CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader (CDTL) Review

Date	03-October-2022
From	Theodore Carver, Ph.D. Senior Pharmaceutical Quality Assessor, Office of Pharmaceutical Quality, ONDP/DNDPIII/NDPB5
Through	Norman Stockbridge, M.D., Ph.D. Director, Division of Cardiology and Nephrology
Subject	CDTL Review
NDA	NDA 209988; Furoscix® (furosemide injection)
Type of Application	505(b)(2)
Applicant	scPharmaceuticals, Inc.
Date of Receipt	8-April-2022
PDUFA Goal Date	8-October-2022
Established/Proper Name	Furoscix®
Strength	80 mg per 10 mL
Route of Administration	Subcutaneous
Proposed Indication(s)	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.
Regulatory Action	**Approval**

This CDTL review is based on the primary reviews, memos, and documented review input, as listed below:

Material Reviewed/Consulted	**Review Team**
OPQ's Integrated Quality Review (DARRTS, dated 30-September-2022)	Daniel Jansen, Ali Mohamadi, Mark Johnson, Jianli Xue, Parnali Chatterjee, and Theodore Carver
Device Inter-Center Consult Review (dated 28-September-2022)	Jake Lindstrom and Courtney Evans
Clinical Safety Update (DARRTS, dated 11-August-2022)	Maryann Gordon and Fortunato Senatore

DMEPA Label and Labeling Review (DARRTS, dated 07-September-2022)	Hina Mehta
DMPP and OPDP Patient Labeling Review (DARRTS, dated 21-September-2022)	Shawna Hutchins, Charuni Shah, and LaShawn Griffiths

OPQ: Office of Pharmaceutical Quality; DMEPA: Division of Medication Error Prevention and Analysis; DMPP: Division of Medical Policy Programs; OPDP: Office of Prescription Drug Promotion.

1. Background

Based on the previous review of NDA 209988 (03-December-2020), the Agency issued a Complete Response Letter (CR) dated 03-December-2020. The current resubmission (NDA 209988-SN0058) is intended to address the deficiencies identified in the previous CR letter. The Applicant responded to the facility deficiency by withdrawing and replacing the non-compliant facility used to manufacture alcohol prep pads included in the kit. The Applicant also submitted information in the current resubmission to address device-related deficiencies. The Applicant is seeking U.S. marketing approval for NDA 209988 in accordance with Section 505(b)(2) of the FD&C Act. For the approval of this NDA, the Applicant relies on FDA's previous finding of safety and efficacy for the Listed Drug (LD) Furosemide (Injection, USP, 10 mg/mL; NDA 18667; Hospira, Inc.).

2. Quality Assessment Summary

The proposed co-packaged drug-device combination product is a kit including a single-use, prefilled Crystal Zenith® (CZ) cartridge containing 80 mg/10 mL furosemide, a single-use, wearable, pre-programmed, on-body Infusor, which is based on the SmartDose® Gen II 10 mL delivery system, and two alcohol prep pads.

2.1. Drug Substance (Furosemide) :

The furosemide 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 Drug Master File (DMF) (b) (4) which was previously reviewed and remains adequate after review of minor changes to the DMF. The drug substance specification complies with the USP monograph.

2.2. Drug Product (Furosemide Injection)

2.2.1. Product Design, Stability and Control Strategies: Furoscix® (furosemide) injection; 8 mg/mL is a clear liquid in a 10-mL cartridge closed with a (b) (4) piston and septum. The proposed 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, 80 mg/10 mL. The drug product was previously reviewed and found to be adequate. The review of the current resubmission included new information regarding impurities, extractables and leachables, and stability data submitted in the NDA resubmission. The review concluded that the drug product remains approvable, the control of impurities is adequate, and that the extractables leachables

studies support the compatibility of the furosemide formulation with the cartridge container closure system and the device fluid path. The stability data for the drug product in the cartridge (24 months), Infusor (12 months), and alcohol pad (60 months) support a shelf life of 12 months when the drug product is stored at 20 to 25°C.

2.2.2. Biopharmaceutics Aspects: A detailed biopharmaceutics review was not conducted as the NDA remains adequate with respect to biopharmaceutics. A bridge between the proposed drug product and the LD has been established, per 21 CFR 320.24 (b)(6), based on comparisons of LD and proposed formulation, including their similar physiochemical properties.

2.2.3. Microbiological Aspects: The NDA remains adequate with respect to microbiological quality. Additional information regarding in-process controls, (b) (4) (b) (4) was reviewed and found to be adequate. All other information supporting the sterility of the drug product have been previously reviewed and support approval.

