	This is reliant on the user's ability to interpret the window and determine if the appropriate dose has been delievered. See HF Consult.
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	See Alarm Summary Below.
		N/A	Single drug/infusion profile.
		Sponsor states the device contains a self-test function	N/A
		See Alarm Summary Below.	See Alarm Summary Below.
		See Alarm Summary Below.	
		See Alarm Summary Below.	See Alarm Summary Below.
		MAF (b) (4) Device description	See Software Review
		(b) (4)	

Reviewer note: Further detail on the device is referenced to be contained in MAF (b) (4) Section 1 (Description). Alarm systems are stated for alarms following IEC 60601-1-8 in (b) (4) MAF (b) (4) A ToC from the MAF hold is needed to locate specific files efficiently. An underdose alarm is stated as present in 3.2.R.1.P.3-device-summary, but is undescribed.

Alarm Summary^

State	Indication	Visual Indication
Device Power-up and standby mode till button activation press	Blue	Blink (at specified time interval)
Delivery start upon button activation press and during Operation	Green	Fade-In / Fade-out
Successful completed Delivery	Green	Constant On
Device completed delivery successfully and was removed from body	None	LEDs Off
Error notification	Red	Blink (at specified time interval)

Reviewer note: The Sponsor has not provided detailed information about the implemented alarms, only the presence of an alarm notification. The following alarms are incompletely described: (b) (4) (b) (4) (b) (4) Deficient.
The (b) (4) alarm requires explanation: (b) (4) (b) (4)

Device Description	Reviewer Comments
If the infusion pump is intended for transport or ambulatory use - description of how it is designed for mobility, various environmental conditions (e g , water exposure, altitude, electromagnetic interference), and ruggedness	The device is designed for (b) (4) flexible use environments, but the device lacks the necessary information to accommodate all these environments (b) (4) (b) (4) (D) (4) EMI/EMC labeling is not present These factor into the lack of declaration of factors which impact flow accuracy Deficient
For each route of administration, the Sponsor identified a legally marketed drug or biologic to demonstrate that at least one such product is approved or licensed for infusion through the pump for the proposed route of administration and at the proposed dosage	N/A – Single drug indicated via NDA for use with device
If the infusion pump is labeled for use with a specific device, drug, or biologic, the labeling of the products should be consistent	Consistently identified drug (LD)

Accessories

Infusion Pump Accessories Description

The device is packaged as a kit and contains alcohol prep pads These are not being reviewed specifically for performance, not be included in CDRH's determination of acceptability for this NDA/ICC, as the alcohol prep pads are considered low-risk and appear to be a device already available for interstate commerce and no specific requirements of the prep pads are needed within this review Thie Lead Reviewer considers this kit component to be low risk and will not be pursued further in this review 3 2 P 3 1 identifies the Alcohol Prep Pad as being manufactured by (b) (4) (b) (4)) A Kit Certificaiton could not be located

Infusion Pump Accessories Technological Characteristics Comparison & Description

Characreristic	Subject Device
Infusion set/Syringe not loaded properly	Device is understood to be single use/only functional with door closed
Panel unlocked / door open	Device is understood to be single use/only functional with door closed
Syringes Compatible	Proprietary drug cartridge
Syringe Identification features	N/A
Device Description	**Subject Device Attribute**
Pump (b) (4) (b) (4)	Subcutaneous infusion (b) (4) pump

Infusion Pump Software Characteristics Comparison & Description

SE Comparison	Subject Device	Comments
A drug library or other dose error reduction mechanism	N/A	Single drug used No library
Infusion Pump Management Software	Interal software drives microcontroller	Version of software is not identified Deficient
Real-Time Display	N/A	Communication accomplished via LED/speaker
Level of Concern	Major/Class C	Appropriate
Dose Calculator	N/A	Single drug preprogrammed flow rate No dosing calculated based on patient metrics described
Other Software Feature (e g Physician/Patient Portal)	N/A	N/A
Device Description	**Yes**	**N/A**
(b) (4)		X – Single use
	N/A	
	(b) (4)	
		X – Single use
	Function is described as present, but incompletely described	
	Function is described as present, but incompletely described	

The Sponsor provices the following documents in support of the design approach.

Document Reference	Title	Description
Device-DIR-0013	Furoscix On-Body Infusor Development Plan	A summary of activities, processes, responsibilities, and deliverables identified for the development of the combination product Furoscix Infusor.
Device-DIR-0011	Furoscix On-Body Infusor Target Product Description	A description of the critical performance and quality attributes of the intended Furoscix Infusor drug-device combination product.
Device-DIR-0010	Furoscix On-Body Infusor Intended Use	Information identifying the combination product indications for use and intended use, including appropriate user populations, use environments, and limitations of use.
Device-DIR-0009	Furoscix On-Body Infusor User Requirements Specification	Identification of user interface and use requirements for the Furoscix Infusor.

Document Reference	Title	Description
Device-DIR-0012	Furoscix On-Body Infusor Packaging and Labeling Requirements Specification (PLRS)	Identification of packaging and labeling requirements for the combination product and each of its constituent parts.
Device-DDP-0038	Design Verification and Validation Plan	The planned verification and validation activities for the Furoscix Infusor.
Device-DD-0090	Usability Studies (Human Factors) Plan for the Furoscix Infusor	A summary of the activities, processes, responsibilities and deliverables to support usability engineering planning for the Furoscix Infusor.
Device-DD-0092	Essential Performance Requirements for the Furoscix Infusor	A list and justification of the selection of Essential Performance Requirements (EPR) for the Furoscix infusor.
MAF (b) (4)	SmartDose Gen II 10mL (b) (4)	West Pharmaceuticals master access file for SmartDose Gen II 10mL (b) (4)
Section 3.2.R.1.P.3.6	Design Verification and Validation Summary	Summary of, and reference to, the verification and validation evidence that the requirements set forth for the Furoscix Infusor have been met.

These documnts are reviewed where appropriate, as needed (Labeling, Design Controls, Safety Assurance Case).

4.2. Steps for Using the Device

Reviewer Note: From Instructions for use SN0034 1.14.13 label-0063-ifu:

(b) (4)

Steps for using the device in labeling and MAF description appear to match. Acceptable.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☑ Yes ☐ No ☐ N/A	☐ Yes ☐ No ☑ N/A	☑ Yes ☐ No ☐ N/A

Reviewer Comments

The following are pertinent to the NDA submission primarily; however, the Lead Review believes that the NDA sponsor does not know the details needed to answer these questions and will likely require interfacing with the MAF holder.

1. A more detailed explanation of the features present in the device to identify the specific drug cartridge with the device (i.e. to prevent misuse) is requested.
2. Device not recommended to be used during transit, (b) (4) and discouragement of use during transit should be clearly stated in the device's labeling. It is not in the Instructions for Use. Deficient.
3. (b) (4), the limitations to this use are incompletely captured in the labeling. Examples:
   a. Water exposure: The Sponsor states this is sufficient mitigation against fluid exposure. This requires clarification, as the device is intended to be used on a patient population likely to be in poor health, predisposed to sweat, and for use in flexible evironments (up to 40 C). While the labeling may provide some mitigation against voluntary fluid exposure, it provides no mitigation against involuntary fluid exposure. This is an electrical safety issue. Deficient.
   b. Ambient operating pressure (altitude): The Sponsor states a maximum (b) (4) kPa is acceptable It is possible to experience pressures greater than this on earth
   c. Electromagnetic interference: no EMC labeling is present in the instructions for use
   d. Ruggedness: see water exposure. The same concern is present for particulate ingress.

The explanations for these limitations are incomplete, the labeling to control use is incomplete, and the Sponsor does not declare the factors which could impact flow accuracy.

4. The Sponsor does not state the flow accuracy rating, the min and max flow rates, or delivery limits associated with the drug. The total dose accuracy is only described in the labeling/device summary information.
5. The Sponsor's descriptions of alarms are lacking. The following are specific to the combination product as implemented. Generic/higher level alarm questions are raised to the device's manufacturer:
   a. The following alarms are incompletely described or inapplicability unjustified:
   (b) (4)
   b. The (b) (4) alarm functionality and limits is incompletely described: (b) (4)
   (b) (4)
6. A Kit Certificaiton could not be located.
7. Version of software in this device is not identified. This should be clearly identified in the submission and in the labeling information.

See IRs 1-4 below.

The following are pertinent to the MAF holder.

1. It is difficult to rapidly locate files in MAF (b) (4) A Table of Contents is requested.
2. The MAF/Sponsor's descriptions of alarms are lacking. (b) (4)
   (b) (4)

See IRs 5-7 below.

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☑ **Yes** ☐ **No**

For NDA Sponsor	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #1	Your device is described in your device summary in 3.2.R.1.P.3 to contain a drug cartridge and a device constituent which are copackaged. You have not discussed design features to prevent deliberate or accidental misuse of your drug container or infusion-pump with other matching the design. Design features are the safest methods to inhibit device misuse. Please describe the design feature(s) in your system and how these were challenged through testing to ensure that your drug container is only used with your infusion pump.	
Sponsor Response	The Furoscix Infusor combination product consists of Furoscix (Furosemide Injection, 80 mg per 10 mL) contained in a prefilled, Crystal Zenith® (CZ) cartridge, and a proprietary wearable, pre-programmed on-body subcutaneous (SC) delivery system, the Infusor, based on the SmartDose® Gen II 10 mL platform (West Pharmaceutical Services, Inc). Section 1.1.1 Titled "Combination Product for Use with scPharmaceutical drug Furoscix®" has	

	been included with Section 01 of MAF (b) (4) The single use combination product constituents, comprising pre-filled drug cartridge, sterile single-use delivery device and accessories for use (e.g. alcohol prep pads), are co-packaged in a kit available by prescription only. The co-packaged kit is a design feature that is a risk control against accidental misuse: • Only one dose is included, therefore there is no incentive to misuse by breaking into the drug reservoir to split the dose into multiples. Furthermore, there are no empty drug cartridges provided to a user to facilitate splitting doses. • Device is already included, therefore there is no incentive to use another device. • Significantly reduced opportunity to mix up the drug with another medicine. • The product was tested in Human Factor studies with participants demonstrating an understanding that the Cartridge is to be used with the device provided in kit. The statement in the IFU that the Furoscix cartridge was to only be used with the On-body Infusor was tested in the knowledge task portion of our human factors validation study (b) (4) (b) (4) Two participants did not comprehend the statement in the IFU version that was tested in the human factors validation study. When the moderator explained what the statement was intending to communicate, both participants suggested that the statement in the IFU be updated to clarify the message. Accordingly, the Sponsor updated the statement as follows: "*The on body infusor can only be used with the prefilled FUROSCIX cartridge supplied in the kit. Do not use any other cartridges or medicine inside the on-body infusor*." The statement in the submitted version of the IFU (label-0063-IFU, R07) reflects the recommendation. Further testing was not required. In addition, the kit constituents (pre-filled and labeled primary container assembly and labeled device) are customized for use in combination, once the cartridge is loaded into the device, a re-use prevention feature ensures the device cannot be opened and re-used with a different drug product. Design features for the cartridge and the device are described below: • The prefilled primary container assembly (cartridge) as a standalone does not include a mechanism or components of expelling the drug without the Infusor. The prefilled primary container assembly does not include a plunger rod (or push rod) and the plunger does not include an interface (e.g. thread) to an external plunger/push rod. In addition, the prefilled primary container assembly includes a capped septum, which DOES NOT use a Luer lock. The customized cap dimensions and septum thickness require a specific customized needle interface on the matching infusion pump. • The customized device requires a specific primary container assembly design: o The Infusor (b) (4) was designed to interface with the prefilled labeled primary container assembly by design o The specific drug (b) (4) dimensions, (b) (4) (b) (4) are customized for interface with the customized pre-filled primary container (10 mL West CZ primary container assembly). o Device (b) (4) needle length suitable for specific primary container septum thickness.

	○ Device includes an (b) (4) (b) (4) mechanism that interfaces with the primary container assembly plunger. All the above-mentioned design interface features are control measures by design for the prevention of deliberate or accidental misuse of the West SmartDose Gen II device with other containers or West SmartDose Gen II Container with other infusion pumps.
Reviewer Comments	The Sponsor states the packaging configuration as the mitigating feature to prevent the stateds "deliberate or accidental" misuse. This only addresses accidental misuse. The Sponsor points to HF studies as a means of demonstrating the cartridge is to be used with the device provided in the kit. This only addresses accidental misuse. The Sponsor states the IFU was updated as a result of the HF validation to include language to not use other drugs in the kit. This addresses accidental and deliberate misuse, but is not a design feature. The Sponsor explains the design of the device and cartridge are intended to prevent expelling the drug and replacing with another and designed to be non-standard to prevent misuse. This addresses delviberate misuse and are design features.
Response Adequate:	☑ **Yes** ☐ **No**

For NDA Sponsor	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #2	Your device is designed for (b) (4) use, as described in your device summary in 3.2.R.1.P.3. You state that your device is not recommended for use during transit in Table 4 of this document. (b) (4) (b) (4) Particularly, environmental changes could impact flow and dose accuracy, and these are not discussed in your labeling. Please update your labeling, and provide justification, for the following items to describe the use-limitations of your system. Please ensure your labeling updates are supported by your testing, as applicable: 21. We understand your intent is to prevent use outside of the home/clinical environment, while allowing flexible use within those environments. Please update your device's Instructions for Use to warn against use during transit/outside of the home or clinical environment. 22. You state that warning against getting the device wet is sufficient mitigation against fluid exposure. While labeling may provide some mitigation against voluntary fluid exposure (i.e. bathing), it provides no mitigation against involuntary fluid exposure (i.e. sweating). Please explain the intention of this statement and justify the lack of fluid/particulate testing, considering your user-population and their known poor-health. Alternatively, provide fluid/particulate testing and labeling commensurate with the use-case. 23. Your Instrcutions for Use (label-0063-ifu) states the maximum pressure of use is (b) (4) (b) (4) Please justify the stated maximum rated use-pressure. Alternatively, revise your Instructions for Use to match your use-case and ensure your design verification testing supports this revised use case. 24. Your Instrcutions for Use (label-0063-ifu) lacks electromagnetic interference/limit information. Please update your Instructions for Use to declare the limits of known acceptable interference with your device, as described in Annex B of IEC 60601-1-2: 2014 *Medical electrical equipment – Part 1-2 General requirements for basic safety and essential performance – Collateral standard Electromagnetic compatibility –*	

	Requirements and Tests. We recommend you discuss the contents of this labeling update with West Pharmaceutical Services AZ, Inc. (i.e. the MAF (b) (4) holder). 25. Your Instrcutions for Use (label-0063-ifu) does not declare the factors which could impact flow accuracy. Please provide these (i.e. pressure, temperature, etc), and the expected variance for each, so the user is aware of the limits of the system and the factors which could cause them to experience an under/over dose event. Please ensure that these factors are supported by your testing.
Sponsor Response	a. 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) The statement in Table 4 in 3.2.R.1.P.3 about use (b) (4) (b) (4) is qualified by the requirement for easy access to the bathroom due to practical clinical considerations. The device has been tested in conditions simulating transportation (see below), but furosemide is a potent diuretic that causes significant increase in urine production. This may make travel during the 5-hour infusion, and for up to several hours after the completion of infusion, impractical and potentially inconvenient, but not impossible, and the device is tested to ensure it can operate in this use condition. We have provided important information for the patient in the IFU on the need to make frequent bathroom visits and to have access to a bathroom for up to 8 hours after starting the infusion: • IFU Important information: "*You should notice an increase in urine production in about an hour after the infusion is started and may need to make frequent bathroom visits. Be sure you have access to a bathroom for up to 8 hours after starting the infusion*." This statement was tested in the knowledge task portion of our validation human factors study (rpt-0333) where 60/60 (100%) participants comprehended the need to ensure access to a bathroom during the infusion. In addition, in scP-00-003 study, the effectiveness of the adhesive was evaluated during a 6-hour wear period whereby subjects were permitted to leave the research center and resume normal daily activities after the Infusor was applied to the abdomen by the subject (scp-00-003-study-report). While wearing the Infusor, 36/36 (100%) subjects reported walking, 30/36 (83.3%) reported using the bathroom and 31/36 (86.1%) reported driving a car. There were no subjects that experienced a complete device dislodgement of the device during this study and therefore (b) (4) did not impact the effectiveness of the adhesive. The Infusor specifications for operating temperature (15oC - 40oC, requirement 2.8.a) and atmospheric pressure (b) (4) (requirement 4.4.a), and the associated testing results, are presented in Section 9 of MAF (b) (4) (Table 9-2 and Table 9-5, respectively). The Infusor has been tested and proven to meet 95%/95% reliability/confidence at these conditions. Refer to West report (b) (4) where 124/124 devices met specifications when tested at each end of the operating temperature limits (248 devices total) and West report (b) (4) where 93/93 devices met specifications when tested at each end of the operating pressure limits (186 devices total). In addition, the Infusor specifications contain requirements to operate under (b) (4) conditions which are stated in ISO (b) (4) (b) (4)

	(b) (4) (b) (4) The device has been tested (b) (4) (b) (4) 95%/95% reliability and confidence was confirmed at this condition with 93/93 devices meeting requirements at this condition (verified under West Report (b) (4)). The sponsor believes that no further information or restrictions are warranted in the IFU. b. The sponsor acknowledges that labeling will not provide mitigation against involuntary fluid exposure. Involuntary fluid exposure such as sweating is mitigated by the design and geometry of the device. (b) (4) (b) (4) (b) (4) (b) (4) The potential areas where sweat/liquid might leak into the device are parallel to the administration area (i.e. abdomen): • Device Safety Latch which is flush against patient body (to enable patient needle to protrude) • Device Button Activation areas, after being pressed for activation. In order for sweat/liquid to leak into these areas (button or safety latch), drops of moisture would need to travel perpendicular to the administration area. Any such liquid would be likely to drain along the device encasement walls, and pool/accumulate in the lower area of the device (depending on gravity), depending on the device orientation. The rate of occurrence of such a failure is expected to be very low. The user-population with New York Heart Association Class II/III heart failure reflected by our proposed indication and usage are defined by fatigue and dyspnea with ordinary (Class II) and less than ordinary (Class III) physical activity resulting in slight or marked limitation of physical activity (Yancy-2013). Adult patients who display reduced responsiveness to oral diuretics and experiencing worsening congestion due to fluid overload in NYHA Class II/III heart failure are not expected to be exercising to the point of causing excessive sweating. The potential failure modes of the Infusor due to particulate ingress include (b) (4) (b) (4) (b) (4) The use environment needs to be a location with access to a bathroom, which includes home or clinic setting that will be void of the gross levels of contamination (b) (4). The simulated use study to validate the effectiveness of the adhesive under routine daily activities (b) (4) (b) (4) study scP-00-003). This study tested the use of the device (applied on the abdomen as the intended administration site) for a 6-hour wear; no device failed due to moisture or particulate ingress and there was no evidence of excessive particulate exposure observed.

c.
The IFU (label-0063-IFU) and primary carton (label-0069) provided in the resubmission incorrectly list the maximum pressure of use. The product requirement is for operating pressures from (b) (4) (requirement 4.4.a – requirement and associated testing in Section 9 of MAF (b) (4) Table 9-5). This requirement has been validated to a 95%/95% confidence and reliability level with 93/93 devices meeting all requirements while being operated at each of the atmospheric pressure limits (186 devices total) as reported in West document (b) (4). The sponsor will correct label-0063 to include (b) (4) the upper operating limit for atmospheric pressure. In addition, the sponsor will update the primary carton labeling (label-0069) to include the (b) (4) correction. The Sponsor will make these changes at the same time as other labeling changes requested by FDA.

d.
The instructions for use (label-0063) contains the following statement in the Important Information section in the top-middle panel of the instruction sheet:
"***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).*"
Comprehension of this statement was tested in human factors testing and presented in Report-0333 (rpt-0333). Human factors testing showed that users were able to find and correctly comprehend this information.
The Infusor has been tested for compliance to IEC 60601-1-2 (reference West report (b) (4) Rev. 2.0, for more details). The tested devices were exposed to radio frequency (RF) proximity fields during delivery, based on Table 9, clause 8.10 of the standard, "Test specifications for ENCLOSURE PORT IMMUNITY to RF wireless communications equipment." The devices delivered the full dose, created proper user notifications and met the predetermined acceptance criteria during this RF exposure, successfully passing the test. As the testing was conducted with RF sources 0.3m from the device, the testing supports the informational statement listed above.
In addition, compliance to the applicable requirements in IEC 60601-1 for labeling (section 7.9.2.2) was evaluated by a third-party certified external test house and included in West's internal electrical safety testing report for IEC 60601-1 (Figure 1).

7.9.2.2	Instructions for use include all warning and safety notices	LBL-0063 (Sec. Important Information)	P
	Warning statement for CLASS I ME EQUIPMENT included	Not Class I equipment	N/A
	Warnings regarding significant RISKS of reciprocal interference posed by ME EQUIPMENT during specific investigations or treatments	Single use- The duration of use is limited to 5 hours only	N/A
	Information on potential electromagnetic or other interference and advice on how to avoid or minimize such interference	LBL-0063 (Sec. Important Information)	P
	Warning statement for ME EQUIPMENT supplied with an integral MULTIPLE SOCKET-OUTLET	No multiple Socket-Outlet	N/A

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e.
The sponsor acknowledges that external factors such as changes in ambient temperature, fluid temperature/viscosity, atmospheric pressure, head height, and back pressure can affect infusion pump dose accuracy, depending upon the product design. The West

	Infusor design has been developed to accommodate changes to these factors and still deliver within delivery rated specification. (b) (4) (b) (4)
	The external factors which would reasonably be expected to be encountered according to the intended use of the device and could affect dose delivery have been considered in the Infusor design and have been minimized to the point where they do not cause the device to operate outside of specification in the intended use of the device. These factors are discussed individually below: **Ambient/Fluid Temperature and viscosity:** The storage temperature of the drug product is room temperature, 15oC to 25oC and as such, the fluid temperature can be considered to be within the ambient temperature and will be discussed in terms of ambient temperature. The device operating temperature is 15oC to 40oC. Operating temperature changes can affect the viscosity of the drug product being delivered as well as affect the materials of construction of the mechanism responsible for moving the drug product. The West Infusor does not depend upon fluid viscosity to control the flow rate by design and is not affected by the possible changes in viscosity in the drug product in the operating temperature range. The Furoscix drug product is a (b) (4) olution (b) (4) (b) (4). As the West Infusor design uses a piston (b) (4) (b) (4) (b) (4) the viscosity of the drug product does not affect the dosing performance. The relatively slow rate of delivery for Furoscix combined with the short fluid path assembly ensures there is not enough flow resistance, which would be dependent upon viscosity, to interfere with the drug delivery. (b) (4)
	To ensure all the above rationale is correct, 248 devices were tested, 124 device each at the high and low end of the specified operating temperature range with results captured in West report (b) (4). Requirement 2.8.a and associated testing are listed in Section 9 of MAF (b) (4) Table 9-2). All devices completed delivery providing greater than a 95% confidence of 95% reliability at the operating temperature limits. Based upon the product design and test results, the device operates as intended in the operating temperature range. **Atmospheric Pressure**: Atmospheric pressure changes on a loaded infusion pump may cause air in the system to expand or contract, affecting dosing performance. The West Infusor is an on-body delivery system using a prefilled cartridge, which greatly reduces

	the potential for air in the system to affect dose delivery performance. (b) (4) (b) (4) (b) (4) Hold up volume is specified as less than (b) (4) (b) (4) and has been tested for conformance as documented in West report (b) (4) (b) (4) nd not expected to affect delivery performance outside of specification or impact the patient's health. The pre-filled cartridge is specified (b) (4) stopper settings along with fill volumes are controlled and monitored (b) (4) (b) (4) to ensure compliance. (b) (4) (b) (4) (b) (4) The Sponsor has worked with West to establish a short-term delivery specification based upon literature found for patient tolerable subcutaneous injection rates with minimal backflow (Heise et al., 2014). The short-term delivery specification (requirement 2.4.e) is specified (b) (4) and is greater than the (b) (4) rug product that could theoretically be possible in an atmospheric pressure change (b) (4) during the delivery. The product has been tested at the low and high limits of atmospheric pressure (b) (4) (b) (4) per requirement 4.4.a) as documented in West report (b) (4) with 93/93 devices completing delivery requirements (b) (4) (b) (4) (186 devices total) providing a 95% confidence of 95% reliability at these possible pressure extremes. The sponsor believes that no further information is warranted in the instructions other than the operating limits for atmospheric pressure. **Head height:** As the Infusor is an on-body delivery system with a piston (b) (4) delivery mechanism, head height and head height changes cannot cause an appreciable change in the device flow rate that could cause risk to the patient. (b) (4) (b) (4) The force required to move the piston based upon break loose glide force testing is approximately (b) (4) N (b) (4) (b) (4) The sponsor believes that no information is warranted in the instructions for head height. **Back Pressure**: The West device is designed to accommodate physiological changes in back pressure. (b) (4) (b) (4)