2.2.4. Manufacturing: The manufacturing process for commercial production of Furoscix (Furosemide Injection), at Swissfillon AG, Visp, Switzerland (Swissfillon), utilizes typical pharmaceutical unit operations associated with the SVS (small volume parenterals) profile class, such as (b) (4) solution preparation, (b) (4), cartridge filling and stoppering, labeling, and packaging. Comments provided in the CR letter relating to the manufacturing process and controls were addressed by the Applicant in the NDA resubmission. The proposed manufacturing process and control strategy have been reviewed and are adequate to support the quality of the drug product constituent of the drug-device combination product.

2.2.5. Device Evaluation: The device components of the proposed combination product consisting of Crystal Zenith® (CZ) cartridge, and a proprietary wearable, pre-programmed on-body injection 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 healthcare professional at home or in a clinic/hospital 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 as part of the manufacturing process 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 a window for viewing the dose delivery. The 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.

The CDRH review of the NDA resubmission, including information provided to address device deficiencies, concluded that the device constituent of the drug-device combination product is approvable. The Applicant addressed the risks that were identified during the previous review cycle that previously precluded approval of the Infusor device. Specifically, the Applicant addressed risks associated with device modifications, biocompatibility, chemical characterization, and potential

impact on critical tasks associated with safe and effective use of the device. Based on the current CDRH classification of the infusor device as an injection device, rather than an infusion pump, the information provided by the Applicant is adequate to address risks associated with used of the device. The Applicant modified the labeling as necessary to mitigate risks that were not otherwise addressed during device development. The device constituent of the combination product is recommended for approval by the CDRH review team.

2.2.6. Assessment of Manufacturing Facilities:

The (b) (4) facility, responsible for the manufacturing of the sterile disposable alcohol prep pads included in the Furoscix® kit, was in an unacceptable state of compliance, resulting in a Withhold recommendation overall for facilities in the previous review cycle. The Applicant withdrew this manufacturing facility in the current NDA resubmission and replaced it with a new facility that is approved for this NDA (b) (4) (b) (4) Two other facilities, West Pharmaceuticals Services AZ, Inc. (FEI: 3001155023) and Sharp Corporation (FEI:3004161147), were unable to be inspected during the last review cycle, 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 outcome of this inspection. The Sharp Corporation (FEI:3004161147) secondary packaging facility was withdrawn, and the secondary packaging facility included in this NDA resubmission (b) (4) (b) (4) has been approved based on previous history. All other facilities are recommended for Approval based on previous history. Therefore, all facility deficiencies have been resolved and all inspections and reviews completed with an overall approval recommendation with respect to manufacturing facilities for NDA 209988.

3. Non-clinical Pharmacology/Toxicology

The previous nonclinical pharmacology/toxicology review concluded that NDA 209988 is approvable, and, as no new nonclinical or other pertinent information was submitted in the NDA resubmission for review, it remains approvable with respect to the nonclinical evaluation.

4. Clinical Pharmacology

N/A

5. Statistical-Evaluation

N/A

6. Clinical Studies/Financial Certification Disclosure

No clinical studies have been performed in support of this 505(b)(2) NDA. Hence, there is no financial information to disclose. The review of a clinical safety update report concluded that no unexpected safety issues were presented.

7. Advisory Committee Meeting

N/A

8. Pediatrics, and Other Relevant Regulatory Issues

N/A

9. Labeling

The review team completed the review of the labels and labeling, including the container/closure labels, the prescribing information, and the Instructions for Use (IFU), and the Applicant has incorporated recommended changes to all labeling to address deficiencies identified in the previous review cycle. Specifically, the Applicant addressed deficiencies relating to inadequate technical device information and potential risks related to performance of critical tasks. The DMEPA review notes that additional human factors studies were not required based on agreement with FDA (Type A meeting, 28-January-2021) and were not included in the NDA resubmission. The CDRH, DMEPA, DMPP, and OPDP review teams jointly concluded that the labeling as revised by the Applicant, including revisions to warnings in the IFU, adequately addresses potential use-related risks that were identified for the drug-device combination product.

10. Recommended Regulatory Action

The OPQ, CDRH, DMEPA, and other review teams have recommended Approval of Furoscix® (furosemide injection); NDA 209988, after review of the NDA resubmission (SDN0058). I concur with this recommendation based on the primary reviews, memos, and documented review input for NDA 209988, including previous reviews of NDA 209988.

Theodore Carver
Senior Pharmaceutical Quality Assessor,
CDER/OPQ/ONDP/DNDPIII/NDPB5

APPEARS THIS WAY ON ORIGINAL

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/

MOHAN K SAPRU
10/04/2022 10:17:50 AM

NORMAN L STOCKBRIDGE
10/04/2022 10:25:56 AM

Cross-Discipline Team Leader (CDTL) Review

Date	02-December-2020
From	Mohan Sapru, M.S., Ph.D. CMC Lead, Division of Cardiology and Nephrology
Subject	CDTL Review
NDA	NDA 209988-SN0034
Type of Application	505(b)(2)
Applicant	ScPharmaceuticals, Inc.
Date of Receipt	30-January-2020
PDUFA Goal Date	30-December-2020
Established/Proper Name	Furoscix® (furosemide) Injection
Dosage forms; Strength	Injection; 8 mg per mL
Route of Administration	Subcutaneous administration via Furoscix Infusor
Proposed Indication(s)	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
Regulatory Action	***Complete Response***

This CDTL review is based on the primary reviews, memos and documented review input, as listed below:

Material Reviewed/Consulted	Review Team
OPQ's Integrated Quality Assessment (DARRTS, dated 16-October-2020)	Daniel Jansen, Ali Mohamadi, Mark Johnson, Parnali Chatterjee, Jesse Wells, and Mohan Sapru (ATL)
Device Inter-Center Consult Review (dated 13-November-2020)	Max Lerman, and Carolyn Dorgan
Non-Clinical Review (DARRTS, dated 23-November-2020)	Belay Tesfamariam, and Jean Wu
DMEPA Human Factors Validation Study Review, and Labeling Review (dated 17-November-2020)	Colleen Little, Lolita White, Jason Flint, and Danielle Harris
DMEPA' S Proprietary Name Review (dated 09-September-2020)	Manitpisitkul Wana, and Danielle Harris

OPQ: Office of Pharmaceutical Quality; DMEPA: Division of Medication Error Prevention and Analysis

I. Background

Based on review of the original NDA 209988 (SN0001), the Agency issued a Complete Response Letter (CR) dated June-11-2018. The current resubmission (NDA 209988-SN0034) is aimed to address the CR deficiencies. Specifically, to address the CR deficiencies, 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'). Information about the improved device constituent is cross-referenced to Master Access File (MAF) (b) (4) 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.).

2. Quality Assessment Summary

The proposed drug-device combination product contains 8 mg/mL furosemide solution (pH (b) (4) that is to be provided in a sterile, single-use prefilled Crystal Zenith® (CZ) cartridge assembly 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.

2.1. Drug Substance: The furosemide 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 (b) (4) which has been previously reviewed and found adequate. The drug substance specification complies with the USP monograph.

2.2. Drug Product: Furoscix® (furosemide) injection; 8 mg/mL is a clear liquid in a 10-mL cartridge closed with a (b) (4) piston and septum. The proposed 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 has been previously used (as a Tham solution) for approved 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) are tested on release. The Applicant has agreed to include in the submission the statement: "FDA-approved pH specification differs from the USP". 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. The stability data indicate that the drug product is stable at long-term storage conditions (25°C/40% RH) at least up to 9 months (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.

2.3. Manufacturing: The manufacturing process for commercial production of Furoscix® utilizes typical pharmaceutical unit operations such as (b) (4) solution preparation, (b) (4), cartridge filling & stoppering, labeling, and packaging. Each manufacturing unit operation has been evaluated for its potential impact on product quality. The unit operations are well-controlled, and the overall control strategy is adequate.

2.4. 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)

[redacted] 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>).

2.5. Biopharmaceutics Aspects: Per the original submission, the 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 previously established by a two-way crossover bioequivalence study. Hence, no biowaiver has been requested in this resubmission.

2.6. 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 healthcare 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 [redacted] 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 a 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. Changing the device during the review cycle raises additional questions regarding its safety and efficacy and the relevance of all the submitted documentation. In addition, MAF [redacted] cross-referenced for significant documentation to support the device constituent of the 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. Currently unresolved device-related deficiencies to be communicated to the Applicant are described in detail in Appendix-I.

3. 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. Per Official Action Indicated (OAI) status, the [redacted] facility is considered to be in an unacceptable state of compliance with regard to current good manufacturing practice (CGMP).

Thus, the manufacturing inspection recommendation (OMIR) is 'Withhold'. Pre-approval inspections of Sharp Corporation (FEI # 3004161147), and (b) (4) (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. Manufacturing facilities related evaluation and comments to be communicated to the Applicant are listed in detail in Appendix-I.