	[redacted] The sponsor believes that no information is warranted in the instructions for back pressure.
Reviewer Comments	a. The Sponsor states that the design is intended for [redacted] use during the infution and the Sponsor qualifies this [redacted] The Sponsor states testing has been done to support [redacted]. Adequacy is reviewed in SAC (inadequate). b. The Sponsor [redacted] and details the fluid path [redacted] that fluid would need to travel perpendicular to the administration area. The occurance rate of this fauilure is expected to be low. This is a logical rationale without testing to demonstrate the design sufficiently the fluid exposure in the expected use case. In addition, low occurance is not an adequate argulement for a hazard's severity. This may require additional testing to demonstrate safety of their design for fluid ingress. For particulates, the Sponsor contends that the user population is precluded from areas with high levels of particulates (e.g. work site) due to their condition. The sponsor points to the simulated use study (scP-00-0003) [redacted]. This explanation is likely reasonable for the particulate ingress, but may require consultation with a clinician. c. Sponsor states the IFU incorrectly listed the operating pressures. The correct limits are stated as [redacted] validated to 95/95 C/R with 93 devices [redacted] These labeling updates are stated to be incorporated at a later time with others requested d. The Sponsor staes there is a label stating [redacted] and states the device was tested following the requirements in IEC 60601-1-2 [redacted] Rev 2.0, and provides the exerpt from this stating it is a passing item, but does not provide update to the labeling as requested. e. The Sponsor states that changes in ambient temperature, fluid temperature/viscosity, atmospheric pressure, head height, and back pressure can affect dose accuracy. The Sponsor states the device is meant to accommodate these factors and deliver within the rated specification [redacted] This does not address the ask for including these factors in their labeling. It is noted that the described method assumes the dosage is not impacted in the described mitigation. i. Ambient/Fluid Temperature and viscosity: Stated to be [redacted] room temperature for storage, with operating at 15 to 40 C. It is noted that the device has been stated to be [redacted] therefore this temperature range is unacceptable without scientific rationale as the temperature surrounding the device can certainly exceed this range. The Sponsor states the design of the device is *no affected by the possible changes in viscosity in the operating temperature range.* The operating temperature inaccurately captures the use-case. The sponsor states the piston-based design [redacted] is not affected by fluid visocity and the drug is [redacted] The Sponsor does not state the

	freezing point or provide a description of the desity changes as a function of time. A similar explanation is presented for the electromechanial components. The Sponsor pointes to boundary condition testing at operational temperature limits of the device in (b) (4) (requirement 2.8.a) and Section 9 of MAF (b) (4) Table 9-2 to 95/95 C/R. ii. Atmospheric pressure: The Sponsor points toe th preloaded cartridge as reducing possibility of air to be introduced into the system and affect delivery. A low hold-up volume (b) (4) is stated as associated with the dose delivery, refernce din Section 9 of MAF (b) (4) Table 9-2 and (b) (4) (b) (4). The pre-filled cartridge is stated to contain less than (b) (4) of air. At worst case, the Sponsor describes (b) (4) of drug being expelled (b) (4) (b) (4) with a literature reference. This speaks to validation of the design, but does not address the ask for including these factors in their labeling. The Sponsor points to boundary limit testing at (b) (4) 95/95 C/R (b) (4) iii. Head Height: The Sponsor states the head height cannot be adjusted as it is an on-body worn device. The Sponsor contends that (b) (4) (b) (4) does not affect the piston movement. The Sponsor states that head back pressure is approximately (b) (4) and the force needed to move the piston (break loose/glide force) is (b) (4) and a pressure of (b) (4) The Sponsor states that the worst-case change is moving from laying on their stomach to laying on their back. This contradicts their stated use case (b) (4) (b) (4). The Sponsor continues and states that this change in pressure canot move the piston and a change in flow rate would have to come from a flexing in the material, which is likely a reaonsbale scientific argument. The Sponsor also states that fluid path volume/hold-up volume is (b) (4) and a specification that no more than (b) (4) be delivered in (b) (4) econds. The Sponsor contends that this does not warrant labeling instructions. iv. Back Pressure: The sponsor states the device is deigned to accommodate physiolgocail changes, using the design features (b) (4) (b) (4) (b) (4) This does not address the ask for including these factors in their labeling.
Response Adequate:	☐ **Yes** ☑ **No, See CR responses to the NDA holder.**

For NDA Sponsor	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #3	Your device summary information in 3.2.R.1.P.3 lacks descriptions of key functional device limits and safety features specific to your use case with your drug. Therefore, we are uncertain if they are implemented in your combination device as your source it from West Pharmaceutical Services AZ, Inc. Please describe/provide the following for your system and justify the stated limits/specifications, as applicable. a. Flow accuracy rating over entire allowable range (i.e. in both phases of the biphasic delivery and during delivery transition). b. Minimum and minimum allowed flow rate throughout the entire delivery profile		

	c. Dose delivery limits (aside from delivery of 10 mL over 5 hours with a biphasic profile) d. The following alarms including the triggering limits/specifications: (b) (4) e. A Kit Certification: Please include a statement declaring that all Kit Componets (e.g.. your alcohol prep pads) are legally marketed and purchased in a manner consistent with their legally marketed application. For example: "*I certify that the following components of my kit are either (1) legally marketed pre-Amendments devices, (2) exempt from premarket notification (consistent with the exemption criteria described in the classification regulation(s) and the limitation of exemptions for Section 510(k) of the act (e.g., 862.9), or (3) have been found to be substantially equivalent through the premarket notification process for the use(s) for which the kit is to be intended (i.e., I am not claiming or causing a new use for the component(s)). I further certify that these components are not purchased in "bulk", but are purchased in finished form, i.e., they are packaged, labeled, etc., consistent with their pre-Amendments, exemption, or premarket notification criteria and status.*" If you cannot make this statement for all kit components, please provide an itemized list for the item you can make this statement for and a list for which this statement does not apply and the means which they have been established to be legally marketed and the processing steps that you perform during assembly into your final finished combination product's form. f. The software version number of the infusion pump's software. Please also include this information in your Instructions for Use.
Sponsor Response	As a preliminary matter, the Sponsor and West Pharmaceuticals clarify that MAF (b) (4) is specific and exclusive to scPharmaceuticals, Inc. The MAF title with reference to (b) (4) is indicative of the customer number designation from West Pharmaceutical Services. This submission was created as a regulatory output filing (Master Access File) based on the specific development efforts of West Pharmaceutical Services, Inc and ScPharmaceuticals, Inc. for Furoscix® and will neither be referenced by another application nor a different sponsor other than the application referenced within the letter of authorization. With regards to the justification of limits/specifications for dose delivery and alarms, the clinical safety and efficacy of the drug product Furoscix with the active ingredient Furosemide is considered. The listed drug, Furosemide for injection, is administered as two separate 40 mg bolus IV injections over 2 minutes, two hours apart. When compared to a 5-hour subcutaneous infusion of Furoscix 80 mg/10 mL where 3.75 mL is infused over the first hour, followed by 6.25 mL over the subsequent 4 hours, the geometric mean ratios between SC and IV administration for AUClast and AUCinf were 99.50% and 99.65%, respectively, within the BE 90% CI limits of 80.00%–125.00%. In addition, there was no significant difference in pharmacodynamic endpoints (sodium excretion in the urine and urine volumes at 8 and 24 hours) between subcutaneous administration of Furoscix and IV administration of the LD, Furosemide Injection, demonstrating that subcutaneous infusion of Furoscix induces equivalent diuresis to IV administration of the LD at the same total dose (80 mg), regardless of administration time or rate. The duration of the full infusion, within a reasonable range does not pose a clinical impact risk to diuretic efficiency (i.e. under diuresis or over diuresis) and therefore a specification of 5 hours (b) (4) was chosen to keep the infusion with a predictable range for the patient, but that tight of a specification is not required for clinical safety. For additional discussion, please refer to DD-0092, Essential Performance Requirements for the Furoscix Infusor.

a. Flow accuracy rating over entire allowable range (i.e. in both phases of the biphasic delivery and during delivery transition).

The following specifications and limits are implemented in the Furoscix Infusor design input: Following activation, the System shall deliver 10.0 [mL (b) (4) drug product in 5 (b) (4) hours, such that 3.75 [mL] (b) (4) is delivered in the first hour (requirement 2.3.a, MAF (b) (4) Section 9, Table 9-2). This specification is derived from the knowledge of the pharmacokinetics and pharmacodynamics of Furoscix compared to furosemide for injection as noted above, where overall dose delivered is important, along with local tolerability, however variance in the rate of administration across the 5-hour subcutaneous infusion does not drive the pharmacologic effect. A dosing specification strategy consistent with the guidance in the draft standard (b) (4) for volume delivered (Reference figure B.3) was used to control the overall dose in each phase. For the biphasic profile, a maximum and minimum volume limit is established for delivery in the first hour with a window for the maximum/minimum time and maximum/minimum volume at the end of delivery. See Figure 2 below for a graphical representation of dose accuracy requirements and some device volume delivery data taken from design verification test results from West report (b) (4) R1 Section 10.1 – Testing for Dose Accuracy reliability, Time point t=0.

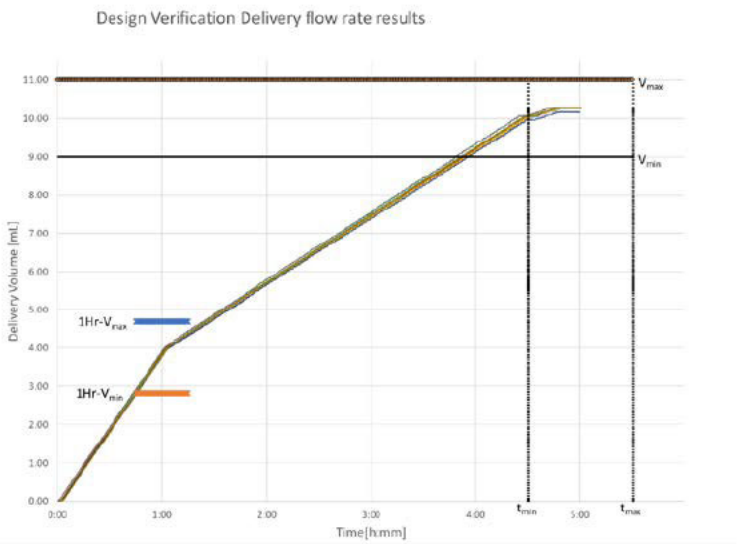
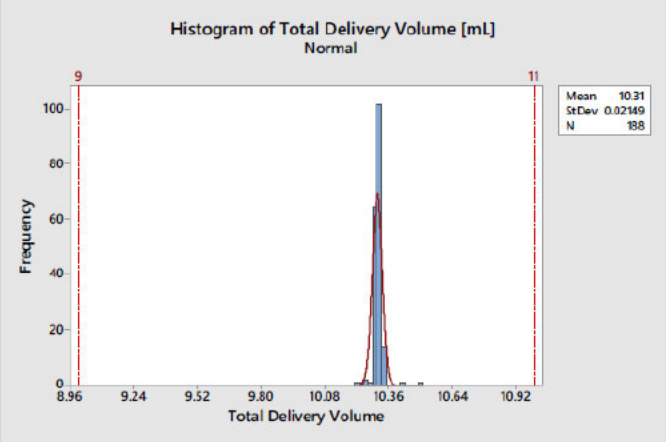


Figure 3 represents the results from the dose delivery reliability test for time point t=0 from West report (b) (4) Results show a very tight distribution with reference to the specification limits.

Figure 3: Dose Delivery Reliability results from Design Verification Report (b) (4)



b. [Maximum] and minimum allowed flow rate throughout the entire delivery profile

The Sponsor has specified a maximum flow rate that is tied to an assessment of potential discomfort ("delivery too quickly") and backflow/leakage as discussed above (requirement 2.4.e) Based on available literature we anticipate that minimal pain and backflow/leakage associated with delivery of a dose too quickly could only occur if the short-term delivery rate were greater than (b) (4) (Heise et al, 2014) or a total dose of 80 mg in 10 mL was delivered over (b) (4) (Caccialanza, 2018). The Sponsor's assessment of potential discomfort associated with the delivery error of "delivery too quickly" is contained in the Hazard Analysis (device-ra0043).

Based on the above analysis showing the total dose of Furoscix is essential for clinical performance and the rate of Furoscix infusion does not drive the desired clinical outcome, the sponsor believes that a minimum allowed flow rate is not required in the current specification, but a minimum dose volume is specified at the one hour point in the infusion and at the end of infusion.

The following specifications and limits are implemented in the Furoscix Infusor design inputs: "Maximum short term delivery rate shall be (b) (4) for the entire delivery profile" (MAF (b) (4), Section 9, requirement 2.4.e) and "Following activation, the System shall deliver 10.0 [mL] (b) (4) drug product in (b) (4) 5 hours, such that 3.75 [mL] (b) (4) (b) (4) is delivered in the first hour" (MAF (b) (4) Section 9, requirement 2.3.a).

c. Dose delivery limits (aside from delivery of 10 mL over 5 hours with a biphasic profile)

The following specifications and limits are implemented in the Furoscix Infusor design inputs: Following activation, the System shall deliver 10.0 [mL] (b) (4) drug product in (b) (4) 5 hours, such that 3.75 [mL] (b) (4) is delivered in the first hour (MAF (b) (4), Section 9, requirement 2.3.a). See explanation in FDA Question #3.

d. The following alarms including the triggering limits/specifications:

A rationale for the inclusion or exclusion of each alarm listed in FDA's question, and alternative mitigations, are provided below.

(b) (4)

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

	(b) (4) (b) (4) The error conditions have been verified as part of the design verification testing, and the error notification has been successfully validated as part of the HF summative study. e. Kit certification A certification statement has been generated to address the kit components, specifically the purchased component Alcohol Prep Pad, and their impact to the use of the kit. That certification statement can be found in Memo-0084 provided in this response (device-memo-0084). f. The software version number of the infusion pump's software. Please also include this information in your Instructions for Use.

	The software version number of the Furoscix Infusor software is SW P/N SW0025 Rev. 02.03 (Per (b) (4) Rev. A04). The Sponsor agrees to include this software version number in the Instructions for Use (lbl-0063) when it is revised per discussion with FDA.
Reviewer Comments	The Sponsor indicates that MAF (b) (4) is *specific and exlusive to scPharmaceuticals, Inc*. This is explained to be an exclusive application. The Sponsor indicates the clinical safety of the drug of interest is considered. Furosemide (IV) is administed as 2 40 mg bolus injections over 2 minutes separated by 2 hours. The Sponsor explains the 5 hours (b) (4) was chosen for familiarity to patients, but this is not related to clinical safety. Reference is made to DD-0092 Essential Performance Requirements. This is reviewed under the Desgin Verification Information. a. Flow accuracy is stated as 10 mL (b) (4) in 5 (b) (4) hours. 3.75 (b) (4) in hour 1. The Sponsor references 2.3.a MAF (b) (4) Sectuib 9 (Table 9-2) and states this specification comes from the PK/PD data . The Sponsor states that the overall does is the important characteristic along with local tolerability, but states the administration rate within the 5-hour window does not drive the pharmacologic effect. The Sponsor points to (b) (4) draft guidance (b) (4) (b) (4). Reference to a draft guidance is not acceptable justification, but the description referenced appears reasonable without this information. The Sponsor continunes saying the biphasic profile for maximum and minimum volume limits are established for the first hour and at end of the deliver, and provides a representation of this and points to West report (b) (4) Section 10.1 Testing for Dose Accuracy reliability, Time point t=0. The Summary information appears reasonable as presented, but complete review of the testing in (b) (4) is needed b. The maximum flow rate is tied discomfort and backflow exceeding 2.4.e requirement. The Sponsor points to literature to support their position (b) (b) (4) (b) (4) Ths Sponsor points to the Hazard Analysis (device-ra00043) for the delivery too quickly error. The Sponsor states that a minimum allowed flow rate is not required based on this but states a minimum dose volume is specified and a minimum allowed flow rate in the first hour. This explanation speaks to safety primarily with efficacy pointeded to in PK/PD data, arguing the true item of importance is total dose. This should be discussed with a clinician. c. Dose delivery limits are pointed to the same as described above in b (10 mL (b) (4) (b) (4) 5 hrs with 3.75 mL (b) (4) in first hour in MAF (b) (4) Section 9 requirement 2.3.a). d. Alarms i. (b) (4)

	(b) (4)
	e. Kit certification is provided in device-memo-0084, is approved through the Sponsor's document control system and states the part in question is exempted from premarket notification and no new use is claimed. This is reasonable. f. The Software (SW P/N SW0025) is stated as Rev 02.03, following (b) (4) Rev. A04 (b) (4) (b) (4)

Response Adequate:	☐ **Yes** ☑ **No, See SAC review and CR response**

For NDA Sponsor	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #4	While you provide a description of the sequence to trigger the (b) (4) alarm in your device summary in 3.2.R.1.P.3, there are key pieces of information missing which impact our understanding of the risks associated with your device: (b) (4) Please provide a complete description of the (b) (4) alarm, the steps needed to initiate an (b) (4) alarm, and justify the design of the (b) (4) alarm in the context of your use-case.	
Sponsor Response	a. (b) (4) trigger limits During the 5-hour drug delivery cycle, the device delivers (b) (4) drug product (b) (4) during an operating window. (b) (4) (b) (4) If an error is detected at any time during the operational flow, an error notification (5 audible beeps and red visible light) will alert the user to the condition and motor operation will terminate. (b) (4)	

(b) (4)

b.i.

(b) (4)

(b) (4) The design of the Infusor and logic behind the algorithm for (b) (4) notification take into account the risk profile for the drug product as well as the need to minimize false, or unneeded alarms. As described in response to FDA Question #3, the total dose delivered is the essential performance parameter for drug delivery. In addition, there is a specification around ensuring a delivery rate is not so fast as to cause patient pain or drug backflow/leakage. The (b) (4) strategy ensures the total dose is delivered in the intended timeframe but can allow deviations from the programmed rate that would not cause risk to the patient.

(b) (4)

b.ii.

As described above, the design of the (b) (4) alarm has been devised in context of the clinical application of Furoscix, and balances the need to detect and inform the user of error situations without causing unnecessary error notifications that could cause dose under-delivery for the patient (b) (4)

(b) (4)

	(b) (4)
Reviewer Comments	a. The Sponsor states that the system is operated (b) (4) but does not provide this specification. Thre is no discussion related to the (b) (4) specifications. (b) (4)
Response Adequate:	☐ Yes ☑ No, See SAC/Software Reviews

For MAF Holder	**Date Sent:** **7/22/2020**	**Date/Sequence Received: SN0036** **7/31/2020**
Information Request #5	The structure of MAF (b) (4) makes it extremely difficult to determine (1) the relevance of repeated information (i.e Sterilization) and (2) the location of specific reports/documents/information (i.e. within the Design Verification Test Reports). A unified table of contents would allow us to rapidly determine the location of necessary, relevant information and facilitate a timely review of the submission. Please provide a unified table of contents which identifies the location of all current documents within the Master Files.	
Sponsor Response	The MAF will be amended to include a unified Table of Contents (TOC). The TOC will allow the reviewer to navigate throughout the entirety of the filing. Each section will retain its own TOC to allow a more granular review within each specific section.	

Reviewer Comments	Table of Contents verified as present.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

For MAF Holder	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #6	The device description in MAF (b) (4) Original Submission Vol_001 /Section 01- Description lacks a complete description of the alarms of your infusion pump. A complete description is necessary to understand how your device is safe to use in scPharmaceutical's New Drug Application, to whom you have provided a Letter of Authorization to your Master File (b) (4) Please describe the following alarms, as applicable, in your on-body infusion device. This discussion should include the trigger mechanism. If any or the items are not applicable, please explain why they are not applicable to your device. (b) (4)	
Sponsor Response	(b) (4)	

	(b) (4)
Reviewer Comments	a: The software ((b) (4)) is described (b) (4) (b) (4) No reference is made to the devide design. Reasonable, pending Software review. b: (b) (4) (b) (4) There is no described sensor or function to monitor pump (b) (4) behavior. This is likely an approvability issue. c: Softwre verified (b) (4) (b) (4) Reasonable, pending Software review. d: The Sponsor describes expected start-up checks, including alarm functionality. Reasonable, pending Software review. e: Sponsor points to MAF (b) (4) ection 9 (b) (4) Design Requirement 5.3c and testing (b) (4) design requirement 2.10 a and b. Testing method is described and reviewed more completely under Design Verification. Human Factors acceptablitly is to be discussed. f: The Sponsor describes expected start-up checks, including alarm functionality. Reasonable, pending Software review.
Response Adequate:	☐ **Yes** ☑ **No, See Software review**

For MAF Holder	**Date Sent:** 7/22/2020	**Date/Sequence Received: SN0036** 7/31/2020
Information Request #7	While your device description in MAF (b) (4) Original Submission Vol_001 /Section 01-Description explains most of the functions of your device, we have identified key items which you incompletely describe which directly relate to the safety and effectiveness of the device. You do not describe how the alarm handler differentiates all alarm notifications/outputs, how your system prioritizes alarms or sensory input, how alarms within the device correlate to user notification, or how your device maintains internal time. These are all necessary to ensure the user is alerted to safe functioning of the device and the device is capable of delivering drug product at a given flow rate. Please describe: a. The alarm handler in your device which sorts and prioritizes sensory input and alarms b. How each alarm correlates to a specific user notification c. How your device measures flow rate and maintains a specificed flow rate within a given unit of time. This discussion should include how your device maintains an internal sense of time. If your device does not maintain an internal timing function,	

		please explain why it is not applicable within your discussion of your device's measurement and calculation of delivered flow rate.
Sponsor Response	a.	There is no set priority of error notifications as there is only one type of error notification to the user for simplicity of this single use device. (b) (4) (b) (4) [redacted] If an error is detected at any time during the operational flow, both audible and visible indicators will alert the user to the condition and motor operation will terminate, if delivery has begun (b) (4) SmartDose® Gen II 10 ml Software Requirement Specification (SRS)) (See MAF (b) (4) Section 10 Software). The device will enter Error state in the following cases listed below: (b) (4) [redacted]

	(b) (4) b. The sponsor has considered ease of use for the patient/caregiver when creating the notification strategy for the Infusor. The goal of minimizing the types of notifications, to minimize potential confusion, was used as a guiding principle in developing the alarm/notification strategy. With that philosophy, a single user notification was implemented for all error states. In every error situation, the desired user response is the same, remove the device and contact their healthcare provider. In every error state situation, the infusion is stopped, regardless of the reason for error, and 5 beeps are repeated along with a continuous blinking red light for the patient notification. It is not important for the user to immediately understand the reason for the error, rather, it is important that user clearly understands that the infusion has stopped and that they can observe the piston position through the cartridge window, so their health care provider can decide on an appropriate next step of action. This notification strategy was tested in Human Factors testing (see rpt-0333) and patients were able to understand the various user notifications, including alarm notification, and what to do in case of an alarm. (b) (4) c. The device doesn't measure flow rate, but rather (b) (4) according to the required pre-programmed delivery rate. (b) (4) (b) (4) (b) (4) This was tested as part of software V&V.
Reviewer Comments	a: The Sponsor states there is no preset priority of error notifications and there is only one type of error. This would default all alarms to high priority alarms. The Sponsor continues ti state the device (b) (4) would trigger an alarm at the first of these indicated erors (a pointer is presented to MAF Sectio 10 for the

	software): (b) (4) (b) (4) (b) (4) Reasonable, pending Software review. b: A single notification is used for all alarms, which defaults them to all being high-priority. The described interrupt is the same for all (stopping of infusion with 5 beeps and continuous blinking red light). The Sponsor contends the need to alert the user to an error state is greater that what the error state is and states the viewing of the cartridge window is meant to aid a healthcare provided on the next appropriate step. Human Factors acceptablitly is to be discussed. c: The Sponsor states the device does not measure time, but controls deliver rate (b) (4) (b) (4) Reasonable, pending Software review.
Response Adequate:	☐ **Yes** ☑ **No, See Softare review**

In Ammendment 3, Section 01, the following System notification summary was provided (Table 1-2):

Use state	Reason or Cause	Indicator	Indicator Behavior	Occurrence
Device Power Up	Drug Compartment opened, supplying power to the product; power-on functionality test is conducted	Buzzer	3 short beeps	Once
		Visual (LED)	1 blink per second, blue color	Continuous, until User activation Button is being pressed, or predefined time elapsed
Activation Button being pressed	Upon Activation Button being pressed	Buzzer	3 short beeps	Once
		Visual (LED)	1 blink per second with fade-in / fade-out feature, Green color	Continuous
Delivery duration	From Delivery Start till completion	Buzzer	OFF	Continuous
		Visual (LED)	1 blink per second with fade-in / fade-out feature, Green color	Continuous
Delivery completion	Upon device recognition of Delivery completion per predefined time	Buzzer	3 short beeps every defined period	Continuous, until predefined time elapsed
		Visual (LED)	ON (Steady), Green color	Continuous, until predefined time
Device Removal from Body	Upon device removal from body, post-delivery completion	Buzzer	3 short beeps	Once
		Visual (LED)	OFF (No light, nor color)	Continuous

Use state	Reason or Cause	Indicator	Indicator Behavior	Occurrence
Error	If error condition is detected by device	Buzzer	5 long beeps every defined period Single error notification every 15 seconds until system is removed from site. Following removal from site and after 30 minutes a single error notification is provided	Continuous, and at least once, until Safety Latch is opened
		Visual (LED)	2 blinks per second, Red color	Continuous, until Safety Latch is opened upon device removal from administration site.

Again, a single error message is displayed for alarms.

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Reviewer Note: Some module numbers noted for SN 0034, unless otherwise specified. It is difficult to find information in the MAF based on its structuring. A Table of Contents .

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		3.2.R.1.P.3		
Device Constituent Labeling		1.14.1		
Letters of Authorization		1.4.2		
Essential Performance Requirements defined by the application Sponsor		3.2.R.1.P.3 referencing further items		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		3.2.R.1.P.3.6		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		SAC contained in 3.2.R which clear pointers to specific reports. Checking of report pointers from DV testing indicated. Sponsor indicated that stability information is in 3.2.P.5.5 (see below)		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		3.2.R		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		3.2.R		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X-various		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X-various		
	Reliability	X-(b) (4) MAF		
	Biocompatibility	X -MAF (b) (4)		
	Sterility	X-MAF (b) (4)		
	Software	X-MAF (b) (4)		

	Cybersecurity	X-MAF (b) (4)		
	Electrical Safety	X-MAF (b) (4)		
	EMC/RF Wireless	X-MAF (b) (4)		
	MR Compatibility	X-Marked MR Incompatible in Instructions for Use		
	Human Factors	5.3.5.4		
	Shelf Life, Aging and Transportation	3.2.R.1.P.3.6 and MAF (b) (4)		
	Clinical Validation	5.2 and 5.3.5.4		
	Human Factors Validation	5.3.5.4		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	3.2.P (drug product) and 3.2.R.1.P.3.3 and MAF (b) (4)		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	Infusor – references MAF (b) (4) Sponsor appears to use Device QSR per 3.2.R.1.P.3.3.		
	CAPA Procedure	3.2.R.1.P.3.3 – device-sop-0036 in response to IR sent (see below)		
	Control Strategy provided for EPRs	3.2.R – Distribution Control Procedure MAF (b) (4) for Manufactruing Controls. 3.2.R.1.P.3.3 indicate that the system undergoes (b) (4) inspection. See belpow for additional		

		files refereces in respose to IR		

Reviewer Comment
In general, the submission appears complete and acceptable for filing. The noted missing files, which are suspected to be an oversight and not to significantly hinder review are:

Report-0332
CAPA Procedure. While 3 2.1.P.3.3 refernece that Quality Assurance is the primary group responsible, there is no reference to the CAPA procedure. This si similarly noted for Complaints. (21 CFR 820.100 and 21 CFR 820 198)

These should be requested via IR/74-day letter.

5.2. Facilities Information

Reviewer Note: SN0034 FDA Form 356h used to populate the following Facilites information.
Reviewer Note: Inspectional History information determined by searching OSAR.

Firm Name:	scPharmaceuticals Inc.
Address:	2400 District Ave. Suite 310 Burlington, MA 01803, USA
FEI:	3013722099
Responsibilities:	Combination Product Manufacturer

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history shows it has not been inspected in the past 2 years.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination product involving the device constituent part.
.

☐ An inspection is not required because Choose an item.

Firm Name:	Swissfillon AG
Address:	Rottenstrasse 7 Visp, Valais 3930, Switzerland
FEI:	3014757826
Responsibilities:	Manufacturing of Drug Product, including filling and inspection of drug product.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:

☑ Inspection was conducted 4/15/2019 to 4/24/2019. The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history shows that it has not been inspected in the past 2 years

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history shows that it has not been inspected in the past 2 years

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history shows that it has not been inspected in the past 2 years.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Firm Name:	Sharp Corporation
Address:	7451 Keebler Way Allentown, PA 18106, USA
FEI:	3004161147
Responsibilities:	Packing of Drug and Device Components (b) (4)

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history shows that it has not been inspected in the past 2 years.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, a recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because Choose an item.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4). The inspection covered (b) (4) and was classified NAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	West Pharmaceuticals AZ Inc.
Address:	14677 N. 74th Street Scottsdale, AZ 85260, USA
FEI:	3001155023 **Reviewer Note:** Revised in SN0037
DUNS	196630557 **Reviewer Note**: DUNS number copied over as the original FEI number listed in 356h SN 0034 does not match the expected numbering sequence.
Responsibilities:	Device manufacturer and manufacturer of sterile carridge and stoppers for Drug Product Primary Container Closure

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☐ Inspection was conducted Click or tap to enter a date. to Click or tap to enter a date.. The inspection covered Choose an item. and was classified Choose an item..

☑ An analysis of the firm's inspection history showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, no inspection has previously been completed of the firm Choose an item.

☐ An inspection is not required because Choose an item.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm Choose an item.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4). The inspection covered drug CGMP and was classified OAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation: ☐ A choose an item inspection is required because: The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and, A recent medical device inspection of the firm Choose an item. ☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations? **Reviewer Note:** No recent inspections for combination product or device manufacturers.	☐ Yes ☐ No ☑ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes? **Reviewer Note**: This definition was expanded to the above three recommended sites to be inspected.	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment Recommend pre-apprivoal inspections of three sites for the device constituenet: scPharmaceuticals Inc. West Pharmaceutical Services Az, Inc.

Sharp Corporation Preapproval inspection recommnedations of Drug Product/Primary Container Closure is deferred to CDER.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☑ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance
☐ No Inspection ☐ N/A

Sites needing inspection:
scPharmaceuticals Inc: Combination Product manufacturer
West Pharmaceutical Services Az, Inc: Device manufacturer
Sharp Corporation: (b) (4)

Reviewer Comments
Recommend pre-apprivoal inspections of three sites for the device constituenet:

The FEI number of West Pharmascutical Services AZ was deteremined to be incorrect. This has been communicated to the CDER Facilities reviewer. The relevant information was located using the DUNS number for the CDRH filing review; therefore, was considered not worth pursuing at this time within the CDRH review.

scPharmaceuticals Inc.
West Pharmaceutical Services Az, Inc.
Sharp Corporation

Preapproval inspection recommnedations of Drug Product/Primary Container Closure is deferred to CDER.

Documents were identified as missing during the Filing Review:
CAPA Procedure
Report-0332

Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A

74-Day Letter Deficiencies: ☑ Yes ☐ No ☐ N/A
We were unable to locate files that we believe are necessary in conducting our review of your marketing application: Your CAPA procedure and Report-0332. Please review your submission and ensure all referenced documents are provided and provide your CAPA procedure and Report-0332s o that we can complete our review in a timely fashion.

For NDA Sponsor	Date Sent: 7/31/2020	Date/Sequence Received: SN0036 Click or tap to enter a date.
Information Request #8	We are unable to locate files which we believe are necessary to conduct our review of your marketing application: Your CAPA procedure and Report-0332. Please review your submission and ensure all referenced documents are provided. Specifically, provide your CAPA procedure and Report-0332.	
Sponsor Response	Reviewed in Quality Systems/Manufacturing Controls Section	

	The Sponsor states report -0332 was contained in 3 2.P.5.5 and provide a summary of the CAPA information in updated 3.2.R 1.P.3.3 and provides the detailed SOP ins device-sop-0036. The Sponsor also noted that DMR (device-sop-0037), NCR (device-sop-0035), and Complaint (device-sop-0015) information was not provided and now is.

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, (b) (4) prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	See Section 3 3 for stated Indications in labeling Sponsor provices device-dir0010 to support Accetable		
Drug name is visible on device constituent and packaging	Present on several labels and Instructions for Use		
Device/Combination Product Name and labeling is consistent with the type of device constituent	Device is labled/pictured as an infusion pump		
Prescriptive Statement/Symbol on device constituent	Prescriptive statement present on drug cartridge. Acceptable.		
Warnings		Could not be determined due to derficient testing information	
Contraindications		Could not be determined due to derficient testing information	
Instructions for Use	Appear appropriate to		

	Lead Reviewer. See HF Consult.		
Final Instructions for Use Validated through Human Factors	See HF Consult.		
Electrical Safety Labeling/Symbols		No Present	
EMC Labeling/Symbols		No Present	
Software Version Labeling		No Present	
MRI Labeling/Symbols	MR Unsafe		
RF/Wireless Labeling/Symbols		No Present	

Reviewer Comments
See labeling concerns communicated to the Sponsor in IRs in Section 4.3. Inadequate responses to many of these with pointers to 'will provide in the future.'

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
‡the intended use environment (e g home, hospital, transport, etc)		Conflicting – (b) (4) testing does not demonstrate this use case.	
‡Intended route(s) of administration *(see note in Comparison of Indications for Use Section)*	Subcutaneous		
‡Intended fluid(s) to be administered by the device	Furosemide		
‡any specific uses for the infusion pump (e g , PCA is a generally accepted specific use)	Subcutaneous infusion of furosemide in biphasic delvier over 5 hours		
‡the indicated treatment population (e g neonate, infant, pediatric, adult)	*"treatment of congestion due to fluid overload in adults with NYHA Class II/III heart failure who display reduced responsiveness to oral diuretics and do not require hospitalization"*		
‡Intended user population (e g lay person v HCP)	Layperson		
MR Compatibility	No		
How the pump will be marketed (e g , sterile, single use, multi-patient use, home use)	Sterile, single use		

‡ *This attribute should be in the indications for use statement*

Infusion Pump Guidance Labeling Recommendations	Yes	No*	N/A
Submission contain proposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for use	X		
Intended Use (Indications for Use Statement along with the intended use information; See Section IV)	X		
Labeling includes a prescription statement (21 CFR 801 109)? The prescription statement/symbol should be on the physical device as well as in the labeling	X		
Adequate Directions for use (*solicit input from clinical/nurse/pharamcists*)	See HF Consult		
If device is intended for home use, does labeling address recommendations from FDA guidance, Design Considerations for Devices Intended for Home Use?		X	
Define the accuracy specifications over the range of selectable flow rates and bolus volumes This may include information such as: o Time period over which accuracy is specified; o Time to reach steady-state flow accuracy; and o Effect of infusion rate changes or bolus delivery on accuracy		X	
Describe any factors that may affect flow accuracy such as ambient temperature, fluid temperature, pressure (e g , head-height, backpressure, atmospheric pressure), fluid viscosity, or changes in flow rate or bolus delivery (e g , such as when titrating medications)		X	
Description of all alarm or information messages and recommended actions when alarms or information messages are provided	Single alarm is used for all device control Instructed to stop infusion		
Alarm limits and ranges		Single alarm is used for all device control No limits for specific entitites in the labeling	
Default settings			N/A - Preset
For infusion pumps containing a reservoir, container, or other components contacting the drug or biological product being infused, include information regarding the stability and compatibility of those fluids with your device	Outside packaging contains storage conditions		
Identify reservoir volume, selectable flow rates and profiles, and residual fluid volume remaining after the infusion is complete	Cartigde: 10 mL	Residual volume undefined	Biphaic profile is preset and not adjustable
An identification of any dedicated administration set or the specifications and/or specific models of infusion sets that are appropriate for use with this pump			N/A – body contacting cartridge included

Cleaning and disinfection instructions for reusable infusion pumps and accessories If the pump is used in the home, please identify cleaning and disinfection agents available to the general public that are suitable for device reuse (cleaning and disinfection)			N/A – Single use
Describe a method or methods that can be used to confirm that the device is in calibration for all relevant delivery features (this is generally applicable to large volume volumetric or syringe pumps)			N/A – Single use
Warning statements on your device regarding the safety of use during diagnostic procedures, such as magnetic resonance imaging (MRI), x-ray, computed tomography (CT), or ultrasound	MR unsafe	No mention of CT, Ultrasound, X-ray	
Labeling should include all recommended information related to EMC, including reference to the appropriate standard, such as IEC 60601-1-2	See Electrical Safety and EMC Sections		
For devices with RF wireless technology capabilities, the labeling should include information about the exact RF wireless technology incorporated or able to be used with your device The information should contain specifics about the technology (e g , IEEE 802 11 b), the frequency of operation and range, quality of service required for the claimed functions, data integrity, recommended security measures for the RF wireless technology (e g , WPA2), coexistence and any limitations (e g , distance between RF devices, EMC limitations)	See RF/Wireless Review Section		

Reviewer Comments
Labeling is missing several items (See Section 4.3). Sponsor has indicated that these will be updated later. These should be addressed promptly. Additional items identified as missing.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by CDER
☐ Insert Consultant Name ; The full memo is located in Appendix B.
☑ The Lead Reviewer
Below is a summary of the review & recommendation: Inadequate (see above)

Clinical review is deferred to CDER. This includes labeling.

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A

Reviewer Comments

The following could not be located in the labeling:

Electrical Safety Labeling
EMC labeling
Software version labeling
Use environment/home use considerations (https://www.fda.gov/media/84830/download)
Factors affecting accuracy
Residual volume
CT, Ultrasound, X-Ray.

General comment recommended for both home-use and infusion pump guidances.
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X - Inadequate		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X - Inadequate		
Mitigations are adequate to reduce risk to health	X - Inadequate		
Version history demonstrates risk management throughout design / development activities	X - Inadequate		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X - Inadequate		
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X - Inadequate		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			Given the issues with the verification testing and unknown device used, device reliability review is deferred to the next review cycle.

Traceability demonstrated for specifications to performance data		X – Documentation strategy makes it extremely difficult to located required testing.	

Reviewer Comments
See SAC review.

7.2. Design Inputs and Outputs

Essential Performance Requirements: See SAC review in Section 9

Reviewer Comments
See SAC Review in Section 9

7.3. Applicable Standards and Guidance Documents

Reviewer Note: The Sponsor provides a reference/listing of standarsds in 3.2.R.1.P.3.2 and states the Specific Conformance information is contained in verification/validation information in 3.2.R.1.P.3 (device-summary).
Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2019	N
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-16	Distribution cycle used and assurance level used unknown
IEC 60601-1-2:2014	See EMC Review
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Stated as applicable
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Stated as applicable
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Stated as applicable – See Biocompatibiltiy review
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents:
Sponsor provided response:

Table 1 List of Device Standards, Guidance Documents and References

Standard, Guidance or Reference	Title
ISO 13485:2016	Medical Devices – Quality Management Systems –Requirements for Regulatory Purposes
ISO 14971: 2019	Medical Devices - Application Of Risk Management To Medical Devices
ISO 15223-1:2016 ISO 15223-2:2010	Medical devices - Symbols to be used in the medical device labels, in labeling and information to be supplied - Part 1 and 2 General requirements and Symbol Development, selection and validation
ISO 14155-1 & -2: 2011	Clinical Investigation of medical devices for human subjects – General Practices and Clinical Investigation Plans
ASTM D4169-16	Standard Practice for Performance Testing of Shipping Containers and Systems.
ISO 11607-1: 2006/Amd 1:2019	Packaging for Terminally Sterilized Medical Devices-Part 1: Requirements for Materials, Sterile Barrier Systems and Packaging Systems.
ASTM D7386 -16	Standard Practice for Performance Testing of Packages for Single Parcel Delivery Systems
ASTM F1886 /F1886M-16	Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection
ASTM D4332 2014	Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing
ASTM D5264: 2019	Standard Practice for Abrasion Resistance of Printed Materials by the Sutherland Rub Tester
ASTM F88/F88M-15	Standard Test Method for Seal Strength of Flexible Barrier Materials
ASTM F2096 -11(2019)	Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)
ASTM F1980 -16	Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
ASTM D2979 -16	Standard Test Method for Pressure-Sensitive Tack of Adhesives Using an Inverted Probe Machine

Table 1 List of Device Standards, Guidance Documents and References

Standard, Guidance or Reference	Title
	(b) (4)
IEC 60601-1:2012 Ed.3.1	Medical Electrical Equipment - Part 1: General requirements for basic safety and essential performance
IEC 60601-1-2:2014 Ed.4	Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests
IEC 60601.1.6:2010	Medical electrical equipment - Part 1.6: General requirements for basic safety and essential performance - Collateral standard: Usability
IEC 60601-1-8:2006 Medical electrical equipment -- Part 1-8:	General requirements for basic safety and essential performance -- Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems
FDA Guidance	Guidance for Industry and FDA Staff; Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (June, 2013)
ISO 10993-1:2018	Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process
FDA Guidance	"Use of International Standard ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing Within a Risk Management Process" (2016)
ISO 10993-4:2017	Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
ISO 10993-5:2009	Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity
ISO 10993-6:2016	Biological Evaluation of Medical Devices – Part 6: Tests for local effects after implantation
ISO 10993-7:2008	Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals
ISO 10993-10:2010	Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization
ISO 10993-11:2017	Biological evaluation of medical devices – Part 11: Tests for systemic toxicity
ISO 10993-12:2012	Biological Evaluation of Medical Devices – Part 12: Sample preparation and reference materials
ISO 10993-17:2002	Biological evaluation of medical devices – Part 17: Establishment of allowable limits for leachable substances
ISO 10993-18:2005	Biological evaluation of medical devices – Part 18: Chemical characterization of materials
ISO/TS 21726: 2019	Biological Evaluation of Medical devices – Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents.
ISO 11135:2014	Sterilization of health-care products – Ethylene Oxide – Requirements for the development, validation and routine control of a sterilization process for medical devices.
	(b) (4)

Table 1 List of Device Standards, Guidance Documents and References

Standard, Guidance or Reference	Title
	(b) (4)
ISO 23908:2011	Sharps injury protection -- Requirements and test methods -- Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling
FDA Guidance	Guidance for Industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features (2005)
ISO 7864:2016	Sterile hypodermic needles for single use – Requirements and test methods
	(b) (4)
ISO 13926-1:2018	Pen systems – Part 1: Glass cylinders for pen-injectors for medical use
ISO 15510:2014	Stainless Steels – Chemical composition
ISO 9626: 2016	Stainless steel needle tubing for the manufacture of medical devices - Requirements and test methods
FDA Guidance	Guidance for Industry and FDA Staff: Infusion Pumps Total Product Life Cycle (December 2014)
FDA Guidance	Guidance for Industry and FDA Staff, Design Considerations for Devices Intended for Home Use. (August 2014)
FDA Guidance	Design Control Guidance For Medical Device Manufacturers. Date March 1997
FDA Guidance	Final Guidance for Industry and FDA Staff, General Principles of Software Validation. Date January 2002
FDA Guidance	Guidance for Industry and FDA - Current Good Manufacturing Practice for Combination Products (January 2017
FDA Guidance	Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development, Draft Guidance for Industry and FDA Staff (February, 2016)
FDA Guidance	Contents of a Complete Submission for Threshold Analysis and Human Factors Submissions to Drug and Biologic Applications, Draft Guidance for Industry and FDA Staff (September 2018)
IEC/EN 62366-1:2015	Application of usability engineering to medical devices
IEC 62304:2006	Medical device software – Software life cycle processes
ISO 11040-4:2015	Pre-filled syringes: Glass barrels for injectables and sterilized subassembled syringes ready for filling

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A
Reviewer Comments Sponsor references the use of many standards. The SAC/Risk analysis reviews identified the information contained within the submission as inadequate. These comments are addressed there.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

Document Number	Document Title
device-SOP-0034	scPharmaceuticals Risk Management Procedure
device-RA-0042	scPharmaceuticals Risk Management Plan
device-RA-0043	Furoscix Infusor Hazard Analysis
device-RA-0044	Use Related Risk Analysis
device-RA-0045	Furoscix Infusor System dFMEA
device-RA-0047	Furoscix Infusor Risk Analysis
device-RA-0048	Furoscix Infusor Safety Assurance Case
device-RA-0049	Furoscix Infusor Risk Management Report

SAC: device-RA-0048 and device-RA-0048.html

8.1. Risk Management Plan

Reviewer Comments
See SAC review in Section 9

8.2. Hazard Analysis and Risk Summary Report

Link to Infusion Pump SAC Reviewer Guide

Reviewer Comments
See SAC review in Section 9

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☑ N/A	Final Deficiencies: ☑ Yes ☐ No ☐ N/A
Reviewer Comments See SAC review in Section 9		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9. DESIGN VERIFICATION REVIEW

Performance Testing OR Verification & Validation

Safety Assurance Case Review

Reviewer note: Initial review based on device-ra0048 and the accompanying HTML version from SN0034

Safety Assurance Case Argument Structure Review

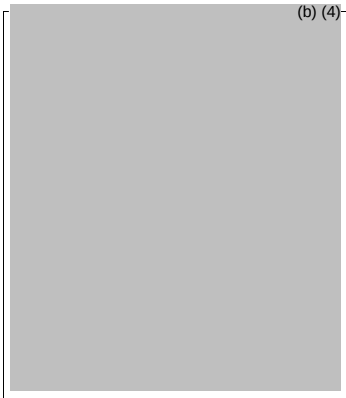
Reviewer note: Sponsor uses Context (Ct) and Assumption (As) abbreviations, Sposnsor points to Hazard Analysis RA-0043 and Risk Analysis RA-0047 for system hazards evaluation and the SAC reviews other systems

The top level goal is asserting device safety, is propositioned as a true/false statement and is consistent with FDA definitions (i.e. Device X is safe for its intended use)	*Claim (S#16421)* *Device design is adequately safe for its intended use* *Ct In support of the 505(b)(2) New Drug Application (NDA) for the Furoscix Infusor, the Sponsor is relying upon the FDA's previous findings of safety and efficacy for the proposed listed drug, Furosemide Injection (Hospira, NDA 18667) (Hospira (2019) in conjunction with information from Sponsor-conducted studies and a complete verification and validation program.* *As Furosemide has been approved in the United States (US) since 1966 as an oral tablet form and later approved in 1968 as an injection formulation for IV and IM administration and as an oral solution.* *There are currently no approved furosemide products for subcutaneous administration.*

Reviewer note: The Sponsor provides a statement as a verifiable true/false argument. Reasonable.

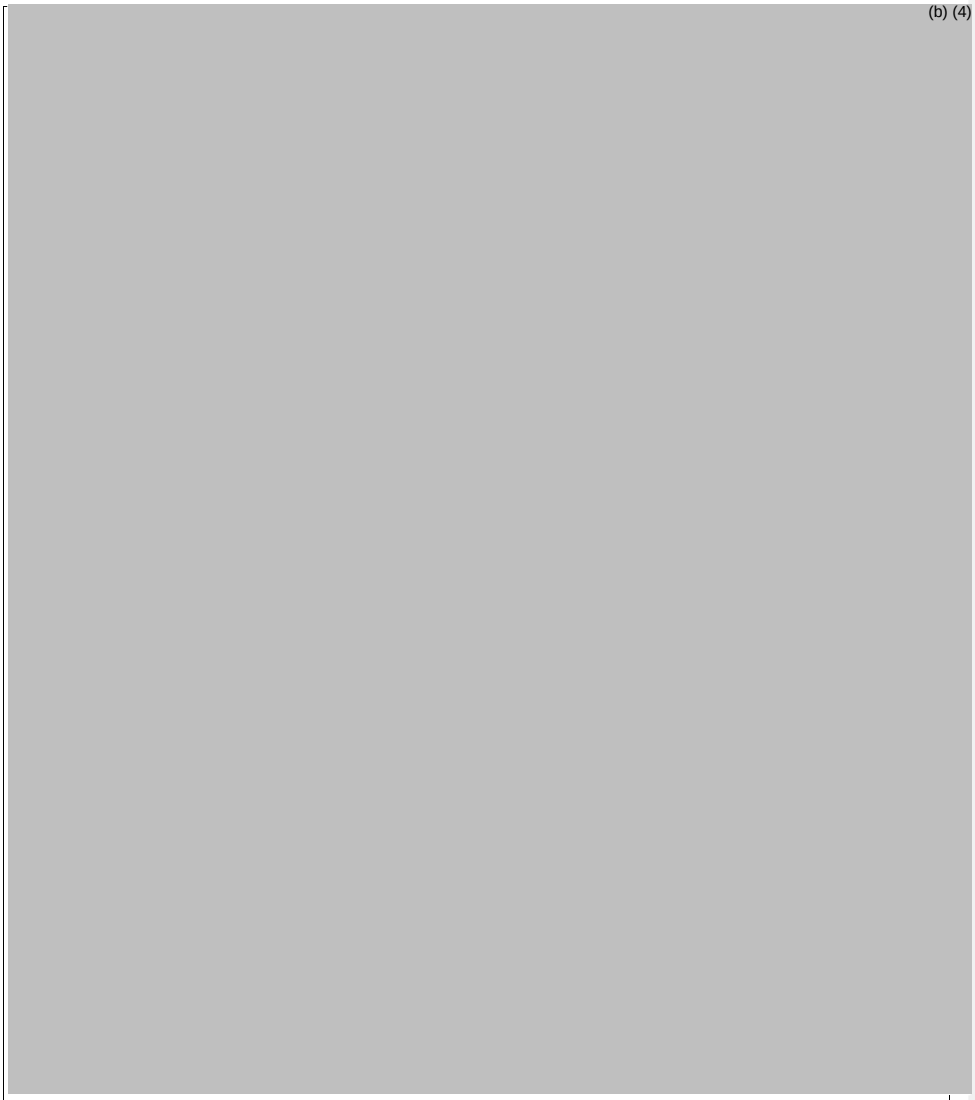
Acceptability of risk mitigations
Review of how the safety case includes System Level Requirements and corresponding traceability to the performance testing and hazard analysis.
The Sponsor uses a (b) (4) approach to build their SAC. The issue with this approach is (b) (4) (b) (4) unclearly defined as to how they relate. For example, specific to System level requirements tracing to performance testing and hazard analysis (and by extension, system level reliability), the following is performed. Claim S#16426 *Specific device models/configurations under the assurance case scope are defined* should connect to System level hazards. (b) (4) (b) (4)

(b) (4)



The Sponsor provides 3 relevant claims to this discussion under S#16427 *Device design requirements are adequate for the intended use and adequately…verified and validated.*

(b) (4)



The Sponsor points to the Design Input/Output document requirements document (DD-0094) for tracability. While this document contains tracing between inputs-outputs-verification-validation, there is no link to the hazard analysis or risks associated with each. The Hazard and Risk Analyses (RA-0043 and RA-0047) define the sources and causes and provides a table for maping or risk controls to user requirements. However, not all requirements could be located here. Therefore, the linking is incomplete. In addition, there is no ‘cross-connection’ between S#16431 and S#16433, meaning it is not clear if the found items are as the Sponsor intended or not.

(b) (4)	
In conclusion, the structure of the SAC contains fundamendal flaws maining relating to specificity of the evidence and tracing.	
Review of the argument structure for the risk mitigations:	*Do the claims and arguments for the risk mitigation have a logical flow?* No. See above. – There is no clear link between the defind requirements and the presented mitigations. (b) (4) (b) (4) *Does the SAC provide a justification for why the risk mitigations are appropriate to mitigate the hazards?* Yes – In general, the Sponsor provides arguments to support their mitigation claims and to explain why the presented evidence is applicable. The noted issues remains with how these mitigations align to all stated requirements.
Adequate design verification and validation of device specifications	
Review of how the safety case includes references to the traceability of the design requirements to the verification and validation documents.	
Yes: For Essential performance requirements (S#17035):	

(b) (4)	
Review of the argument structure for the design verification and validation:	*Do the claims and arguments for that the design verification and validation of the specifications have a logical flow?* Yes – The Sponsor breaks these up into categories which each containing specific mitigations/errors: (b) (4) These (b) (4) point to specific items for supporting evidence. The arguments presented appear to align to the stated items and the Sponsor describes controls which appear to align to the stated risk described. (b) (4) (b) (4)

	(b) (4)
	In general, the arguments presented appear to align between the stated item being verified and the evidence described. The Sponsor provides different notes for validation (typically though HF). It is noted that many of thse items point generally to the MAF for evidence. A ToC has been requested from the MAF holder to aide in location of specific data. *Does the SAC provide a justification for why the specifications are appropriate for the intended use?* No – There is not justification for these items found.
Adequate device reliability	

Review of how the safety case identifies the reliability requirements and corresponding traceability to the performance testing.	
The Sponsor provides stated reliability requirements with pointers to documentation to build the argument. The Sponsor points generally to the MAF for evidence location for many items, which is non-specific to the data being used to support the item (b) (4) Sponsor includes software in their argument and describes the use of 'worst-case' for system items. A reliability memo in device-memo-0079 appears to contain the logical argument for how this is built from a technical perspective (e.g. failure rate calcualtions).	
Review of the argument structure for the device reliability:	*Do the claims and arguments for that the device is reliable have a logical flow?* Yes – The Sponsor separates this into system reliability, reliability undergoing verification/validation, and software reliability. These generally point to specific data which should suppor the stated arguments. See above for example. *Does the SAC provide a justification for why the reliability specification is appropriate for the intended use?* No – The Sponsor separates their arugment and provides justifications specific to the systems. The Sponsor justifies the high level argument based on several items. However, the sponsor does not include a clear link to the associated clinical arugments for why the device should function. (b) (4) (b) (4) *Discussions with the Food and Drug Administration have indicated a 95% reliability level is reasonable for essential performance requirements."* (b) (4) (b) (4) and the device is outside the scope (b) (4) The Lead Reviewer notes the referenced communication (Response to a Type-A meeting) where the Agency committed to 95%/95%. The logic here appears to be not necessarily based on the Sponsor's identification of clinical risks and verifying these. See above for example.

Part 1: Acceptability of Risk Mitigations

Risk Management Plan/Strategy
The Sponsor defines the Severity ratings in the Risk Management SOP (SOP-0034):

Table A-1: Severity Ratings

Severity (S) Rating	Patient Safety Severity Evaluation Criteria
1	(b) (4)
2	
3	
4	
5	

Reviewer note: The sponsor does not clearly defined the difference (b) (4)

(b) (4)

This procedure defines the process for estimating and evaluating risks in a review period:

Figure 1: Risk Management Process Flow

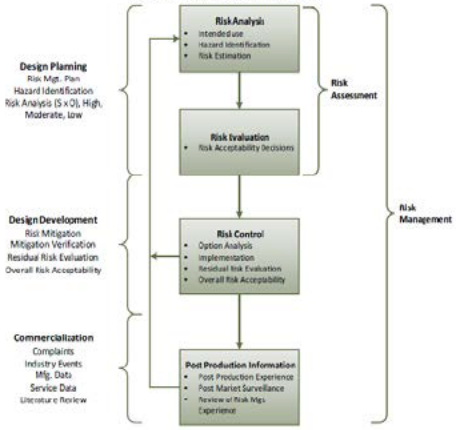
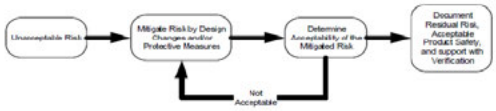


Figure 2: Risk Control Process Flow



The Sponsor notes that safety information and labeling is not considered mitigation per the EU (ISO 14971: 2012)
The Sponsor points to the need to do production and post-production reviews, safety signals (MDRs. AEs, SAEs, CAPAs) for information to inform this process.
The Sponsor states the need to have traceability to the Risk Analysis, Risk Evaluation, Implementation and verification of Risk Control Measures, and Assessment of the Acceptabiltiy of the Residual Risk in the description of the requirements for the Risk Management File in Section 5.8 3 of SOP-0034.
The Sponsor provides RPN and Risk Level Matricies for assessing risks. These seemed appropriate.

The Sponsor provides a summary for Risk Based Sampling for thie approach based on RPN and Severity.

Risk Acceptability Zones (Table A-1 and Table A-5)	Reliability Level (Power)	Confidence Level (Alpha)	(LTPD) Upper confidence limit on population % outside tolerance interval or limit	Attribute Sampling Plan Defect Classification	Attribute Sampling/ Acceptable Quality Level (AQL)
High					(b) (4)
Moderate					
Low					

The Sponsor provides the Risk Management plan in device-RA-0042:
In this document, the Sponsor provides a description of the device to inform the assessment which aligns with the understood device design.
Responsibilites and review timing are defined in a clear manner.
Risk Acceptability Criteria are defined in Section 7. These discuss the clinical context for risks. In summary:

- Condition is chronic. Congestion is the most common symptom
- Results from impeded ability of heart to pump blood
- Congestion leads to extra fluid, which causes a variety of symptoms
- Motivation comes from a need to prevent Emergency admissions and better control symptoms
- Diuretic therapy (loop diuretics) are a common therapy to manage conditions by removing excess salt and water through kidney (increased urine output)
- The intent seeks to overcome limitations of oral furosemide in patients with hear failure who respond inadequately to oral therapy and do no require hospitilzation
- The Sponsor points to PK/PD validation for bioavailability at 99.6%, indication of the drug for IM administration, and the need to administer many doses to achieve clinical affect.
- Final assessment and threshold criteria will be performed basd on review of the information.

The Sponsor discusses V&V activities, at a high lelve, for demonstrating meeting product requirements.

In general, the Sponsor unclearly defines severities (b) (4) This informs the approach to the Hazard Analysis review.

A risk Mitigation Summary is presented in Appendix 2 of this document. This is used to fill in the table below for risk management..

Risk Management Report in device-RA-0049
The Sponsor states the purpose of the document is to provide tracability to each hazard to the risk analysis, evaluation, and implemented verification of the risk control measures.
The Sponsor states that Risk in the Moderate risk zone must be addressed with at least one mitigation, based on the following table from SOP-0034:

Table A-4: Risk Level Matrix (S x O) for Risk Analysis and FMEA

(b) (4)

The Reviewer disagrees with this this approach, (b) (4) Thus, based on the Sponsor's definition of Severity, anything as (b) (4) should be mitigated.
The Sponsor present a summary of their anticipated benefits. Review of the device is focused on safety and effectiveness. Review of a risk/benefit argument may be considered after other mitigations are considered. The Sponsor provide inadequate mitigation arguments at thnis point in the review; therefore, deficiencies focus on these.
The Sponsor provides a summary of their risk documentation in Appendix 1 and a summary of their hazard mitigations in Appendix 2. See below table for tracing of hazards to mitigations.

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Hazard Analysis Review
The Sponsor provides the Hazard Analysis in RA-0043 (SN0036).
The Sponsor provide Safety Considerations in Section 2.2. These include:

- Single use, sterile device
- No user interface to motify delivery of the fixed dose
- Single (b) (4) battery provides power
- Audible and visual notifications are present and cannot be silenced or disconnected
- No communication connections
- Drug reservoir/fluid path are integral to device (i.e. self-contained)
- Moving parts are covered
- No maintenance is required.

The Sponsor continues with explanation in evaluating the severities of harms with detail provided for the most commone ones.

- Over dieresis is defined as the risk associated with overdose. This could lead to electrolye imbalance andsignificant health hazards (S4). The sponsor justifies this with clinical literature. This seems reasonable.
  - The Sponsor states that "*because the combination product administers a single fixed dose of 80mg of furosemide, an over-dose leading to over diuresis would be* (b) (4) (b) (4) This is un-justified. Previous discussions with clinicians suggest to the Lead Reviewer that the delivery accuracy and dose could impact over dieresis. Therefore, the Lead Reviewer disagrees with this specific justification. This fact was brought up in the original review and the CDER clinical division confirmed that a rapid devilery or over-fill of the cartridge could lead to over diuresis requiring medical intervention.
  - The Sponsor states that the maximum daily human dose of furosemide is 600 mg and systemic toxicity from an over-dose would require 8 doses from the device in a 24 hour period. This relats to dose delivery but not flow rate accuracy.
  - The Sponsor states that a malfunction delivering the total dose at maximum speed would be "*well below the maximum dose. The concerntraions that would be anticipated is well below the Cmax of an 80 mg IV or IM injection…* (b) (4) (b) (4) (b) (4) The Sponsor's justification (b) (4) (b) (4) does not fully address the time which the body will remain at saturated urine output, which could certainly impact the risks associated with electrolyte imbalance.
  - The Sponsor states that injection speed is a factor which "*influences subcutaneous injection site pain and tolerability*," and references literature in the justifying pain would only be expected if the total 80 mg/10 mL dose was delivered in (b) (4) This discussion appears reasonable.
- Under diuresis is defined as the risk with receiving too little drug or missing a dose. The hazard associated is stated as worsening symptoms due to congestion. (b) (4) (b) (4) " The Sponsor states the (b) (4) has been agreed upon with the Agency in references to 4335753. The severity is reasonable, however the Agency disagreed (b) (4) (b) (4). Regardless, the severity is what is driving mitigationsand seems reasonable.
- The Sponsor states that Delay in Therapy (Other) "*is considered to be a delay in administering the dose that is currently being delivered during a treatment*…[and] *would then only be used in cases where the current unit being used for a treatment was able to be used to finish delivering the intended dose.*" It remains possible that a device malfunction could result in therapy delay (e.g the unit in-use/pre-use malfunctions).

The Sponsor references the recommendations in ISO 14971:2007 for developing their 5-point severity scale

The Sponsor provides the following identification of primary system hazards in Table 1:

(b) (4)

These assignements seem appropriate. It is noted that the Sponsor unclearly defines the severity (b) (4) (b) (4) and it is understood that (b) (4) is this severity assignment.

The Sponsor points the Infusion Pumpts Total Product Lifecycle Guidance for identifying 8 sources of hazardous situations (Operation, Environmental, Electrical, Hardware, Software, Mechanical Biological and Chemical, Use) and the Sponsor states the Hazard Analysis reflects these in the connects of its use-case.

While the Sponsor provides Table 2 (summarized below) there are no provided RCMs or verification pointers. This makes this analysis incomplete. RCM and RCM analysis is present as a summary in Appendix 2 of device-ra0049 Risk Management Report. The Lead Reviewer performed a cusory review and determined that the 'Reason for Acceptance' column lacks specific pointers for many of the stated hazards and it is unclear that the Sponsor has mitigated al (b) hazards based on their described approach in device-ra-0049

(b) (4)

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Table 1 System Hazards, hazardous situations, sources, risk controls, and risk levels

System Hazard	Hazardous Situation	Sys Events/ Conditions	Sys Risk Controls	Sub-Causes	Add Risk Controls	Safety Harms	Safety Initial Severit y	Occurr ence	Initial Risk	Post-control occurr ence	Final Risk

(b) (4)

In Table 2, the Sponsor provides a mapping to user requirements. There are two noted issues: (1) not all user requirements could be found and (2) there is no statement of the implemented mitigation. ee screen-shot below for example. Thus, the above table remains incomplete, as the Lead Review is unable to determine the implemented mitigations.

Table 2 Mapping of risk controls to user requirements

RISK CTRLS AND MEASURES	Requirements	Requirement Description

(b) (4)

Part 2: Adequate Design Verification & Validation of the Device Specifications

APPEARS THIS WAY ON ORIGINAL

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Design Verification Plan

Include discussion on sampling plan, statistical analysis, aging plan, etc

Reviewer note: Please see Hazard Analysis for sampling selection from the NDA Sponsor. The Lead Reviewer disagrees with the stated sampling approach, which may impact performed testign. The MAF holder points to (b) (4) Design Verification Master Plan and (b) (4) Product Requirements, but does not provide thse documents. For each test, assessment of sample size is provided, but it is not clear how these were determined.

Device-ddp0038 is references as the Verification and Validation Plan (SN0034)
The Sponsor describes the intent is to ensure system-level requiremtns are met, with lower-level inputs/outs referenced and documented.

The Sponsor provides a summary for V&V tasks considered, with a pointer to the FDA Infusion Pumps Guidanc Document 5C-5F for building these. Namely, these include operational safety (including infusion accuracy and reliability analysis), environmental safety, electrical safety, hardware safety, softwere safety, mechanical safety, Biological Safev Use Safety. It is noted that the Sponsor discusses device impreoments to the device and its use case (e.g. SN0040), specifically addressing a device improvement (b) (4) (b) (4) and software changes (b) (4)

(b) (4)

Sampling plan:
Statistical Approaches:
Aging Plan:
Samples:

(Missing)

Reviewer note: 3.2.R.1.P.3.6 Performance testing contains a file for the summary information. This points to device-memo-0079 (SN0034) which establishes system reliability. Design Verification and Validaiton Plan is contained in device-ddp0038 SN0034.
There is no statement found regarding the commercial device being used for testing or differences between the engineering test samples and the to-be-marketed devices. Deficient.

Verification & Validation of Design Requirements Summary

Reviewer note: device-rpt-0360 SN0034 contains the Summary Verification and Validation Report. This contains a table to trace requirements to design outputs, verification, validation, and results. This is used to fill in the table.

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(b) (4)

Sponsor refers to Table 3, 4, 5 for labeling items (b) (4). Tables could not be located in file RPT-0360; therefore, this reference is unknown.
There is no requirement for flow rate accuracy, only dose delivery.

Reviewer note: It is understood based on NDA 209988 SN0040 that the device has been updated based on found premature errors notifications. Specifically, based on Section 1.12.4.2, "[Following NDA submission,] *scPharmaceuticals and West have subsequently explored a further modification* (b) (4) *and a corresponding software parameter adjustment*." (b) (4) (b) (4)

The Sponsor continues, "*The Sponsor is now exploring how to improve the device further prior to marketing* (b) (4)." This indicates the Lead Reviewer that all the device data may be suspect and may not be representative of the to-be-marketed device.

Programmed rate of deliver is stated as 0.0625 mL per minute with (b) (4)
(b) (4) for delivery due to an open safety latch
(b) (4) needle depth equivalent depth for subcutaneous space? – validation data
scP-00-004 evaluated (b) (4) modifications to challenge delivering full dose

The Sponsor provides device-dd0092 for Disucssing/Defining the Essential Performance Requirements for the Furoscix Infusor
The Sponsor defines the Essential performance following IEC 60601-1, with additional items added to this list.
Stated to include:
Dose delivery: (80 mg/10 mL)

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Device Adhesion
Needle Length
Occlusion Detection

The Sponsor states "Variation in the fractional dose administered between hours 0 and 1, 1 and 2, 2 and 3, 3 and 4 and 4 and 5 does not pose a clinical risk and thus the dose delivered over an individual hour does not constitute an essential performance requirement. The duration of the dose, within a reasonable range, also does not pose a clinical risk. A specification of 5 hours (b) (4) is chosen to keep the infusion with a predictable range for the patient, but that tight of a specification is not required for clinical safety. These conclusions are based on clinical data from two studies." The Sponsor specifically excludes dose accuracy. The Sponsor supports this argument with clinical data from Diuretic Optimization Strategyies Evaluation trial from 2011, comparing bolus and infusion of loop diuretics, showing no significant difference between patient assessment. While this is reasonable clinical justification, the design intent of the device does not align with this argument.

Activation force and needle protection are not considered essential performance, but are stated as remaining important features

The Sponsor points to MAF (b) (4) document (b) (4) for essential performance requirements. This document could not be rapidly be located.

Test Method Review
Reviewer Note: MAF (b) (4) Volume 9 from Ammendment 1, Volume 11 Ammendment 4 is understood to contain Design Verification Testing. An overview is presented stating the testing was performed following (b) (4) EO sterilization. The phrasing of scope indicates it includes environmental, vibration, free-fall, alarms, and safety latch testing.

Test Method #1 – (b) (4) Shelf Life Protocol Rev. 3.0, -1R, -R3, -R4, -R5

Title:	SmartDose Gen II 10 mL (b) (4) Shelf Life Design Verification Test Protocol / Report *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	Meets diesng input requirements at T0 and over shelf-life following (b) (4) Design Verificaton Master Plan for inputs defined by (b) (4) , Product Requirements, and User Requirements: Protocol

#	Test	Description in Section No.	Related Design Requirements (b) (4)Per DVMP]	Comments
1	T0 Reliability- Dose Accuracy with (b)% reliability at a 95% confidence level	10.1	2.3.a, 2.4.a, 2.4.b, 2.4.d	Based on (b) (4) section 10.2
2	System Hold up volume	10.2	2.4.c	NA
3	Delivery of defined volume and time	10.3	2.3.a, 2.4.d, 4.1.a, 4.1.b	NA
4	*Maximal* Short-term Delivery Rate	10.4	2.4.e	NA
5	Needle stick	10.5	8.8.a, 9.6.a	ISO 23908 2011 Annex B
6	Button Activation Force	10.6	3.1.g	NA
7	Needle Deployment Length	10.7	1.2.a	NA
8	Label and Pad Printing Durability	10.8	6.4.d, 6.4.f	Based on 60601-1 7.1.3.b
9	Liner Removal Force	10.9	3.1.f	NA
10	Adhesive pressure-sensitive tack	10.10	3.2.c	NA
*	Fluid path occlusion detection during delivery and fault condition indication	Separate Protocol	2.10.a, 2.10.b	NA

T5 Timpoint Summary

Table 1. Tests and Related Design Requirements

#	Test Description	(b) (4)Rev.2.0/Rev. 3.0* Protocol Section No.	(b) (4)R4_R5 Report Section No.		Related Design Input Requirement # (Based on (b) (4)
			T4 Time Point	T5 Time Point	
1	Delivery of defined volume and time	10.3	10.1	15.1	2.3.a, 2.4.a, 2.4.b, 2.4.d
2	System Hold up volume***	10.2**	10.2	15.2	2.4.c
3	Short term Delivery Rate	10.4	10.3	15.3	2.4.e
3	Needle stick	10.6	10.4	15.4	8.8.a, 9.6.a
4	Button Activation Force	10.7	10.5	15.5	3.1.g
5	Needle Deployment Length	10.8	10.6	15.6	1.2.a
6	Label and Pad Printing Durability	10.9	10.7	15.7	6.4.d, 6.4.f
7	Liner Removal Force	10.10	10.8	15.8	3.1.f
8	Adhesive pressure-sensitive tack	10.11	10.9	15.9	3.2.c

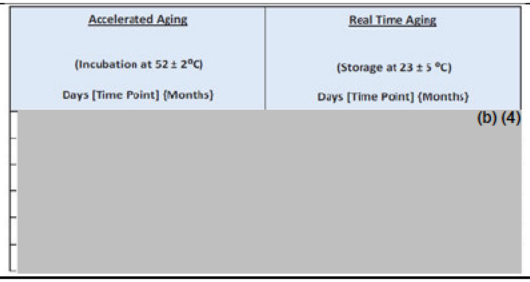
* Button activation force, label and pad printing durability, liner removal force for T5 time point and adhesive probe tack tests were carried out after (b) (4)was revised to Rev.3.0. Therefore, for these tests, (b) (4)Rev.3.0 protocol was utilized.

** Sections 10.1 and 10.2 of the protocol are related to T0 reliability testing for which the evaluation is summarized in DVT report (b) (4)R1.

***Hold up volume test #10.2 was carried out for both T4 and T5 Time points for information only.

Reviewer note: The Sponsor states that some requirements (delivery volume and time and system hold up) are only related to T0 and reliability evaluation and hold-up volume is only performed for information only. This is concerning as this is the timepoint which the Sponsor should demonstrate that their device fuctions at expiry.

Sponsors states that all requirements met (passing tests)

	The Sponsor states that the delivery volume changed from (b) (4) mL to 10 mL. This realtes to the original IRs. The Sponsor captures this as a deviation and states there is no impact to the testing performed based on TD-20-031 The Sponsor removes the time requirement of 5 (b) (4) is moved to be associated with a different requirement. The adhesive pressure tact limits were updated and verification was performed to the new requiremetns. These are not explicitly stated, but referenced to be in ECO 20-032. It is difficult to review testing without knowning the acceptance criteria clearly. The Sponsor acknowledges a change in the (b) (4) update to (b) (4) The Sponsor states the change (b) (4) is captured in (b) (4) design change assessment. *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*
Acceptance Criteria (including confidence/reliability):	Sample size and analysis methods are dependent on the requirement. See Results for summary information. (b) (4) is pointed to for sampling size justification (file not provided.) *Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.*
Methods:	

	Samples (b) (4) EO, transported following (b) (4) for Compression, High Altitude Simulation, and Concentrated Impact. **Reviewer Note**: There is no stated Distribution Cycle/Assurance Level for the shipping challenge information Drug is aged separately according to (b) (4) Plan. Drug and Device allowed to come to ambient conditions for at least 4 hours prior to testing. Execution occur @ 23 +/- 5 C and 50+/-25 %RH Dose Accuracy: 95 (b) (4) C/R qith 188 samples at Acc (b) (4) of dose completion, delivery 10 mL (b) (4) (b) (4) and in (b) (4) 5 hours with 3.75 mL (b) (4) n the first hour (b) (4) Unjustified/relevance explained. This standard is not recognized for infusion pumps. (b) (4) stated for measuring delivery volume and time in a continuous manner by using an analytical balance. Entire method is not provided **Reviewer Note**: Test method is stated as being validated for this and delivery requirement, pointing to TMV Report #3967-R Rev 1.0. This file could not be located. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. System Hold Up Volume Less than (b) (4) of hold up volume at 95/95 C/R. 59 Samples (b) (4) Weigh device before and after cartridge delivery. Calculate: (b) (4) Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. Delivery of defined volume over time 10 mL (b) (4) and in 5 (b) (4) hours with 3.75 mL (b) (4) in the first hour, minimum shelflife (b) (4) months Follow (b) (4) stated for measuring delivery volume and time in a continuous manner by using an analytical balance. Entire method is not provided Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found.

	95/95 C/R at (b) (4) with 124 samples and (b) (4) for Timepoints T4 and T9 Maximal Short Term Delivery Rate (b) (4) over entire profile (b) (4) stated for measuring delivery volume and time in a continuous manner by using an analytical balance. Entire method is not provided Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. 95/(b) (4) C/R With (b) (4) with 188 specimens at T0, 124 with Acc (b) (4) for others, except T4 and T9 with 93 Samples with (b) (4) Needle Stick Sponsor states the intent is to comply with ISO 23908, Safey latch fully deployed after removing tape and finder shall not touch patient needle Follow (b) (4). Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. 95/95 C/R with 93 samples (b) (4) Button Activation Force Activation force between (b) (4) N (inclusive) (b) (4) to measure force. Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. 95/95 C/R with Ppk greater than (b) (4) for 40 samples. **Reviewer note**: There is no requirement for normality.

	Needle Deployment Length Length of 6 (b) (4) mm from based of device to distal end of needle. (b) (4) is the method of reference. Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. 95/95 C/R with (b) (4) 59 samples. Label and pad printing durability Comply with IEC 60601-1 Section 7.1.3 b with device permanently marked over lifetime (b) (4) is referenced for method to check indelibility. Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. 95 (b) (4) C/R with 29 samples (b) (4) Liner Removal Force Less than (b) (4) Follow (b) (4). Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. **Reviewer Note**: Test method is stated as being validated for this and delivery requirement, pointing to TMV Report #3966-R Rev 1.0. This file could not be located. 95/95 C/R with 59 samples with (b) (4) Adhesive Pressure-sensitive tact Adhesive pressure-sensitivce tack between (b) (4) N (inclusive) Follow (b) (4) Probe Tack to measure. Method is not provided. Sampling is stated to be based on the highest severity risk of (b) (4) dFMEA. This file is not found. Data collection see is included in protocol.

Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)

#	Time Points	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/Type Test)
1	T1 (=T0)	T0 Reliability-Dose Accuracy	2.1.a, 2.4.a, 2.4.b, 2.4.d	***Following activation, the System shall complete delivery with*** (b) ***reliablity at a 95% confidence level*** Following successful delivery completion, the defined volume delivery accuracy of the System (10.0[mL] (b) drug *product*) shall have (b) reliability at a 95% confidence level. Following activation, the System shall deliver 10.0 [mL] (b) drug *product in 5* (b) *ours*, such that 9.75 [mL] (b) is delivered in the first hour. The full ***delivered*** dose ***shall be*** 10.0 [mL] (b) drug ***product.***					(b) (4)
2	T1 (=T0)	System Hold up volume	2.4.c	The System Hold-Up Volume shall be (b) (4)					

#	Time Points	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/Type Test)
3	T2-T11	Delivery of defined volume and time	2.1.a, 2.4.d, 4.1.a, 4.1.b	Following activation, the System shall deliver 10.0 [mL] (b) drug *product in 5* (b) *ours*, such that 9.75 [mL] (b) is delivered in the first hour. The full ***delivered*** dose ***shall be*** 10.0 [mL] (b) drug ***product***. Combination Product shelf life shall be minimum (b) months. The System shall function as intended** following a minimum period of warehouse storage of device in its primary package as follows: (b) (4)					(b) (4)
4	T1(=T0)-T11	***Maximal*** Short term Delivery Rate	2.4.e	Maximum short-term delivery rate shall be (b) (b) (4) for the entire delivery profile					

Results:

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#	Time Points	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)
5	T1(=T0)-T11	Needle stick	8.8.a, 9.6.a	The System shall incorporate a passive needle protection mechanism, such that after system removal, the needle tip shall be inaccessible. The System shall comply with the applicable requirements of ISO 23908: Sharps Injury Protection-Requirements and Test Methods-Sharps Protection Features for Single-Use Hypodermic Needles, Introducers for Catheters and Needles Used for Blood Sampling					(b) (4)
6	T1(=T0)-T11	Button Activation Force	3.1.g	The System shall be activated by a single motion on part of the user; the force required to press the activation button when the loaded System is applied to the injection site shall be in the range of (b) (4) [N]					
7	T1(=T0)-T11	Needle Deployment Length	1.2.a	The device shall have a (b) (4) needle with deployment length of (b) (4) [mm] as measured from the bottom of the device to the distal end of the needle					

#	Time Points	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)
8	T1(=T0)-T11	Label and Pod Printing Durability	6.4.f, 6.4.f	The device labeling shall comply with the durability test for markings requirement of IEC 60601-1 section 7.1.3 b. The device shall shall be permanently marked and readable throughout its lifetime.					(b) (4)
9	T1(=T0)-T11	Liner Removal Force	3.1.f	The force required to remove the adhesive liner shall be (b) (4)					
10	T1(=T0)-T11	Adhesive pressure-sensitive tack	3.2.c	The pressure-sensitive tack of the adhesive shall be in the range of (b) (4) [N]					

(b) (4)

There is no verification activity or stated requirement for flow rate accuracy.

Reviewer note: Shelf-life is stated as (b) (4) Months.

T5 is the Accelerated aging timepoint which relates to (b) (4) months. These are reviewed below. There Sponsor does not submit real-time aging this, but the protocol is submitted for all relative timepoints.

Shipping simulation, sterilization, and specimine lots recorded for tests. Acceptable.

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The Sponsor states the (b) (4) changed from the initial build to the final build. Different items:

(b) (4)

This appears to be a a description of the device to contain the later assembly. Reasonable.

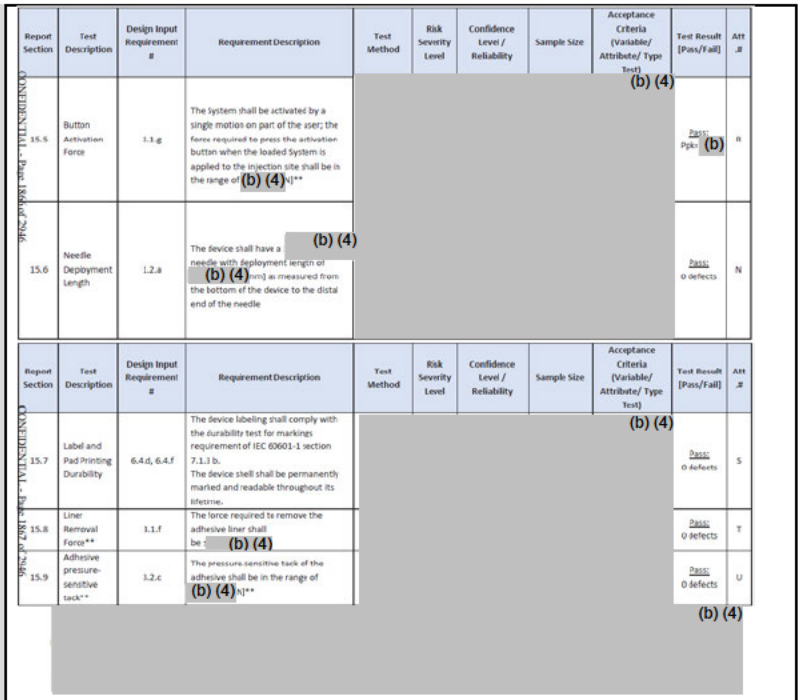
T5 Summary Data:

Reviewer note: T4 data is also included in the same report. Review focused on T5 data as this is the expiration time point. It is noted that several devices were reported as out of specification.

Table 28. Tests Results Summary

Report Section	Test Description	Design Input Requirement #	Requirement Description	Test Method	Risk Severity Level	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result [Pass/Fail]	Att .#
15.1	Delivery of defined volume and time	2.3.a, 2.4.d, 4.1.a, 4.1.b	Following activation, the System shall (b) (4) (b) (4) drug shall be delivered in 5 (b) hours. Combination Product shelf life shall be minimum (b) months. The System shall function as intended** following a minimum period of warehouse storage of device in its primary package as follows: (b) (4)	(b) (4)				(b) (4)	Pass: 0 defects	N

Report Section	Test Description	Design Input Requirement #	Requirement Description	Test Method	Risk Severity Level	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result [Pass/Fail]	Att .#
15.2	System Hold up volume	2.4.c	The System Hold-Up Volume shall be ≤ (b) (4)					(b) (4)	Pass: 0 defects	N
15.3	Short term Delivery Rate	2.4.e	Maximum short term delivery rate shall be (b) (4) for the entire delivery profile						Pass: 0 defect	N
15.4	Needle stick	8.8a, 9.6.a	The System shall incorporate a passive needle protection mechanism, such that after System removal, the needle tip shall be inaccessible The system shall comply with the applicable requirements of ISO 23908: Sharps Injury Protection-Requirements and Test Methods-Sharps Protection Features for Single-Use Hypodermic Needles, Introducers for Catheters and Needles Used for Blood Sampling						Pass: 0 defects	N



Report Section	Test Description	Design Input Requirement #	Requirement Description	Test Method	Risk Severity Level	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result [Pass/Fail]	Att .#
CONFIDENTIAL - Page 1847 of 2946	15.5 Button Activation Force	1.1.g	The System shall be activated by a single motion on part of the user; the force required to press the activation buttan when the loaded System is applied to the injection site shall be in the range of (b) (4) N]**	(b) (4)					Pass: Ppk= (b)	n
	15.6 Needle Deployment Length	1.2.a	The device shall have a (b) (4) needle with deployment length of (b) (4) mm] as measured from the bottom of the device to the distal end of the needle						Pass: 0 defects	N

Report Section	Test Description	Design Input Requirement #	Requirement Description	Test Method	Risk Severity Level	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result [Pass/Fail]	Att .#
CONFIDENTIAL - Page 1847 of 2946	15.7 Label and Pad Printing Durability	6.4.d, 6.4.f	The device labeling shall comply with the durability test for markings requirement of IEC 60601-1 section 7.1.3 b. The device shell shall be permanently marked and readable throughout its lifetime.	(b) (4)					Pass: 0 defects	S
	15.8 Liner Removal Force**	1.1.f	The force required to remove the adhesive liner shall be (b) (4)						Pass: 0 defects	T
	15.9 Adhesive pressure-sensitive tack**	1.2.c	The pressure-sensitive tack of the adhesive shall be in the range of (b) (4) N]**						Pass: 0 defects	U

(b) (4)

Dose Delivery: Data meets requirements. However, method is not provided, therefore, acceptability of data is unknown.
9 devices are stated as being out of specification.
1 device failed as a error notification determined to be because of (b) (4). The Sponsor states " (b) (4) " and describes this in further detail in Attachment O: The following does not make sense pg: 371/417 part 2 (b) (4)

(b) (4)

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	(b) (4) In the referenced Appendix, the determined root-cause is (b) (4) This contradicts the stated non-failure as this appears to be evidence that your device, as designed, failed to mainint its function throught the labeled shelf life. This root-cause is referenced fro several out of scpeciication devices and appears to be a systemic failure mode of your device. (b) (4) Rev 1.0 1 device failed with a root cause (b) (4) (b) (4) The Sponsor indicates the implementation of (b) (4). Attachment P is referenced for full detail. 7 devices failed when delivery did not begin delivery when the button was pressed. This is determined to be a result (b) (4) Pressing the button again started the delivery. This was considered an observation in Attachment Q. Described event is 23/40 devices did not produde produding needl.e This is rationalized on 388/412 of Part 2 that "captured forces are valid and represent device performance (see Appendix #4…" but this appears to demonstrate the device does not meet its design intent. The discussed root-cause is (b) (4), which requires (b) (4) improvement to mitigate. This is noted as being present in T0 devices as well."Root cause was identigfied (b) (4) Material properties can change over time and this is not discussed. This is a device failure and not acknowledged as such. Hold Up Volume: Data meets requirements. It is noted that the reported data has the same number of significant digits as the requirement. The Sponsor states this data was not requiremed for this timepoint, but the device still met the specification. This is described in Attachment X. The Sponsor states devices are out of specification. A reference is provided for detail in 15.1.8.1 1 and 15.1.8.1.2. However, these sections could not be located in the file. 2 devices are noted as not starting when started by operator. This was considered an observation in Attachment Q, and described similarly as in Dose Delivery.

	Short term delivery rate: The Sponsor's assessment of the short term rate does not align to the stated requirement. The Sponsor states, "*As was defined in verification protocol* [redacted] *maximum short term delivery rate is calculated for* [redacted] *This is based on prior knowledge from engineering verification testing in which the obtained delivery rate* [redacted] *did not exceed* [redacted]" The understood acceptance criteria is [redacted] over the entire delivery profile. The Sponsor points to [redacted] for verifying [redacted]. This is not explained as a deviation. Given the flow rate is given as mL/min, measurement resolution of [redacted] is likely reasonably, but should be clearly explained in the individual report, such that each report can stand as an independent verification record. The Sponsor contends that the presented data conforms to the original acceptance criteria as the values ranged from [redacted] This is discussed further in Attachment Y. The Sponsor describes this as being done for "*Ease of analytical scale data compilation*" with no risk stating that the delivery rate during the first phase is higher, therefore, this time frame represents the maximal delivery rate. This does not demonstrate the device meets flow accuracy over the entire dose delivery. Out of Specification devices refer to the record under delivery of defined volume and time. Needle Stick: Data record as passing. Devices are noted as being out of specification. A reference is provided for detail in and 15.1.8.1.2. 3 devices are noted as being being able to start delivery with button depression. his was considered an observation in Attachment Q, and described similarly as in Dose Delivery. Button Activation Force: Variable data recorded. Devices recorded as meeting specification. Data is described as non-normal, and a goodness of fit test is used [redacted] This is unjustified, but as a physical process with a physical stop, it is reasonable to use a non-normal data analysis method. With this, a Ppk of [redacted] is reported. Empty cartridges are noted as being used and are described in Attachment Z. 23/40 devices are noted as not deplying the button following the button depression. This was considered an observation in Attachment Q, and described similarly as in Dose Delivery. Needle Deployment Length: Devices noted as passing. 2/59 devices are noted as incurring the same button delivery issue. This was considered an observation in Attachment Q, and described similarly as in Dose Delivery. Label and Pan Printing Durability: Devices noted as passing. The severity assignment is changed from the protocol. 29 samples are recorded with Attribute data recorded. No out of specification data.

	Linear Removal Force: Variable data recorded. Data meets specifications, and is discussed with Attribute analysis. Data meets attribute stated requirements. No deviations or out of specification data presented. Adhesive pressure-sensitive tact: Data recorded as passing. No deviations or out of specification devices. Deviations (Accelerated Aging T5): Similar notes for changes to the requirments (b) (4) and Design I/O document (b) (4) are referenced. In addition, the Sponsor provides refernces additional changes in risk assessment and uses these for sampling. This is specifically noted for Label and Pad Printing Durabiltiy, with a revised risk level of (b) (4) and 29 devices used to satisfy 95/(b) (4) C/R (b) (4) reliability is too low of an acceptance criteria and th severity assignment provided by the Sponsor is questioned. Device evaluated to a different requirement (10 mL (b) (4) vs. (b) (4) Data meets revised requirement. The drug cartidges are noted as being stored below the required number of hours for accelerated aging. The Sponsor addressed this by adding additional time beyond the missed time (b) (4) This is reasonable. Equipment noted as being in calibration. Several scanned pages are difficult to read (e.g. 172, 226, /339 of Part 1, Attachment 11-7) Need to use consistent dating convention: Page 128 of Part 1 Attachment 11-7 uses, what is believed to be Month/Day/Year. Page 1/412 of Part 2 Attachmen 11-7 uses, what is believed to be Day/Month/Year. Need to know what date convention is being used where. Attachment C contains the chamical/environmental handling testing to ASTEM D4169-16. Schedules are defined, but no overarching distribution cycle or assurance level (defined per test as Assurance Level II). Not clear why temperatures were chosen for temperature and humidity challenge. Different records of device shipping conditioning provided for various tests.

	Drug cartridge aging is noted to include deviations outside the stated limits for T5 timepoint. These are not explained in the summary information. Portions of the file are in German (e.g. 241 – 328/412 Part 2 of Attachment 11-7). Highest attachment lettering noted as U. File believed to be incomplete. Attachments V-BB could not be located. *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	Unacceptable: No methods. Data incomplete. Cannot locate data locations *Holistically do you find that the objective has been met? If not provide further explanation.*
	Acceptable: [ ] Yes [X] No

Test Method #2 – MAF (b) (4) R1 Attachment 9-12 in Ammendment 003

Title:	(b) (4) Congirugation (b) (4) Design Change (b) (4) (b) (4) Design Verification Test Report Rev 1.0
Scope/Objective:	Meet following requiremetns defined by by (b) (4) Product Requirements for the (b) (4) configuration. | #	Test Description	(b) (4) Protocol Section No.	(b) (4) R1 Report Section No.	Related Design Input Requirement # (Based on (b) (4)
---	---	---	---	---
1	(b) (4)	10.1	10.1	1.2.b	 **Reviwer note**: Due to the described scope of this report and the known changes to the device, the review of this test data is not completed. *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*
Acceptance Criteria (including confidence/reliability):	*Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.*
Methods:	*Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)*
Results:	*How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	*Holistically do you find that the objective has been met? If not provide further explanation.*
	Acceptable: [ ] Yes [ ] No

Test Method #3 – MAF [redacted] Rev 1.0 Attachment 9-8 in Ammendment 003

<table>
<tr><td>Title:</td><td>Smart Does Gen II 10 mL [redacted] Reliability Design Verification Test Report</td></tr>
<tr><td>Scope/Objective:</td><td>Obtain Results following Design Verification Master Plan [redacted] defined inputs from [redacted] product requiremetns and [redacted] Design I/O Matrix

Retest of #10.1 for 15 C with devices with updated [redacted] criteria following [redacted] Rev 2.0
Results of #10.1 for 15 and 40 C conditions were taken from [redacted], as unaffected by updated [redacted] criteria

Evaluate:
<table>
<tr><th>#</th><th>Test Description</th><th>Protocol Section No.
[redacted]</th><th>Report Section No.
[redacted]</th><th>[redacted]
(Per DVMP Rev.3.0)</th></tr>
<tr><td>1</td><td>Operation temperature at 15-40 [°C], 50 ± 25%RH</td><td>10.1</td><td>10.1</td><td>2.8.a</td></tr>
<tr><td>2</td><td>SL overriding force</td><td>10.2</td><td>10.2</td><td>9.6.a, 8.8.a</td></tr>
</table>
Reviewer note: The requirement referenced in the V&V summary includes pressure. This is not included. Deficient.</td></tr>
<tr><td>Acceptance Criteria (including confidence/reliability):</td><td>Based on a severity of [redacted] following dFMEA [redacted] for [redacted] ' as the highest severities. It is not clear how this document aligns to the NDA severity assignment nor is this document refereced/provided. Deficient.
124 devices for each temperature and humidity condition at accepta at [redacted] or more. No clear how the Sponsor arrived at this number [redacted] Sampling Plans for the Development Phase is not provided). Deficient
In the results summary 10.1 1, the Sponosr states this meets 95% [redacted]. There is no definition of these percentatage and this differes from the acceptace criteria in the table in Section 9.
Attribute data. Pass defined as: Visible means to recogznize end of dose, Needle shielded upon removal</td></tr>
<tr><td>Methods:</td><td>Device: (Section 8.2) [redacted] per DVMP Rev 2.0, [redacted] filled cartidges,</td></tr>
</table>

	Precondition: [(b) (4)] Sterilize, Shipping Simulation per [(b) (4)] excluding compression, high altitude simulation, concentrated impact following [(b) (4)] preconditioned at ambient 23 +/-5 C @ 50+/-25 %RH ASTM D4169-16 Schedule A (FDA Recognized) and [(b) (4)] [(b) (4)](not FDA recognized, [(b) (4)] [(b) (4)] are referenced as the technical sources for Environmental and Mecahnical Laboratory Test Report in Appendix B. No Distribution cycle stated or assurance level stated for all schedule testing nor the choice of these justified for individual ones stated for D4169-16 test; therefore, the scope of the testing is unknown. Deficient – Unable to review data for acceptability without understanding methods. The Sponsor references individual Test Schedules, but no over-arching distribution Cycle. It is noted that the Assurance Level appears to change between individual tests in Schedule A and entirety of schedule appears not to have been performed. Environmental conditioning does not match test method (user requirement) and is unjustified. [(b) (4)]. Unjustified. Deficient. The Sponsor appears to have performed [(b) (4)] This is not how the test method is intended to be performed. Deficient. [(b) (4)] Work Instructions for devices following Environmental Preconditioning [(b) (4)] Sharp Injury Protection – Safety Latch Deployment Time and Finger Jig Test Method [(b) (4)] Safety Latch Challenge Safety Latch Overriding Force (Section 10.2 to verify inputs 9.6.a and 8.8.a to comply with ISO 2390 4.1.2, accidental shaprs injry protection). **Reviewer note**: The Sponos rprovides specific reference to latteral and distal force values [(b) (4)]N) on the needle safety device. This has been determined to have been revised based on SN0040 NDA 209988, where the Sponsor states [(b) (4)] The relevance of this testing is unknown.
Results:	Summary:

#	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute)	Test Result (Pass/Fail)	Att.
1	Operation temperature at 15-40 [°C], 50± 25%RH	2.8.a	The System shall provide its Safety Performance and complete delivery at a temperature range of 15-40 [°C] and Humidity conditions of 50 ± 25% *	(b) (4)					15 [°C] condition Pass: 0 defects 40 [°C] condition Pass: 0 defects	Attachment D
2	SI overriding force	9.6.a***, 9.8.a	The System shall incorporate a passive needle protection mechanism, such that after System removal, the needle tip shall be inaccessible. The System shall comply with the applicable						Lateral orientation Pass: 0 defects Distal orientation Pass: 0 defects	Attachment E

#	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute)	Test Result (Pass/Fail)	Att.
			requirements of ISO 23908: Sharps Injury Protection- Requirements and Test Methods-Sharps Protection Features for Single-Use Hypodermic Needles, Introducers for Catheters and Needles Used for Blood Sampling							

(b) (4)

Schedule testing appears to be performed as described, with acceptance criteria determined by the customer.74

ISO 23908 is referenced for being references as the requirement.

No deviations noted in summary information.

Attachment D documents results of functional testing. Items are noted as failures (with notes of human mistake in recording). These are not discussed as deviations. No methods presented for data.

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	Attachment E. Two devices noted as failing without discussion as deviations. One device noted as being rested without discussion in deviations. No methods presented for generated data Data stated as being analyzed via attribute, whith LCL and UCL presented in Attachment E. This contradicts this statement. One out of specification result was observed: activation button was pressed bu the needle was not exposed immediately, only after re-pressing the button in 4 devices at 40 C. OOS#4376.2 is referenced and provided: The Sponsor states (b) (4) (b) (4) (b) (4) is required to resolve the identified issue. The Sponsor should implement fixes for identified design flaws. Deficient.
Conclusions:	Unacceptable. Methods not presented or justified. Deviations not documented as such and explained. Design improvement refereneced, given the surrounding issues with modifications to the device during review, the implementation status of these is unknown.
	Acceptable: [ ] Yes [X] No

Test Method #4 – MAF (b) (4) Rev 1.0 Attachment 9-11 in Amendment 003

Title:	SmartDose Gen II 10 mL (b) (4) Inspection and Review Report
Scope/Objective:	Meet requirements laid out in (b) (4) Research and Development procedure and (b) (4) Design Berification Master Plan, defined by (b) (4) Product Requrements and (b) (4) Design I/O Matrix (Summarized below under Results).
	Inspection (i.e. parts meet design intent through design/drawing review). (b) (4)
Acceptance Criteria (including confidence/reliability):	Sample size of 1. This is reasonable as a document inspection method However, there appears to be functional verifications as well (b) (4) (b) (4)

	Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.
Methods:	Document inspection *Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)*
Results:	

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
6.2	1.3.a	(b) (4)		Pass
6.3	1.4.a			Pass
6.4	1.5.a			Pass
6.5	1.6.a			Pass
6.6	1.7.b			Pass
6.7	3.2.a			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
		(b) (4)		
6.8	5.2.a			Pass
	5.2.c			Pass
6.9	5.2.d			Pass
	5.2.e			Pass
6.10	5.7.a			Pass
6.11	5.7.b			Pass
6.12	5.8.a			Pass
6.13	5.9.b			Pass
	5.9.c			Pass
	5.9.d			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev./I04 Relevant P/N	Pass / Fail
	5.9.e	(b) (4)		Pass
6.14	5.14.a			Pass
	5.15.a			Pass
	5.16.a			Pass
	5.17.a			Pass
	5.18.a			Pass
6.15	5.19.a			Pass
	5.19.b			Pass
6.16	6.1.a			Pass
	6.2.a			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
	6.2.b	(b) (4)		Pass
	6.2.c			Pass
6.17	6.3.b			Pass
	6.4.a			Pass
	6.4.b			Pass
	6.4.c			Pass
	6.4.e			Pass
	6.6.a			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
			(b) (4)	
6.18	6.5.a			Pass
	6.5.b			Pass
	6.5.c			Pass
6.19	6.7.a			Pass
	6.7.b*			Pass
	6.7.c			Pass
6.21	7.2.a			Pass
6.20	7.3.a			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
6.21	7.4.a	(b) (4)		Pass
	7.4.b			Pass
	7.4.c			Pass
	7.4.d			Pass
6.22	7.4.e			Pass
6.23	8.5.a			Pass
6.24	9.8.a			Pass
	9.9.a			Pass

Report Section	PRD #	Design Input Requirement	(b) (4) Rev.A04 Relevant P/N	Pass / Fail
	9.13.a	(b) (4)		Pass
6.25	10.1.a			Pass
	10.1.b			Pass
6.26	1.2.a*			Pass
	FP-1.1.a			Pass
	FP-1.1.b			Pass
	FP-7.2.a			Pass
6.27	FP-7.1.a			Pass

(b) (4)

Noted as MR unsafe.

One deviation is noted: a test method was not defiend. (b) (4), *Design Verification Master Plan for* (b) (4) *defined to verify PRD 1.2.a as 'Testing' and to*

	verify PRD 6.7.b as Analysis'. Actually, these two PRDs were verified by inspection, not as defined in the protocol. Sponsor attaches what appears to be functional and measurement data records for components in this document (e.g. needle manufacturing). Based on the presented information these are likely superseded by other (e.g. fucntional, biologic, etc.) testing Data records are in what is believed to be German: e.g. Page 76, 205, 206, 216 of 270 . Many scan records are faded and/or difficult to read: e.g. Page 77, 183, 184 (blurry) of 270. *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*		
Conclusions:	In general, the review of records is likely reasonable, but the issue remains verifying equipment and performeding documentation review. There appears to be several items which are stated as a documentation review, which appears to rely on testing from another location		
		Acceptable:	[ ] Yes [X] No

Test Method #5 – MAF (b) (4) Rev 1.0 Attachment 11-2 in Ammendment 004, T5 timepoint in Attachment 11-8

Title:	*Fluid Path Occlusion Confirmation and Detection Test* *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	Fluid Path Occlusion Test for SmartDose Gen II 10 mL (b) (4) following (b) (4) Requirements throughout shelf life. Realtime aging: 23 +/- 5 C Accelerated 45 +/- 2 C *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*
Acceptance Criteria (including confidence/reliability):	(b) (4) delivery rate of (b) (4) mL/min **Reviewer note**: It is not clear if this is flow rate accuracy, and is raised to the NDA holder. The MAF holder is asked to provide their requirements which are used to drive testing.

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#	Time Points	Test Description	Design Input Requirement # (b) (4)	Requirement Description	Test Method	Severity	Confidesce Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)
1	T1(=T0)-T11	Fluid path occlusion detection during delivery and fault condition indication	2.10.a, 2.10.b						(b) (4)

Sample size and C/R appear acceptable. Severity of (b) (4) based on no dose delivered. dFMEA reference (b) (4) is not provided. Severity assignment from NDA holder is more broadly questioned.
Requirement is occlusion is detected. Detailed as:

Visual red LED with audible 5 beeps
(b) (4)
(b) (4)The Early IR response provides a discussion (b) (4) The requirement should alig s inadequate.

Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.

Methods:

Samples (b) (4) sterilized pre testing
Samples subjected to (b) (4)Simluated distribution following (b) (4)
Drug cartidges aged separately following (b) (4)
Devices and containers conditions for at least 4 hours at 23 +/- 5 C and 50 +/- 25 %RH
(b) (4)stated as method with occlusion tested afte (b) (4) activation. This is unjustified.

Sponsor states the test method has been validated for variable data following TMV 4214-R. Method not provided. Data stated as reviewed as attribute.

Protcol reviewed prior to execution, equioment calibration record included in recording form, occlusion confirmation form included (b) (4).

Complete method is not provided, only referenced.

Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)

Results:	**Reviewer note**: T5 Timepoint is reviewed in depth as this is understood to be the 24 month accelerated aging timepoint. These are reviewed in detail. These should supersceed initial testing to demonstrate acceptable function at expiry. Accelerated aging is described similarly as in (b) (4) (Test Method 1). The Reviewer believes the same protocol is used to govern aging. The Sponsor note that the days calculations for 6 month, 18M, and 30M realtime is slightly different. Given these are not reviewed and not being reviewed to support the stated (b) (4) shelf-life, comment on these are reserved for if/when shelflife is updated. Occlusion Data is stated in Attachment K as a Pass. Summary data supports this. See out of specification discussion. Envionrmental Condition: (b) (4) emperature excursion for drug is identified and discussed in Attachment O. Primary Drug Container is deferred to CDER. Acceptabiltiy of device and inputs are reviewed. Device lot numbers are recorded Sponsor states that (b) (4) delivery rate of (b) (4) is examined. This is not within the acceptance criteria. The Sponsor states that occlusion detection is worst case when the detection time is longer. It is not clear what the flow rate is intended to be, given there is no requirement for this discussed. Therefore, this is not understood to be adequate or a boundary condition. Table 6 contains a listing between the built and verified devices (by (b) (4) listing). The following are noted as different: (b) (4) (b) (4) There is no discussion explaining why the change (b) (4) does not impact the described testing. Given the scope of the change, the remaineder of the data will be revirewed.

	Deviation noted for storatge of drug containiner. The Sponsor aged the deivce at RT for longer than the missed accelerated aging time. This is likely reasonable. Several devices are described as out of specification: 6/59 devices had (b) (4). This is clearly a failure of the acceptance criteira and not addressed as such. These are described in Attachment L (b) (4) is to be used in production. This demonstrates that the devices tested are not representative of the to-be-marketed device. (b) (4) Unacceptable. 20/59 devices failed to start at button depression. This is noted as needing re-pressing. This was identified (b) (4) (Test Method #1). The Sponsor discusses the root cause similarly and provides Attachment M. Again, the Sponsor states this is an observation as the device met acceptance criteria. 1 device is noted as not activating after repressing button. However, the Sponsor should consider design changes to fix the issue: their design is inadequate for the described shelf-life. Sterilization records are provided and appear similar to the data preset. Again, records include notes which are faded and cannot be read (e.g. 149/156 Attachmen 8 of Ammendment 4). Attachment C contains shipping challenge information. See comments in (b) (4) Test Method #1) as these appear substantially similar to the previously reviewed approach, which is inadequate. In short, devices failed as out of specification and the Sponsor uses retesting to justify passing. Inadequate. *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	Lacking methods and inadequate data. *Holistically do you find that the objective has been met? If not provide further explanation.*
	Acceptable: [ ] Yes [X] No

Test Method #6 – MAF (b) (4) Rev 1.0 Attachment 9-10 in Ammendment 003

Title:	SmartDose Gen II 10 mL (b) (4) Analysis Report *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	Assess existing design verification data meeting input requirements (b) (4) following (b) (4) Design Verification Master Plan, Product Requirements from (b) (4) and Design I/O (b) (4) *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*
Acceptance Criteria (including confidence/reliability):	The following requiremetns are stated as being in-scope:

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
6.1	1.7.a	(b) (4)	
6.2	2.1.a*		
6.3	2.1.b*		
6.4	2.7.a*		
6.5	3.1.a		
6.6	3.1.b		
6.7	3.1.c		
6.8	3.1.d		

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
6.9	3.1.e	(b) (4)	
6.10	3.2.b		
6.11	3.5.a		
6.12	3.5.b		
6.13	3.5.c		
6.14	4.1.c		
6.15	4.2.d		
6.16	4.3.c		
6.17	5.1.a		
6.18	5.3.a		
6.19	5.3.b		

v

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
6.20	5.3.c	(b) (4)	
6.21	5.4.a*		
6.22	5.5.a*		
6.23	5.6.a		
6.24	5.9.a		
6.25	5.10.a*		
6.26	5.10.b*		
6.27	5.10.d*		
6.28	5.10.e*		

v

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
6.29	5.11.a*	(b) (4)	
6.30	5.11.c*		
6.31	5.11.d*		
6.32	5.12.a*		

ICC2000553
NDA209988 ,Furosemide Pump (Furoscix Infusor)
scPharmaceuticals

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
			(b) (4)
6.33	5.13.a*		
6.34	7.1.a		
	7.1.b		
6.35	8.6.a		
	8.6.b		

v

Report Section	PRD #	Design Input Requirement	Raw Data (report and section)
6.36	8.7.a		(b) (4)
	8.7.b		
6.37	8.7.c		
6.38	FP-2.1.a		
6.38.7	FP-3.1.a		
6.40	FP-3.1.b		

**Note: These PRDs were verified by inspection and not as defined in the Design Verification Master Plan for details see section 7 – Deviation section.*

Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.

Methods:

This document points to several other reports for data (e.g (b) (4), 2006VLD (b) (4), (b) (4)).
These documents could not be located: (b) (4)
(b) (4) is referenced as the software. Software is primarily deferred to the Software reviewer.
(b) (4) challenging of sterile barrier (Secrtions 6.5, 6.6, 6.7, 6.14) is deferred to the sterility reviewer. Some of these are notably related to the primary drug containe, and are likely being deferred by the Sterility reviewer to CDER (6.7, 6.15, 6.16,).

(b) (4) Section 10.4 is stated to contain data on ensuring the force to lock in place is <= (b) (4)
N. **Reviewer note**: while the ToC states R2 (e.g. (b) (4)) the actual file pointed to is

	(b) (4) The relevance of the data are questioned, and therefore, not reviewed. The Sponsor's indidications and pointers do not match the data present. (b) (4) is reviewed in Test Method 1 (b) (4) is pointed to for the force to detach adhesive assembly from the device (b) (4) (b) (4). Given the described changeds to the (b) (4) (b) (4) components, and 2057VLD-R1 objectices (b) (4) (b) (4) these are not reviewed, as the change to the device likely impacts the data contained. (b) (4) is pointed to for the force to activate the buttor (b) (4) (b) (4) Given the described changeds to the (b) (4) components, and 2057VLD-R1 objectices (b) (4) (b) (4) these are not reviewed, as the change to the device likely impacts the data contained. (b) (4) is reviewed below (Test Method #7). (b) (4) is referenced for pre-programming of the device and not having user adjustable settings. This is understood to be the design intent of the device. However, this file could not be located. Biocompatibiltiy/sterility referenced information (ISO 10993-1 documents in WP16VER00021 Rev.001, etc in sections 6.33-6.37) are deferred to the applicable reviewers. (b) (4) is reviewed below (Test Method #8) Attachment A is stated for System providing visual and audible indications in all applicable orientations. Attachment B is stated for fault condition after device power up. *Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)*
Results:	A technical assessment is provided in Section 6. These are broken down by product requirement. PRD 1.7.a: Septum Behavior as a Result of the Prefilled Primary Container Loading: An FEA is used and referenced to be within (b) (4) (previously noted as unable to be located). An FEA assessment is used to support (b) (4) This is not a verification that the design performs as expected, but a review of the design. Referenced document summaries are contained. See above notes regarding these referenced data locations. Attachment A is stated to containe a machnical analysis to ensure the system completes delivery in all applicable orientations. This provides a mathematical calculation to demonsrate the break loose/glide force is (b) (4) compared to the weight of the drug, to simulate dilvery. This is used to

justify that orientation does not have a significant effect of delivery performance for all lab tests. This approach only considers the force to push the dose, but does not consider the device design (e.g. moving the drug through the fluid line). Deficient.

Attachment B is not provided.

Reviewer note: The Sponsor appears to be relying on software testing to demonstrate alarm functionality. This is potentially concerning, unless the software testing considers devices at end of life (e.g. to ensure system functionality is maintained, including Alarms).

One deviation is noted: As discussed in Attachment C, the test method was not specifically defined in the referenced master plan. These are noted as fault condition notifications, (b) (4) (b) (4) Of note, a single device is used (b) (4) (b) (4) These are understood to likely require update, given the discussed changes to the device by the Sponsor to this component.

A configuration analysis is presented in Appendix 1. The following are noteworthy:
The packaing was updated, but this was limited to artwork on the lid, barcode on the lid, and likely has no impact of the data.
The Sponsor states (b) (4) (b) (4)This appears to be a change to the specification to meet requirements without changing the component. The Sponsor provides no discussion as to what the new specification is and how it was determined the new specification was acceptable for the use-case. This is particularly concerning as it relates (b) (4). This is similarly noted for changing the requirement for the patient needle assembly. It should be clearly stated which requirement was challenged (e.g. if it was the current requirement).
Change in the (b) (4) is referenced, pointing to (b) (4) as the reason why no change in the parts has no effect on the test. Given the provided information, a high-level comment is recommended for the Sponsor regarding their device design and finalizing it prior to Agency review.

Appendix 2 contains an analysis of the fluid path components for the data in (b) (4) There are no noted differences, but it is concerning that Appenxi 1 lists the fluid path assembly as being updated. The Sponsor appears to be performing testing on various components in various places. The Sponsor should provide a clear analysis of all their testing which explains any differences in their testing vs. the to-be-marketed device. Particularly given the noted changes being made to the device.

How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?

Conclusions:	*Holistically do you find that the objective has been met? If not provide further explanation.*		
	Acceptable:	[ ] Yes	[ ] No

Test Method #7 – MAF (b) (4) Rev 1.0 Attachment 9-4 in Ammendment 003

Title:	SmartDose Gen II 10 mL Platform Acousting Test Report *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	<table><tr><th>#</th><th>Test Description</th><th>Protocol Section No.</th><th>Report Section No. (b) (4)</th><th>Requirement based on Standard/ Rationale</th><th>Design Input Requirement No. (b) (4)</th></tr><tr><td>1</td><td>System sound pressure level during injection</td><td>9.1</td><td>9.1</td><td>Based on IEC 60601-1 and (b) (4) HF rationale</td><td>5.3.a</td></tr><tr><td>2</td><td>Audible notification sounds during normal operation</td><td>9.2</td><td>9.2</td><td>Based on IEC 60601-1-8 and 2040RDD HF rationale</td><td>5.3.b</td></tr><tr><td>3</td><td>Audible alarm notification of a fault condition</td><td>9.3</td><td>9.3</td><td>Based on Per IEC 60601-1-8 and (b) (4) HF rationale</td><td>5.3.c</td></tr></table> *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*
Acceptance Criteria (including confidence/reliability):	95/ (b) (4) C/R through variable analysis to a Ppk of >= (b) (4) with 35 devices are described. Full acceptance critera and results summary table copied under results. A severity assignment (b) (4) s assigned, based on (b) (4) , from a referenced dFMEA (b) (4) This is not a clearly related hazard: the user needs to perceive alarm notification to know the device is operating properly.

	Requirements are described with specific variable requirements which can be evaluated against. *Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.*
	IEC 60601-1-8:2012, IEC 60601-1 Edition 3.1 are referenced. **Reviewer note**: FDA recognizes 60601-1-8:2012 Ed. 2.1, and is used for reference in review. Samples are stated as being (b) (4) sterilized and ship tested, as previously described in this memo. Shipping has been previously noted as deficient. Samples preconditions at ambient (23 +/- 5 C, 50+/- 25 %RH) prior to test execution Samples used (b) (4) No explanation is presented to justify the use of this surrogate. From referenced stardard: Visual alarm at (b) (4) (only visual analysis), with visual indicator next to light with IEC 60417-5307 compliance checked through several conditions listed. Adutirory alarms in system are known to be high priority: standard specifies requirments for these (e.g.Table 3 and 4 of standard). In short, the Sponsor does not provide analysis to demonstrate meeting these requirements. Delays to alarm system (b) (4) should be disclosed in labeling, per Section 6.4 of the Standard. These are not noted. (b) (4)
Methods:	The Method is stated as the following:

	Test method: *Compliance was checked with the following test:* (b) (4) Particularly, while the Sponsor claims conformance to IEC 60601-1-8, the test lab states that there is no standard being tested against. The method (1) is unjustified and (2) does not support conformity. *Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)*
Results:	Stated as all passing: Sound pressure level, Audible notification, and notification at fault. (b) (4) The Sponsor presents variable analysis for system sound pressure. Non-normal data is used, with a largest extreme value distribution model used. No explanation for why this model is relevant to the system (other than statistical goodness of fit) is presented. This should be explained, particularly since some of the data of the same system is normally distributed.. The Sponsor presented variable analysis for audible notification sounds during normal operation. Normality is demonstrating with (b) (4) Ppk is greater than stated requirement.

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	The Sponsor presents variable analysis for fault condition notification. Non-normal data is used, with a (b) (4) model used. No explanation for why this model is relevant to the system (other than statistical goodness of fit) is presented. This should be explained. *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	Inadequate: Methods and data analysis are deficient. *Holistically do you find that the objective has been met? If not provide further explanation.*
	Acceptable: [ ] Yes [X] No

Test Method #8 – MAF (b) (4) Rev 1.0 Attachment 9-13 in Ammendment 003

Title:	SmartDose Gen II 10 mL Fluid Path Funcionality Verification Report *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	Meet the following requirements: *What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated*

#	Test Description	Protocol Section No. (b) (4) Rev.1.0)	Report Section No. (b) (4) Rev.1.0)	(b) (4) Revision Per DVMP
1	Fluid Path holding pressure	9.1	10.1	FP-2.1.a
2	Cartridge Needle detachment measurements	9.2	10.2	FP-3.1.a
3	Patient Needle detachment measurements	9.3	10.3	FP-3.1.b

Acceptance Criteria (including confidence/reliability):	Attribute data (b) (4) for 93 samples to achieve 95/95 C/R based on a severity assignment of (b) (4) Given no devices are stated as failing, this is reasonable. *Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.*
Methods:	Samples (b) (4) sterilized and shipped in the same manner as previously defined (Test Methods 1-7). Shipping method known to be deficient. Samples preconduitioned, as previously described (Test Methods 1-7) Methods listed/referenced, but not provided. Deficient. *Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)*
Results:	Stated as Pass, with Attachment locations detailed: No deviatiions or out of specification devices noted. Verification records provided as attribute. *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	No methods provided. Deficient. *Holistically do you find that the objective has been met? If not provide further explanation.*

#	Test Description	Design Input Requirement #	Requirement Description	Test Method	Severity	Confidence Level / Reliability level	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result (Pass/Fail)	Att.
1	Fluid Path holding pressure	FP-2.1.a	The fluid path shall withstand Holding pressure of (b) [MPa] for (b)	(b) (4)		95.0% / 95.0%	N=93	(b) (4)	Pass: 0 defects	Attachment D
2	Cartridge Needle detachment measurements	FP-3.1.a	A force value of (b) in the direction of the needle axis shall not cause Cartridge Needle detachment from Cartridge needle hub.			95.0% / 95.0%	N=93		Pass: 0 defects	Attachment E
3	Patient Needle detachment measurements	FP-3.1.b	A force value of (b) in the direction of the needle axis shall not cause Patient Needle detachment from Patient needle hub.			95.0% / 95.0%	N=93		Pass: 0 defects	Attachment F

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Acceptable:	[ ] Yes	[X] No

Test Method #9 – MAF (b) (4) Rev 1.0 Attachment 9-9 in Ammendment 003

Title:	SmartDose Gen II 10 mL (b) (4) Environmental Conditions Verification Report *List test method title and document name. referencing page numbers may also be helpful depending on how the reports are structured*
Scope/Objective:	Verify the following requirements, following the design inputs in (b) (4) roduct requirements and in (b) (4) design I/O matrix. Specifically, the following:

Protocol #:	(b) (4)	Protocol Title:	SMARTDOSE® GEN II 10 ML (b) (4) CONFIGURATION ENVEIRNOMENTAL CONDITIONS VERIFICATION TEST PROTOCOL
Report Section	Description	Result	Att.
9.1	Free fall drop test (b) (4) with cartridge inside (60601-1)	Pass	Attachment C & Attachment D
9.2	Free fall drop test (b) (4) without cartridge inside (60601-1)	Pass	Attachment C & Attachment E
9.3	(b) (4)	Pass	Attachment C & Attachment F
9.4		Pass	Attachment C & Attachment G
9.5			
9.6			
9.7		Pass	
9.8		Pass	Attachment C & Attachment H
9.9			
9.10		Pass	Attachment C & Attachment I
9.11		Pass	Attachment C & Attachment J

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	What is the objective or scope of this test method, what design requirements or risk control measures are being evaluated
Acceptance Criteria (including confidence/reliability):	See summary table in results for descriptions of testing. Acceptance critera pulled from each individual test: Free fall drop from (b) (4) m with cartridge: Severity (b) (4) given. Sponsor states this is a type test with a required sample of 1. Deferred to ELSFT review. Acceptance criteria stated as no unacceptable risks. Free fall drop from (b) (4) m without cartridge: Severity (b) (4) given. Sponsor states this is a type test with a required sample of 1. Deferred to ELSFT review. Acceptance criteria stated as no unacceptable risks. (b) (4)

	Reviewer note: The Sponsor provides reference to this testing twice in the protocol. It is not clear why this is done. Notably, these are to different sample sizes/acceptance criatera. The second reference (Section 9.11) is ot 93 devivces (b) (4) (b) (4)
	Reviewer note: dFMEA table in (b) (4) could not be located, used to generate these severity assignments (b) (4) is used to assign sample numbers and cannot be located. **Reviewer note**: IEC 60601-1 Ed. 3.1, (b) (4) are referenced as external sources. Again, the relevance of (b) (4) is questioned as these standards are for a different device type. It is also noted in the summary information, that some of the requirements which are stated as being used to drive the testing include deviations from those standards. These are not explained for their adequacy.. **Reviewer note**: Function as intended is not necessarily an objective criteria, unless a specific criteria is provided in a test record. Generally, there is lacking information to evaluate the data. *Include the acceptance criteria including the confidence/reliability. Additionally determine whether the acceptance criteria is appropriate to verify the design requirement/RCM being measured.*
Methods:	Samples (b) (4) sterilized and shipped in the same manner as previously defined (Test Methods 1-7). Shipping method known to be deficient. Samples preconduitioned, as previously described (Test Methods 1-7) Free fall drop from (b) (4) m with cartridge: Drop in 3 different orientations (button side, S/N label down, window facing down) to challenge three the interlocking mechanism and accidental needle ejection, TSA connection, and door integrity. Dropping down onto a concrete floor > 600 kg/m^3 density. The Sponsor references IEC 60601-1 Ed. 3 1 Subclause 15.3.4 for generating this testing. Testing standard is to 1 m. Deficient.

	Test method justifies this as a dtop to the counter, as a drop to the floor is stated as being controlled with labeling. This may be reasonable, but should be clearly explained as a deviation, not buried in methods/test reports. Deficient. Free fall drop from (b) (4) without cartridge: Deficient for similar noted reasons above. **Reviewer note**: a (b) (4) rop is significantly shorter than the distance potentially possible for the distance expected with a standing or sitting user of the device to the floor. Deficient. **Reviewer note**: This test is meant to challenge the needle safety functionality. (b) (4) (b) (4). Deficient.
	(b) (4)

(b) (4)

Describe briefly the method including sample sizes and/or data collect rate (how often is the volume collected for a flow rate accuracy test)

Data summary presents data as passing:

#	Test Description	Design Input Requirement #	Requirement Description	Standard	Severity	Confidence Level / Reliability	Sample Size	Acceptance Criteria (Variable/ Attribute/ Type Test)	Test Result (Pass/Fail)	Att.
1	Free fall drop test from (b) (4) with cartridge inside	4.2.a	The Loaded System shall provide its Safety Performance and visual and audible indications after being dropped, prior to attachment (before adhesive liner removal) (b) (4) from a height of (onto a hard surface	IEC 60601-1 :2012 Edition 3.1 clause 15.3.4 [1]	(b) (4)	N/A [2]	N=3 [3]	Type test: According to the standard- Not resulted in unacceptable risk	Pass: Not resulted in unacceptable risk	Attachment C & Attachment D
2	Free fall drop test from (b) (4) without cartridge inside	4.2.b	The Device shall provide its Safety Performance and visual and audible indications after being dropped, prior to prefilled container loading, from a height ((b) (4) onto a hard surface	IEC 60601-1:2012 Edition 3.1 clause 15.3.4 [1]		N/A [2]	N=3 [3]	Type test: According to the standard- Not resulted in unacceptable risk	Pass: Not resulted in unacceptable risk	Attachment C & Attachment E
3	(b) (4)									

Results:

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	(b) (4)
	The Sponsor appears to be using testing from IEC 60601-1 testing within the scope of this review. Electrical Safety review is deferred to the ELSFT reviewer. Sample size is grouped for all orientations (e.g. free fall test) to generate sample N. Confidence and reliability should be based on each orientation, not a single orientation. The Sponsor should demonstrate acceptable performance at boundary conditions with C/R commensurate with risks. Samples are noted as failures, and described as acceptable with reference to a standard which is non-applicable to the device ((b) (4) Deficient. Free fall drop from (b) (4) m with cartridge: no deviations or out of specification devices noted. Free fall drop from (b) (4) m with cartridge: no deviations or out of specification devices noted.
	(b) (4)

(b) (4)

Deviations:
Attachment P: Acceptance criteria revised from (b) (4) to 10 mL (b) (4). No change to method. This is a reasonable, so long as testing supports this stated acceptance criteria.

Attachment Q: Results analyzed as attribute as opposed to defined variable. This is stated as due to lack of normal data, and more samples being used than stated in the protocol. Stated sample sizes align to attribute accept (b) (4) sampling. Reasonable.

Attachment R: Delivery stated to require fixture. Fixture was not used with devices operated manually. This is likely reasonable.

Out of Specification results:
Reviewer note: The Sponsor states these as 'out of specification' and justifies their use to support their deisng is safe and effective. In general, this approach is not acceptable, as these are failures, should be acknowledged as failures, and corrected as system failures.

(b) (4)

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	Reviewer note: Testing report is provided to [redacted] (b) (4) with specific sections referenced. The adequacy of this method is questioned, given the scope of the referenced standard. It is noted that not all sections are challenged. [redacted] (b) (4) (b) (4) **Reviewer note**: Devices are noted as delvierying all in a manner to repliacate a person lying down in atmospheric, vibration delivery challenge. **Reviewer note**: only dose accuracy is evaluated, not flow accuracy. Deficient. **Reviewer note**: Mass and volume delivery record on pages 118- on Part 9 of Section 9 Ammendment 3. There are noted replacement devices used to replace broken/failing components whicha re incomplete replacement (i.e. not all attributes evaluated on the replacement device on page 121, 132-133, 138-139). *How are the result analyzed? Do you agree with this? Were there any deviations or thrown out data points?*
Conclusions:	Methods not provided. Respoonse incomplete. *Holistically do you find that the objective has been met? If not provide further explanation.*
	Acceptable: [ ] Yes [ ] No

Part 3: Adequate Device Reliability

Reliability Plan
Include discussion on Sponsor's approach to reliability and the acceptability of it

Not provided. A reliability memo is provided. Device has also changed. See General CR. Comment.

~~**Reliability Requirement**~~

~~**System Reliability Requirement:**~~	
~~**Method of Verification:**~~	
~~**Results of Verification**~~	

~~Reviewer Conclusion:~~	

~~List of Critical Components/Sub-Systems Reliability Requirements~~
~~*List critical components/sub-systems as defined by the Sponsor.*~~

~~Reliability Requirements Summary:~~
~~*This should include references to the test methods reviewed in Part 2 above. Also make sure that all essential performance (Dose accuracy, dose consistency/flow rate accuracy, bolus accuracy (if applicable), and dose status notification (e.g. occlusion, end of infusion)) are evaluated under worst case conditions challenging the device throughout the use life/shelf life.*~~

~~Design Reliability Requirement~~	~~Verification Method~~	~~Acceptance criteria met~~	~~Validation Method~~	~~Acceptance Criteria Met~~

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Dose Delivery Accuracy	10 mL (b) (4) **Reviewer note**: This specification is on total delivery, not individual rates. This is potentially a problem if the individual rates are not verified, as it is understood that the biphasic delivery is an important aspect, not merely total delivery.	N – Test data is inadequate. See Test Method 1	Not reviewed.	Aging method appears acceptable (accelerated)	Unacceptable.
Needle Length	6 (b) (4) mm	No reviewed – Change in device questions the relevance of provided information.	Not reviewed.	Not reviewed	Not reviewed

Adhesion	Adhesion allows for secure retention in all orientations/sites until removal. **Reviewer note**: This specifition lacks a challengeable quantify (i.e adhesion strength on a given surface over time). One cannot challenge a specification which lacks a verifiable output. Deficient.	No reviewed – Change in device questions the relevance of provided information.	Not reviewed.	Not reviewed	Not reviewed
(b) (4) Alarm	Fault indication provided within (b) (4) detection. **Reviewer note**: Adequacy of this specification requires CDER input: A clinical presepctive is necessary to determine the adequacy. However, the Lead Reviewer believes this is inadequate and likely requires further explanation (b) (4) (b) (4)	N – Test Method #5	Not reviewed.	Aging method appears acceptable (accelerated)	Unacceptable.

Reviewer Comment
The Sponsor describes the Essential Performance Requirements as captured in DD0092 and translated to functional requirements in West Pharmaceuticals document (b) (4), Design Input/Output Matrix in MAF (b) (4) in 3.2.R.1.P.3

9.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)

Reviewer Comment
See SAC review above, design not finalized can't be compelted

9.1.3. Evaluation of Test Methods

Reviewer Comment
See review in section 9 Part 2 Test Methods review.

9.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A
Reviewer Comments High level CR comments on SAC recommended. See CR comments for the NDA and MF holder.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

9.3. Discipline Specific Sub-Consulted Review Summary

☐ No Additional Discipline Specific Sub-Consults were requested
☑ The following additional Discipline Specific Sub-Consults were requested:
Reviewer note: Hemocompatibility of the device is tested. Determination of relevance is needed with CDER Clinical. Standard referred is recognized (at least -17 version is) F756.

Discipline-Specific Design Verification / Validation adequately addressed

Discipline	Consult needed			Consultant	Section	Adequately Addressed (Y/N/NA)
	Yes	No	N/A			
Engineering (Materials, Mechanical, General)			X	Lead Reviewer Performed	7 - 12	N
Biocompatibility: Biocompatibility Chemical Characterization: Toxicological Risk Assessment:	X X X			Rong Guo Gang Peng and Samanthi Wickramasek Caroline Pinto	9	N
Sterility:	X			David Wolloscheck	9	N
Software / Cybersecurity	X/X			Marc Neubauer (Both)	9	N
Electrical Safety / EMC	X/X			Ethan Cohen/Bonhye Koo	9	N/N
Human Factors	X			Janine Purcell	11	N
Clinical			X	N/A		Lead reviewer determined device changed during cycle. Clinical Validation information's relevance is questioned. Deficient.

CDRH sent Deficiencies or Interactive Review Questions to the Sponsor	☐ Yes ☑ No

9.3.1. Biocompatibility Review

The following Biocompatibiltiy review was completed by Rong Guo. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

"A biological risk assessment program was planned for the Furoscix Infusor, broken into three main testing arms: device, drug product, and the combination product. The service provider for the biocompatibility testing of the product is (b) (4).

(b) (4) conducted biocompatibility testing per ISO10993-1 on the Infusor with the fluid path classified as a prolonged contact, external communicating device with blood path, indirect contact. Biocompatibility testing was completed in three categories of components based upon their patient contact."

The following deficiencies are noted:

26. 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 final finished device.

27. 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 injection/infusion drugs, we recommend particulates testing using USP <788> method 1 light obscuration method. Please clarify which method was used, and if method 2 was used, please provide particulates testing per USP <788> method 1 light obscuration method. See deficiency 1.

28. In report "3.2.R.1.P.3 – Device Summary", table 7 Test Plan and Results Summary, (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. Please (b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

9.3.2. Chemical Characterization Review

The following Chemical Characterization review was completed by Gang Peng and Samanthi Wickramasek. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

The Sponsor appears to be providing biocompatibility and chemical characterization end-points. The following were recommended:

29. 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) . 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.

30. In the GC/MS direct injection results, you reported the recoveries of the spikes. However, (b) (4) (b) (4) it is unclear how you will ensure that the semi-volatile and volatile compounds of the sample will be detected. Provide a rationale justifying that the methods are appropriate for detecting semi-volatile and volatile compounds.

9.3.3. *Toxicological Risk Assessment Review*

The following Toxicological Risk Assessment review was completed by Caroline Pinto. The full memo is located in **Appendix B**. Below is a summary of the recommendation:
Information in submission is adequate. No comments.

9.3.4. *Sterility Review*

The following Sterility review was completed by David Wolloscheck. The full memo is located in **Appendix B**. Below is a summary of the recommendation:
During my review, I have identified one deficiency regarding bacterial endotoxin testing of the device constituent parts of the combination product. The Sponsor has not provided sufficient information to support a non-pyrogenic claim of the product. Please see Section VII for the recommended information request. 31. You stated in 3.2.R.1.P.3 Section 7.1 that the device constituent is delivered non-pyrogenic. However, we were unable to locate information regarding bacterial endotoxin testing of the device constituent parts of your proposed combination product. This information is needed to ensure that your device is safe for its intended use. Provide preliminary endotoxin testing demonstrating that the device meets the appropriate limits for endotoxin for a direct or indirect blood contacting device. For further guidance on this issue please refer to ANSI/AAMI ST 72 Bacterial endotoxins – Test methods, routine monitoring, and alternatives to batch testing and Guidance for Industry Pyrogen and Endotoxins Testing: Questions and Answers. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm314718.htm d) Please provide endotoxin unit (EU) limits, test methodology to determine EUs (extraction volume, limit of detection with the given volume, inhibition/enhancement testing), and test reports for bacterial endotoxin demonstrating acceptable EU limits. e) Please specifically address the number of devices tested per lot, and lot size. f) Please indicate whether batch testing or an alternative sampling plan will be utilized. **Lead Reviewer note**: Steriltiy consultant did not evaluate the (b) (4) month timepoint. It is understood that this data was not available at the time of submission originally. A high-level deficiency is drafted by the Lead Reviewer due to the incomplete submission and is revised to specifically mention these data.

9.3.5. *Software/Cybersecurity Review*

The following Software/Cybersecurity review was completed by Marc Neubauer. The full memo is located in **Appendix B**. Below is a summary of the recommendation:
Level of Concern – Adequate, Major **Software Description – Adequate**

Device Hazard Analysis – Inadequate

Note to Lead Reviewer: We could not find their dFMEA document in their submission and their software section states the software risk analysis is in this FMEA document. Please add the following software related comments to your general risk deficiency. We recommend that software only related hazards are classified by severity (b) (4) (b) (4) since it is not possible to accurately predict software only hazards. You may use a probability of harm if the software hazard occurs.

In an IR, the Lead reviewer asked about the potential need for (b) (4) (b) (4) I do not believe they need these (b) (4)…

Software Requirements Specifications (SRS) – Inadequate

The following SRS deficiencies were asked:

a. In your SRS document, please provide quantitative definitions with ranges, tolerances and units, where applicable, for your software alarms/errors.
b. Please clarify the number of software algorithms used in your firmware (b) (4) and provide SRS requirements that describe how these algorithms work and performance requirements (i.e. sensitivity/specificity, etc.) to ensure the algorithms work appropriately (i.e. do not have too many false alarms).

Architecture Design – Adequate

Software Design Specification – Inadequate

Traceability Analysis – Inadequate

Software Development Environment Description – Inadequate

Testing (Verification/Validation) – Inadequate

Provide system level verification protocols (i.e. test steps, acceptance criteria) and reports (i.e. raw data and conclusion) for all applicable errors/alarms which should include:

- Testing at the boundary conditions for each SRS, where applicable.
- System level testing with an adequate sample size that meets the definition of your reliability specifications, where appropriate.

Revision Level History – Adequate

Unresolved Anomalies (Bugs or Defects) – Inadequate

Cybersecurity - Adequate

The sponsor provided a cyber security risk assessment using our premarket cybersecurity guidance document.

Although this document provides most of the required information, I recommend they provide a threat model that includes additional information. See Deficiency.

1. DEFICIENCIES

1. In Amendment 3, you provide additional information regarding your alarms/errors into your description document; however you did not update your software requirements specification document or software design specification document. In addition, you did not provide quantitative triggering definitions including all appropriate ranges, tolerances and units for all alarms/errors where applicable, provide SRS specifications that define your algorithms (b) (4) nd their performance requirements (i.e. specificity/sensitivity) to ensure unnecessary false alarms do not occur, trace these requirements to their risk hazards and verification testing, provide verification testing that ensures the boundary conditions are tested where applicable, and for system level alarms/errors that include software and hardware components, test a representative sample of pumps per your defined reliability specification. This information is important to determine if your errors/alarms are adequately defined for their intended use and will trigger reliably in the field. Please provide the following information:
    e. In your SRS document, please provide quantitative definitions with ranges, tolerances and units, where applicable, for your software alarms/errors.
    f. Please define the sound pressure level for your alarms and provide a justification for this specification.
    g. Please clarify the number of software algorithms used in your firmware (b) (4) and provide SRS requirements that describe how these algorithms work and performance requirements (i.e. sensitivity/specificity, etc.) to ensure the algorithms work appropriately (i.e. do not have too many false alarms).
    h. For all SRS requirements, including those that define errors/alarms, provide a traceability table that traces the SRS requirement to its risk hazard, if appropriate, and verification testing.
    i. Provide system level verification protocols (i.e. test steps, acceptance criteria) and reports (i.e. raw data and conclusion) for all applicable errors/alarms which should include:
        iv. Testing at the boundary conditions for each SRS, where applicable.
        v. System level testing with an adequate sample size that meets the definition of your reliability specifications, where appropriate.
        vi. Please provide this testing in one document or groups these documents in one section for ease of review.
    j. Please update your safety assurance case including your reliability specifications for your system level alarms/errors.

2. In your document, SmartDose Gen II 10 ml SW Code Review, you provide your static code analysis and state it is for a full code coverage of SW Revision SW0025.02.03. This does not provide us adequate assurance that you have rigorously conducted your unit testing since you have not defined code coverage requirements (i.e. statement coverage, branch coverage) and provided evidence that you have met your requirements.
    k. Please provide a list of software modules with a short description of the functionality, the IEC 62304 safety classification and your predefined code coverage requirements taking a risk based approach.
    l. Provide a summary report that demonstrates you met your code coverage requirements for each module. If you do not meet the requirements for some modules then provide a risk based justification.
    m. Update your safety assurance case so the software reliability section includes your code coverage requirements for static testing.

3. Please address the following concerns regarding your software development environment and software defects:

    n. You state your software configuration and defect handling procedure is included in (b) (4) Software Life Cycle Procedure but you did not provide this procedure. For Major Level of Concern software, this documentation is required. Please provide (b) (4) Software Life Cycle Procedure. In addition, we recommend your software defect procedure quirements that open defects include a risk severity and a risk based justification for not addressing the defect in the current software release.

o. In the aforementioned list of open software defects, the sponsor should discuss the potential harm and severity score associated with defect, and the clinical justification why they do not have to address this defect in the software version they intend to release to the market. See Deficiency.

4. You provided a document titled SmartDose® Gen II 10 (b) (4) SW Cybersecurity Risk Assessment. This document discusses your assets, threats and controls; however this document is not complete and additional information is needed for us to analyze the controls you have in place. Please address the following deficiencies:

p. We recommend you provide a threat model that describes for each unique asset/vulnerability combination, you include a description of the attack vector, the severity score and description of the associated harm, the chain of events to carry out attack, the level of skill required for the attacker to compromise the asset/vulnerability, your control measures, NIST core function classification of the control (i.e. protect, detect, etc.), reference any requirement (i.e. SRS), and provide link to FMEA.

q. This document does not discuss if there is any off-the-shelf (OTS) software used in your pump. It is important to list the OTS software and discuss if there are any known vulnerabilities. Please state if you incorporate any OTS software. If you do then update the assets on your risk document and for each OTS asset, list any known vulnerabilities and how you plan to address them.

r. It does not appear your cybersecurity includes the hazardous situation of malicious programming that may lead to a higher programmed rate than acceptable per your specifications. An unauthorized user may be able to program a higher rate and which may lead to harm of overinfusion. Please add this harm and reassess if you need additional controls. For example, if a higher rate may lead to serious harm then you should consider stronger controls (b) (4) (b) (4).

s. You state the controls you have in place at manufacturing (b) (4) (b) (4) however you do not provide the specification/requirements for these controls or provide your manufacturing procedure that controls this process. It also appears you do not assume you may have a rogue employee. Please provide the specifications/requirements for your controls, provide your manufacturing procedure, and discuss how you may mitigate against a rogue employee. Please ensure your passwords are not documented in your SOP.

9.3.6. Electrical Safety Review

The following Electrical Safety review was completed by Ethan Cohen. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

Significant documentation could not be located. The following deficiencies are recommended:

Deficiency 1. We cannot find your electrical safety evaluation checklist performed by your testing house. Please be aware that your device should conform to the FDA recognized standard AAMI/ANSI ES60601-1-1:(2005) R2012 Part 1 Medical Electrical Equipment General requirements for basic safety and essential performance. Please supply the missing testing house checklist to assure patient safety with your combination product.

Deficiency 2. We cannot find your home healthcare electrical safety evaluation checklist performed by your testing house. Please be aware that your device should conform to the standard IEC 60601-1-11 Medical electrical equipment –
Part 1-11: General requirements for basic safety and essential performance – Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment Please

supply the missing testing house checklist to assure patient home healthcare safety with the combination product.

Deficiency 3. Please supply a water ingress rating (IPX) for your product, as we do not see any IPX rating to assure patient safety on either the product labeling or patient instructions for use.

Deficiency 4. In volume 10, software risk management, we cannot find your risk management document (b) (4) to show conformance to ISO 14971. To assure patient safety, adequate risk mitigation, please supply the missing dFMEA (failure mode and effects analysis) document in section 10.8.

Deficiency 5. Alarms: You state in your device "Instructions for use" the product contains visible and audible red alarm indicators. Please demonstrate your device is in conformance with IEC 60601-1-8, Medical electrical equipment –Part 1-8: General requirements for basic safety and essential performance –Collateral standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems.

9.3.7. Electromagnetic Compatibility Review

The following Electromagnetic Compatibility review was completed by Bonhye Koo. The full memo is located in **Appendix B**. Below is a summary of the recommendation:

EMC testing was conducted in accordance with the following standards:

- IEC 60601-1-2: 2014 (4th edition)
- (b) (4).

The testing information is summarized below:

- Equipment Under Test (EUT): On page 7 of Attachment 9-5, the sponsor stated, "All tests were performed on SmartDose® Gen II 10 mL (b) (4) Rev.A.02, with Bi-phasic delivery of 10.0 [mL] (b) (4) drug in 5 (b) (4) ours, (b) (4) configuration." However, the sponsor did not clarify if the tests were conducted with the final version of the device. **The sponsor should clarify this. If not, the sponsor should provide a justification on why this does not affect the test results.**
- Essential Performance:
  - Delivery of 10.0 mL (b) (4) of Furoscix.
  - Needle length of 6 mm (b) (4). **Note: This is out of scope of essential performance to be demonstrated through the EMC testing. However, (b) (4) ecommends visual inspection, this is acceptable.**
  - Adhesion: The means to affix the System to the injection site shall be sufficiently robust as to secure retention in all prescribed orientations/sites until removed by the user. **Note: This is out of scope of essential performance to be demonstrated through the EMC testing. However, this does not cause any risks.**
  - (b) (4) Alarm: The system shall detect (b) (4) during delivery and provide fault condition indication (b) (4), even during the slowest delivery phase. Note: I

recommend that the lead reviewer checks with the electrical safety and software consultants if the electrical safety and software testing complied with IEC 60601-1-8:2006 for the alarm system and the alarm activation criteria is clinically acceptable.

The dose accuracy was not evaluated during the ESD and RF immunity testing. However, ***this is acceptable since this is in accordance with*** (b) (4)***.***

Lead Reviewer Note: The Consultant uses the Sponsor justification for use of (b) (4) for testing scope. The Lead Reviewer disagrees with this assessment, as the device is not one of the device types recognized by FDA for this testing. This feeds more generally into justifying their methods for their device and should be explicitly discussed.

- Adaptations/deviations:
  - Delivery was performed using the real drug (b) (4) and not using a mimic solution as defined in the protocol. The sponsor justified that the density of the mimic solution is same as the real drug solution. Since the real drug simulates the clinical use, I believe that ***this is acceptable.***
  - 'Function as intended' definition is not as defined in the PRD. During the EMC test, " (b) (4) was used as the acceptance criteria, which is not as defined in the PRD: "Provide Safety Performance, audible and visual indications, and resulting in Delivery Complete". The sponsor stated that safety performance is defined as: "The System provides visible means to recognize the end of discharge status via the drug compartment window and shielding of the patient needle upon removal. The sponsor justified that test methods and the process were not affected, the 2 tests for verifying the safety performance acceptance criteria were successfully performed and the results are ***acceptable.***

Recommendation

The sponsor should address the following deficiencies:

Major Deficiency

1. According to the EMC test report, the battery specification is (b) (4). However, you did not provide the manufacturer, the type, and the power of the battery. As this information is recommended by IEC 60601-1, please provide the manufacturer, the type, and the power of the battery.

2. On page 7 of Attachment 9-5, you stated, "All tests were performed on SmartDose® Gen II 10 mL (b) (4) (b) (4) Rev.A.02, with Bi-phasic delivery of 10.0 [mL] (b) (4) drug in 5 (b) (4) hours, (b) (4) configuration." you did not clarify if the tests were conducted with the final version of the device. All tests should be conducted with the final version of the device, alternatively, a valid justification should be provided to ensure the validity of the tests. Please clarify if the tests were conducted with the final version of the device. If it was not, please provide a justification on why this does not affect the test results.

3. In the EMC test report, you did not clarify if there are device modifications. This information is needed to ensure that the tests were adequately conducted. Please clarify if there were device modifications. If there was, please justify the modifications do not affect the validity of the tests.

4. According to page 84 of attachment 9-4, the function of the subject device is defined as delivering of 10 (b) (4) ml of drug in (b) (4). Youj marked pass for all EMC tests; however, according to pages 97 – 98 of attachment 9-5, the dose accuracy of two side was (b) (4) after ESD precondition, and (b) (4) after RF precondition. Also, during ESD, RF, and power frequency magnetic fields immunity tests, dose delivered was measured more than (b) (4) The acceptance criteria of the EMC testing should be based on the expected functions of the subject device and the pre-defined acceptance criteria should be met. Please re-conduct the EMC testing to address that the subject device met the acceptance criteria or provide a justification on why this does not affect the patient safety and the validity of the testing.

Minor Deficiency

1. 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 information. As this information 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.”

2. label-0063-ifu does not include essential performance information. As this information is recommended by clause 5.2.1.1.b of IEC 60601-1-2:2014, please include essential performance in label-0063-ifu.

While the following comment is out of scope of EMC review, but electrical safety, I recommend that the lead reviewer talk to the electrical safety consultant.

5. The subject infusor includes a battery. However, label-0063-ifu, label-0068, label-0069, label-0072, and label-0073 do not contain the battery information (battery specifications including the type, RATED voltage, and power). Since this information is recommended per IEC 60601-1, please provide the battery information (battery specifications including the type, RATED voltage, and power) in label-0063-ifu, label-0068, label-0069, label-0072, and label-0073.

10.CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

☐ There is no device related clinical studies for review

☑ There are clinical studies for review
This information was obtained from the following documents:

PK/PD study not conducted with the to-be used device. A comparative study was performed scP-01-002. This was deteremind to be acceptable by the Agency, provided that using a commercial pump in the study could be found to have similar peroframnce. A dose accuracy reliability study was performed and is summarized in 2.7.1.2.5. This is also understood as the briding study. Clincal validation CP-00001. scP-01-002 statistical analysis to compare pumps

It was determined that no new clinical validation data was needed at this review cycle.

Given the changes noted regarding the device, review of adequacy of these are deferred to the next review cycle.

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☑ N/A
Reviewer Comments Deferred to next review cycle.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☑
Human Factors deferred to DMEPA	☐

CDRH Human Factors Review incorporates comments and considerations by the multi-disciplinary review team.

- Lead Reviewer – Max J. Lerman, PhD
- Human Factors Consultant – Janine Purcell, full memo located in Appendix B
- Clinical Consultant – N/A

Documents Reviewed

Human Factors Documentation Supporting the Combination Product

Study Protocol/Report	Study Title
Report: rpt-0333 R02	Furoscix SmartDose Gen II Human Factors Validation Study Report

11.1. Review Summary and Recommendations

CDRH finds the Human Factors/Usability Report (Data):

☐ Acceptable and have no additional recommendations.
☑ Not Acceptable. We have additional comments to convey, see Sections 11.1.2 and 11 1.3.

There are other sections within the lead review memo which may impact the review of the Human Factors Validation. Please see the box below describing these issues:

The Sponsor has stated the intent to change the device prior to marketing. Therefore, the relevance of the provided data are questioned. DMEPA was tasked with drafting a high-level CR deficiency for the Sponsor to demonstrate and discuss all differences between their performed testing and the to-be-marketed device.

11.1.1. High-Level Reviewer Conclusions

Lead Reviewer Conclusions

Below is a summary of the recommendation:
The final to-be-marketed device was not used in the HF study. The Sponsor updated the device during the review cycle with an unsolicited amendment changing user-interface functions, among other things, this invalidates the performed Summative Validation. Because of this, a high-level deficiency is recommended. Use-task do not identify what would be expected of all critical tasks: re-use the device, recognizing finished delivery, inspecting product for damage

Human Factors Consultant Conclusions

The following Human Factors Consulting review was completed by Janine Purcell. The full memo is located in Appendix B. Below is a summary of the recommendation:
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:* *8. History of chronic skin conditions requiring medical therapy.* *9. History of allergy to medical adhesives.* *10. Received oral antihistamines (e.g. Benadryl, Allegra, Zyrtec, etc.) or systemic steroids (e.g. prednisone, dexamethasone, etc.) in past 7-days.* *11. Used body lotions, oils or ointments on abdomen (adhesion area) within past 24 hours.* *12. History of major abdominal surgery affecting the site of device placement.* *13. Any local abdominal skin condition on the day of treatment i.e. sunburn, rash, eczema,* *etc.* *14. 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.

Clinical Consultant Conclusions

☑ No Clinical Consult was Issued

11.1.2. Comments to DMEPA

N/A

11.1.3. 'Letter-Ready' Deficiencies

☐ CDRH has no Human Factors related Major Deficiencies

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

☑ **HFPMET Concurrence** with Major Deficiencies below

Major Deficiencies

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 (e.g. 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.

11.2. Combination Product Background Information

	~~Summative Study~~	~~Marketed/Intended~~
~~Environment of use/ Conditions of use~~		
~~Test Participants/Users~~		
~~Description of Device used and how it compares to the to be marketed device~~		
~~Training~~		

Reviewer Comments
The final device was not used in testing. A high level comment is being drafted by DMEPA regarding this point.

11.3. Human Factors Report Review

The following review is based on content described in "Applying Human Factors and Usability Engineering to Medical Devices Guidance for Industry and Food and Drug Administration Staff," issued February 3, 2016. Sponsors are not required to submit in the prescribed format of the guidance document, however, the report should contain all the same elements as described in the table below. Per this guidance, CDRH defines a critical task as the following: *"A user task which, if performed incorrectly or not performed at all, would or could cause serious harm to the patient or user, where harm is defined to include compromised medical care."*

Lead Reviewrer Coment: Full Human Factors review deferred to next review cycle given device changes.

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Human Factors Report Context	Intended use and operational contexts of use	-	-
	Intended user population(s) and meaningful differences in capabilities between multiple user populations that could affect user interactions with the device	-	-
	Number and type of test participants	-	-
	Use environments and conditions that could affect user interactions with the device	-	-
	Test environment and conditions of use	-	-
	Graphical representation of device and its user interface	-	-
	Description of device user interface	-	-
	Device labeling	-	-
	Overview of operational sequence of device and expected user interactions with user interface	-	-
Reviewer Comments			

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Training	Training provided to test participants and how it corresponded to real-world training levels	-	-
Reviewer Comments			

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Summary of known use problems and formative human factors/usability studies	Known use problems with previous models of the subject device	-	-
	Known use problems with similar devices, predicate devices or devices with similar user interface elements	-	-
	Key results of formative human factors/usability studies	-	-
	Key findings that informed the human factors summative test protocol	-	-
Reviewer Comments			

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Description and categorization of critical tasks	Process used to identify critical tasks	-	-
	List and descriptions of critical tasks	-	-
	Categorization of critical tasks by severity of potential harm	-	-
	Descriptions of use scenarios that include critical tasks	-	-
	Critical Tasks list is adequate	-	-
Reviewer Comments			

Report Contents		Present (Y/N/NA)	Adequate (Y/N/NA)
Analysis of hazards and risks associated with use of the device	Potential use errors	-	-
	Potential harm and severity of harm that could result from each use error	-	-
	Risk management measures implemented to eliminate or reduce the risk	-	-

	~~Description and categorization of critical tasks~~	-	-
~~Reviewer Comments~~			

~~Report Contents~~		~~Present (Y/N/NA)~~	~~Adequate (Y/N/NA)~~
~~Human Factors Protocol Details~~	~~Rationale for test type selected (i.e., simulated use, actual use or clinical study)~~	-	-
	~~Critical tasks and use scenarios included in testing~~	-	-
	~~Definition of successful performance of each test task~~	-	-
	~~Description of data collection plans for objective and subjective data.~~	-	-
	~~Description of plan for data analysis and closure of the Human Factors Validation activities.~~	-	-
~~Reviewer Comments~~			

~~Report Contents~~		~~Present (Y/N/NA)~~	~~Adequate (Y/N/NA)~~
~~Human Factors Result Details~~	~~Test results: Observations of task performance and occurrences of use errors, close calls, and use problems~~	-	-
	~~Test results: Feedback from interviews with test participants regarding device use, critical tasks, use errors, and problems (as applicable)~~	-	-
	~~Description and analysis of all use errors and difficulties that could cause harm, root causes of the problems, and implications for additional risk elimination or reduction~~	-	-
	~~Statement that the device has been found to be safe and effective for the intended users, uses, and use environments~~	-	-
	~~Brief summary of HFE/UE processes and results that support this conclusion~~	-	-
	~~Discussion of residual use-related risk~~	-	-
Reviewer Comments The final device was not used in testing. A high level comment is being drafted by DMEPA regarding this point.			

11.3.1. Discussion of Results and Use Errors

Analysis Table Compiled from HF Validation Results

~~Use Errors/Close Calls/Difficulties~~	~~Where Captured/Subtask~~	~~Root Cause Analysis~~	~~Potential hazard or harm~~	~~Further risk control necessary?~~

11.3.2. Device Modifications after Summative Study

Reviewer Comments The final device was not used in testing. A high level comment is being drafted by DMEPA regarding this point.

11.4. Human Factors Review Conclusion

HUMAN FACTORS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☑ N/A	**Final Deficiencies:** ☑ Yes ☐ No ☐ N/A
Reviewer Comments		

The final device was not used in testing. A high level comment is being drafted by DMEPA regarding this point.
CDRH sent Human Factors Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

Review deferred to next cycle, given the identified issues in the submission.

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☐
CDRH Quality Systems Documentation Review was not conducted	☑

Review deferred to next cycle, given the identified issues in the submission.

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Review deferred to next cycle, given the identified issues in the submission.

Essential Performance Requirements Control Strategy Table

~~** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency use)*~~

~~Essential Performance Requirements~~	~~Control Strategy Description – The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:~~	~~Acceptable (Y/N/NA)~~
~~EPR #1~~		
~~EPR #2~~		
~~EPR …~~		

Reviewer Comments
Review deferred to next cycle, given the identified issues in the submission.

~~Control Strategy Conclusion~~		
~~The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.~~	~~☐Yes~~	~~☐No~~

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☑ N/A	Final Deficiencies: ☑ Yes ☐ No ☐ N/A
Reviewer Comments **Review deferred to next cycle, given the identified issues in the submission.**		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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/s/

MOHAN K SAPRU
12/01/2020 11:55:04 PM

Recommendation: **COMPLETE RESPONSE**

NDA 209988
Review #1

Drug Name/Dosage Form	Furosemide Injection
Strength	80 mg/10 mL (8 mg/mL)
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	scPharmaceuticals Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original	23-AUG-2017	*Amendment*	17-JAN-2018
Amendment	30-AUG-2017	*Amendment*	07-FEB-2018
Amendment	27-SEP-2017	*Amendment*	22-FEB-2018
Amendment	31-OCT-2017	*Amendment*	27-FEB-2018
Amendment	08-NOV-2017	*Amendment*	12-MAR-2018
Amendment	11-DEC-2017	*Amendment*	22-MAR-2018
Amendment	19-DEC-2017	*Amendment*	23-MAR-2018
Amendment	21-DEC-2017		

Quality Review Team

DISCIPLINE	PRIMARY/SECONDARY REVIEWER	OPQ OFFICE
Drug Substance	Sharon Kelly/Charles Jewell	ONDP
Drug Product	Mariappan Chelliah/Wendy Wilson-Lee	ONDP
Process	Peter Guerrieri/Derek Smith	OPF
Microbiology	Yan Zheng/Erika Pfeiler	OPF
Facility	Cassandra Abbellard/Christina Cappaci-Daniel	OPF
Biopharmaceutics	Parnali Chatterjee/Jing Li	ONDP
Regulatory Business Process Manager	Grafton Adams	OPRO
Application Technical Lead	Wendy Wilson-Lee	ONDP

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Review Date	Comments
(b) (4)	II		(b) (4)	Adequate	30-JUN-2016	
	III			-	-	Sufficient information in NDA
	V			-	-	Sufficient information in NDA
	V			-	-	Sufficient information in NDA
	V			Adequate	28-FEB-2018	Sterilization validation and media fill info
	III			-	-	Sufficient information in NDA
	IV			Adequate	16-APR-2018	

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	118919	Furosemide injection for subcutaneous administration

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	Complete	36 month shelf life acceptable	22-MAR-2018	Zhuang Miao
CDRH	Complete	Complete Response		Carolyn Dorgan

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends a complete response action for NDA 209988 Furosemide Injection, 80 mg/10 mL (8 mg/mL) due to inadequate controls for microbiological quality. The basis for the complete response recommendation is insufficient data included in the submission to demonstrate container closure integrity as well as the lack of a bioburden control for the pre-filtration bulk solution.

II. Summary of Quality Assessments

A. Product Overview

Proposed Indication(s) including Intended Patient Population	***Edema associated with heart failure in adults***
Duration of Treatment	(b) (4)
Maximum Daily Dose	***80 mg over 5 hour infusion***
Alternative Methods of Administration	***None. For subcutaneous administration with the Infusor wearable drug delivery system only.***

B. Quality Assessment Overview

Furosemide is a widely used parenteral diuretic and it has been in clinical use for nearly 50 years. The drug is typically administered via intravenous infusion by healthcare professionals. The listed drug product is Hospira's Furosemide Injection, USP, 10 mg/mL. The proposed drug product is furosemide injection, optimized for subcutaneous delivery, which can be self-administered by patients using a dosing pump. The bridge between the proposed drug product and the listed drug is established by a two-way crossover bioequivalence study. No biowaiver is requested in the submission.

Furoscix (SCP-101) is a drug-device combination product. The drug component is single vial containing 80 mg of furosemide in 10 mL sterile solution. It is packaged in 10 mL (b) (4) glass vial with a (b) (4) stopper and sealed (b) (4) Each vial is co-packaged with (b) (4) all patient-contacting or drug contacting single-use components. The Infusor is a wearable drug delivery system that is composed of two primary components, the Cartridge (single-use) and the Activator (b) (4), as the assembled infusion pump. The Infusor includes adhesive for direct application to the abdomen. A subcutaneous needle contained within the Infusor with automated needle insertion and

retraction facilitates subcutaneous infusion. The Furoscix Infusor is intended to be used in both clinical and home-care settings.

SCP-101 is intended for subcutaneous administration via Furoscix Infusor: 80 mg in 10 mL dosed over 5 hours using the Furoscix Infusor. The Infusor's piston pump is used to (b) (4) propel the medication through the fluid path and deliver the drug formulation through a thin needle that is placed in the subcutaneous space. Each rotation of the pump corresponds to a 10 mcL administration of drug formulation.

The drug product does not contain any rate limiting excipients, therefore an in vitro drug release testing is not applicable for batch release or stability testing of the proposed drug product. The To-Be-Marketed/registration batch (Lot 006E14) was used in the pivotal bioavailability/bioequivalence studies (ScP-01-001, 002, 003 and CP-00001). There is no need for formulation bridging. The application does not contain in vitro biopharmaceutics data. Therefore, a Biopharmaceutics review is not necessary for this NDA.

As this formulation is intended for subcutaneous administration, the proposed acceptance criterion (b) (4) does not meet the USP criterion of 8.0 – 9.3 for Furosemide Injection. The current USP monograph is based on product administered intravenously. To minimize the skin irritation during the subcutaneous infusion, the Sponsor targeted a neutral pH range for the formulation. During the review cycle, we recommended that the Sponsor contact USP to request revisions to the official monograph under the USP Pending Monograph Process so that the pH criterion meets the monograph.

The Applicant indicated that they did wish to pursue a monograph revision and did not intend compliance with USP monograph. We reiterated that a drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). The Applicant indicated acceptance of the FDA recommended label statement on the product label, i.e., FDA approved pH specifications differs from the USP to resolve this issue. This statement is intended for the carton and container labels only and will not be included in the prescribing information or other labeling.

Another issue resolved during the review cycle was determining an acceptable allowable excess fill volume for the product. Per USP <1151>, for a 10-mL labeled volume, the allowable excess volume is 0.5 mL. Per 21 CFR 201.51(g), the excess volume in injection liquids, including any fill-variation, must meet USP <1151>. The proposed criterion of (b) (4) mL exceeds the allowable excess volume of 0.5 mL. However, given that this vial is to be used with a device for delivery, it can be considered to functions as a cartridge (or a pre-filled syringe), for which the requirement of 21 CFR

201.51(g) does not apply. The device already has the several performance attributes for the injection volume (i.e. controls on total injection volume and injection volume during the first hour of infusion). The CDRH reviewer found this criterion acceptable. Additionally, because of difficulty involved in testing for this complex drug-device product, we will not ask the Sponsor to include 'deliverable volume' as a routine test in the drug product specification.

Based on the stability data provided and in accordance with ICH Q1E, a shelf-life of 36 months is granted when the drug product is stored at 25°C/60%RH. Continued monitoring of leachables – namely (b) (4) – is planned through 36 months as these identified, non-volatile leachables continue to increase during storage. At the end of 36 months, the Applicant proposed reassessment of these compounds. The proposed limits for these three non-volatile leachables do not present a safety concern based on the amounts observed in the product, the permitted total daily intake, and proposed dosing regimen. Although not a deficiency for this action, this issue will need to be re-evaluated based on any new data provided in the resubmission.

The manufacturing process for this sterile, aqueous solution is a (b) (4) (b) (4)

The hold time proposed for the (b) (4) product is (b) (4) Hold time studies evaluated pH, osmolality, appearance, degradants, particulate matter, bioburden and endotoxins over this time period, and the results support the proposed hold time.

Particulates which were attributed to (b) (4) were observed in the drug product after storage at (b) (4) (b) (4) The recommended storage condition for the commercial drug product is room temperature.

The method of sterilization for the drug product is (b) (4) (b) (4) The environmental monitoring, (b) (4) depyrogenation validation, and (b) (4) (b) (4) validation are adequate. The depyrogenation requalification and sterilization validation (b) (4) is adequate. (b) (4) (b) (4)

The applicant does not propose a bioburden specification (b) (4) (b) (4) (b) (4). The applicant commits to propose an appropriate acceptance criteria via the annual report when sufficient data is available; however, this specification is

necessary for assessment of the overall microbiological control strategy. In addition, additional data and information is required to fully assess the container closure integrity. The current submission does not include adequate controls (i.e. positive and negative, method validation) for the dye ingress test. In addition, a pressure or vacuum challenge was not applied as part of the microbial immersion test. Several rounds of information requests were sent to the applicant during this review cycle to resolve these issues. The applicant was not able to provide the required information to satisfy these concerns and hence, these issues are listed as product quality deficiencies and serve as the basis for the complete response recommendation.

The Applicant's calculation of expected introduction concentration (EIC) of the active moiety into the aquatic environment is in accordance with the "Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications ". The projected EIC is far below the 1 ppb threshold that would trigger the environmental assessment per 21 CFR 25.31(b). The Applicant also states that to the best of scPharmaceuticals' knowledge, no extraordinary circumstances exist under 21 CFR 25.31. Therefore, the Sponsor's request of categorical exclusion from environmental assessment is acceptable.

A review of the application and inspectional documents of the facilities responsible for manufacturing Furosemide Injection per NDA 209988 has determined that there are no significant outstanding issues with the firms involved in the manufacturing of the product. All facilities are deemed acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

We reserve additional comment on the proposed labeling until the application is otherwise adequate.

D. Final Risk Assessment (see Attachment I)

E. Deficiencies for Complete Response (see Attachment II)

ATTACHMENT I: Final Risk Assessment

Drug Product Final Risk Assessment – NDA 209988 Furosemide Injection, 8 mg/mL for use with Infusor Drug Delivery System, Subcutaneous route of administration

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Sterility	Formulation Raw Materials Container Manufacturing Scale Equipment Site	**High**	(b) (4)	**Not acceptable**	
Endotoxin/Pyrogens		**Medium**		**Not acceptable**	
Assay		**Low**		**Acceptable**	
Solid State		**Low**		**Acceptable**	
Uniformity of Dose		**Low**		**Acceptable**	
Osmolality		**Low**		**Acceptable**	
pH		**Low**		**Acceptable**	
Particulate Matter		**Medium**		**Acceptable**	

From Initial Risk Identification			Review Assessment		
Critical Quality Attribute	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations**
Leachables/Extractables		**Low**	(b) (4)	**Acceptable**	Monitor stability to ensure leachables do not exceed levels of toxicological concern on storage
Appearance		**Low**		**Acceptable**	
Delivered Volume		**Not assessed**		**Acceptable**	
Fill Volume		**Not assessed**		**Acceptable**	

ATTACHMENT II: List of Deficiencies for Complete Response

1. 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 result of microbial ingress test where (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).

2. It is acknowledged that the applicant commits 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.

ADDITIONAL COMMENTS FOR COMPLETE RESPONSE

Carton Label

1. For the excipients sodium chloride and tromethamine that are listed in the drug product composition, include in parenthesis the actual amounts in mg.

Container/carton/device labels

1. The labels should prominently display the following statement: "FDA approved pH specifications differs from the USP".
2. Edit the storage conditions so that °F or °C follows all the temperature digits. For example, the edit for the container label will look like: Store at 68°F to 77°F (20°C to 25°C).
3. Provide actual NDC numbers.
4. We recommend replacing the (b) (4), in front of the expiration date with 'EXP'.

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LABELING

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Furoscix™(furosemide injection)
Dosage form, route of administration	Injection; subcutaneous administration via the Infusor (Furoscix Infusor)
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	FUROSCIX (furosemide injection), 8 mg furosemide per mL ((b) (4)) and the Infusor

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	80 mg in 10 mL
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Does not contain description of identifying characteristics.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yes
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	NA
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes.
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	Yes (diuretic which is an anthranilic acid derivative)
Chemical name, structural formula, molecular weight	Yes
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Yes

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes. (but needs actual NDC#)
Special handling (e.g., protect from light)	Protect FUROSCIX from light. Do not remove from carton until ready for use. Protect the (b) (4) Infusor from water. (b) (4).
Storage conditions	Store at 20 to 25°C (68 to 77°F); (b) (4) (b) (4) Do not refrigerate or freeze. Excursions permitted between 59° to 86° F (15° to 30° C) [See USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	This is missing.

Reviewer's Assessment of Package Insert: ***Deferred*** Because complete response was expected for this NDA, the clinical team decided not to work on the labeling in this review cycle. Accordingly, this reviewer did not fully evaluate the PI. We will evaluate the PI section once the Sponsor resubmits this application to address the deficiencies raised in the CR letter.

II. Labels:

1. ***Container and Carton Labels***

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	(b) (4)	FUROSCIX™ (furosemide injection
Dosage strength	80 mg/10 mL (8 mg/mL)	80 mg/10 mL (8 mg/mL)
Net contents	10 mL	10 mL
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	No. Not required for small labels	Yes (but the actual numbers ND# needs to be printed)
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes	Yes
Bar code (21CFR 201.25)	Yes (2D)	Yes (2D)
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	--	--

➢ **Reviewer's Assessment of Labels:** ***Deferred***

Because complete response was expected for this NDA, the clinical team decided not to work on the labeling in this review cycle. Accordingly, this reviewer did not fully evaluate labeling. However, we have several comments for the Sponsor (see below). We will evaluate the container/carton once the Sponsor resubmits this application to address the deficiencies raised in the CR letter.

Labeling comments to be communicated in the CR letter:

Carton Label:

For the excipients sodium chloride and tromethamine that are listed in the drug product composition, include in parenthesis the actual amounts in mg.

Container/carton/device labels:

1. The labels should prominently display the following statement: "FDA approved pH specifications differs from the USP".
2. Edit the storage conditions so that °F or °C follows all the temperature digits. For example, the edit for the container label will look like: Store at 68°F to 77°F (20°C to 25°C)

3. Provide actual NDC numbers.
4. We recommend replacing the (b) (4)' in front of the expiration date with 'EXP'.

Overall Assessment and Recommendation: Evaluation deferred until future resubmission

Primary Reviewer: Mariappan Chelliah (see below for date)

Secondary Reviewer: Wendy Wilson-Lee (see below for date)

Mariappan Chelliah

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Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 4/12/2018 12:26:03PM
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CHAPTER VII: BIOPHARMACEUTICS

NDA: 209988
Drug Product Name / Strength: Furoscix™ (furosemide injection) / 8 mg/mL
Route of Administration: Subcutaneous Injection via the infusor
Applicant Name: scPharmaceuticals, Inc.

Background: scPharmaceuticals, Inc. is seeking approval for Furoscix™ (furosemide injection) in a sterile single-use prefilled (b) (4) to be administered subcutaneously with the Furoscix Infusor drug-device combination product for the treatment of edema associated with congestive heart failure, (b) (4) in adults *via* the 505 (b) (2) path. The listed drug (LD) is Furosemide Injection, USP, which was approved under NDA 18667.

REVIEW SUMMARY:

The bridge between the proposed drug product and the listed drug is established by a two-way crossover bioequivalence study. No biowaiver is requested in the submission. The drug product is a clear and sterile solution for subcutaneous injection that does not contain any rate limiting excipients, therefore an in vitro drug release testing is not applicable for batch release or stability testing of the proposed drug product. The To-Be-Marketed/registration batch (Lot 006E14) was used in the pivotal bioavailability/bioequivalence studies (ScP-01-001, 002, 003 and CP-00001). There is no need for formulation bridging. The Application does not contain in vitro biopharmaceutics data, and a Biopharmaceutics review is therefore not necessary for this NDA.

OVERALL REVIEW RECOMMENDATION:

There is no biopharmaceutics information contained in the submission, and therefore a Biopharmaceutics review is not needed for this NDA.

SIGNATURES

Primary Biopharmaceutics Reviewer Name and Date:
Parnali Chatterjee, PhD 11/01/2017

Secondary Reviewer Name and Date:
Jing Li, PhD 11/01/2017

Parnali Chatterjee

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Date: 11/01/2017 03:20:48PM
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Jing Li

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Date: 11/01/2017 03:28:16PM
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MICROBIOLOGY

IQA Review Guide Reference

Product Background:

NDA: 209988

Drug Product Name / Strength: Furosemide Infusor

Route of Administration: Subcutaneous

Applicant Name: ScPharmaceuticals Inc.

Manufacturing Site:

(b) (4)

Method of Sterilization: (b) (4)

Review Recommendation:

Review Summary: Not recommended for approval

List Submissions Being Reviewed: 8/23/2017; 9/27/2017; 10/31/2017; 2/7/2018; 2/27/2018; 3/12/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: This is eCTD submission.

Concise Description Outstanding Issues Remaining: container closure integrity data is not adequate; missing bioburden specification (b) (4).

Supporting Documents:

(b) (4)

S Drug Substance

No review was conducted on the drug substance as the drug product is sterilized (b) (4) (b) (4).

P.1 Description of the Composition of the Drug Product

- **Description of drug product –**
  The product Furoscix Infusor consists of a Furosemide drug vial, a single-use cartridge, (b) (4) and accessories (antiseptic wipes, skin-protecting barrier film).
  The Furosemide drug vial is a 10mL glass vial containing 10mL clear liquid.
  The cartridge contains a pump, which (b) (4) (b) (4) propels the medication through the fluid path for subcutaneous administration. (b) (4) (b) (4).
- **Drug product composition –**

Ingredients	Quantity	Function	Reference to Standard
Active Substances(s)			
Furosemide	80.0 mg	Active ingredient	USP/Ph. Eur.
Excipients		(b) (4)	
Tris HCl	78.8 mg		Bio Excipient
Sodium Chloride	58.4 mg		USP/NF, Ph. Eur., JP
Hydrochloric Acid	qs to pH 7.4	pH adjustment	USP/NF, Ph. Eur., JP
Sodium Hydroxide	qs to pH 7.4	pH adjustment	USP/NF, Ph. Eur., JP
Water for Injection	qs (b) (4)		USP/NF, Ph. Eur., JP

Table reproduced from the submission.

- **Description of container closure system –**

Container component	Manufacturer/Supplier
10mL (b) (4) vials, (b) (4)	(b) (4)
20mm stopper (b) (4)	West Pharmaceutical
20mm Seal	West Pharmaceutical

Notes to reviewer:
CDRH will cover the (b) (4) cartridge (including the needle), (b) (4).

Reviewer's Assessment: ***Adequate***

The product description is acceptable.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity (SCP-101, 3.2.P.2.5)

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(b) (4)

[redacted]

List of Deficiencies:

The following deficiencies are considered: ☐ Major ☒ Minor

1. 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 result of microbial ingress test [redacted] (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)

2. It is acknowledged that the applicant commits 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) the Agency's (b) (4) (b) (4) guidance on (b) (4) bioburden.

Primary Microbiology Reviewer Name and Date:

Yan Zheng, Ph.D. 3/12/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Erika Pfeiler, Ph.D. QAL

Yan Zheng

Digitally signed by Yan Zheng
Date: 3/13/2018 09:12:54AM
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Erika Pfeiler

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Wendy
Wilson- Lee

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Date: 4/23/2018 03:55:30PM
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