4. Non-Clinical Pharmacology/Toxicology

The nonclinical information on furosemide relies on the LD. Based on non-clinical evaluation of the Applicant's current data, subcutaneous infusion of furosemide at doses up to 60 mg/kg (HED 19.5 mg/kg), which is approximately 15-fold the human dose of 80 mg (1.33 mg/kg), is not associated with local toxicity. This indicates that Furoscix® administered subcutaneously is well-tolerated. However, these nonclinical studies have not been conducted using the new to-be-marketed Furoscix infusor, and hence the approvability of the drug-device combination product will rely on the performance of the new device system.

The proposed formulation does not involve use of any novel excipients. (b) (4) a drug product degradation impurity, has been toxicologically qualified based on a wide margin of safety data generated in three studies, including a 6-day subcutaneous toxicity study with a (b) (4) structural analog in the rabbit, a 13-week oral (diet) (b) (4) rat toxicity study, and a 28-day dermal (b) (4) toxicity study in rats. Studies in transgenic mice show that (b) (4) is non-genotoxic, and studies in the rat and rabbit show that (b) (4) s also non-teratogenic. Extractable studies performed by GC-MS have identified several organic chemicals in the cartridge, but none are at levels of > (b) (4) µg/device, which is below the threshold of toxicological concern (1.5 µg/day/lifetime, ICH M7).

5. Safety; Statistical Evaluation, Pediatrics; Advisory Committee Meeting

N/A

6. Labeling

Due to the Complete Response action, the product labeling has not been reviewed in detail.

7. Recommendations Regulatory Action

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209988-SN0034; Furoscix® (Furosemide) Injection is not recommended for approval because of unresolved deficiencies, primarily the device-related deficiencies that are listed in Appendix-1. Satisfactory resolution of all these outstanding deficiencies is required before this application may be approved. I agree with this assessment and recommend the Complete Response regulatory action for this NDA. The detailed deficiencies listed in Appendix-1 will be communicated to the Applicant via the Complete Response letter.

11 Pages Have Been Withheld As A Duplicate Copy Of The Complete Response Letter Dated December 3, 2020 Which Is Located In Other Action Letters File Of This NDA Approval Package.

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/

MOHAN K SAPRU
12/03/2020 11:26:41 AM

NORMAN L STOCKBRIDGE
12/03/2020 11:29:11 AM

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 209988 Furosemide (b) (4) (Furoscix).

Sponsor: scPharmaceuticals

Review date: 11 June 2018

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's decision to issue a Complete Response for this application. There is a CDTL memo (Rose; 8 June 2018) providing the rationale for this decision. I am in complete agreement with that memo.

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/s/

NORMAN L STOCKBRIDGE
06/11/2018

Division of Cardiovascular and Renal Products
Cross-Discipline Team Leader Review

Date	June 7, 2018
From	Martin Rose, MD, JD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 209988 (original)
Applicant	scPharmaceuticals
Date of Submission	8/23/2017
PDUFA Goal Date	6/23/2018
Proprietary Name	Furoscix (b) (4)
Established or Proper Name	Furosemide for injection (to be delivered subcutaneously by the device component of this combination product)
Dosage Form(s)	Solution for subcutaneous (SC) administration, 8 mg/mL, in a sterile, single use vial containing 10 mL (80 mg furosemide), to be used with the Furoscix Infusor
Applicant Proposed Indication(s)/Population(s)	For use "in adult patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome."
Applicant Proposed Dosing Regimen(s)	Not for chronic use. (b) (4) (b) (4)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not applicable.
Recommended Dosing Regimen(s) (if applicable)	Not applicable.

I recommend a Complete Response (CR) for this application for approval of the Furoscix Infusor, a drug/device combination product including furosemide solution for subcutaneous injection (80 mg furosemide in a 10 mL vial), along with a wearable infusor. This recommendation is based on the failure of the product to meet its prespecified primary endpoint relating to device reliability in the Applicant's confirmatory trial, the "Product Design Clinical Validation" (PDCV) study. This result was due to (b) (4) failure to deliver the full contents of the Furoscix vial to 4 of 67 completing subjects due to filling errors (b) (4) (b) (4) The (b) (4) incomplete delivery of the furosemide dose has not been mitigated by the Applicant. In addition, these device failures, which were possibly related to errors in setting up the infusion, occurred in a trial where site staff were responsible for this task. The failure rate might be higher in the postmarketing setting, where patients or caregivers would often handle this task. As described below, device failure, especially if repeated over several days, could lead to fluid overload and hospitalization for ADHF, with a resulting increase in the risk of death. Finally, there are concerns about microbiological quality of the drug product that should be resolved.

1. Introduction and Summary of Conclusions

The Furoscix Infusor is a drug/device combination product consisting of a sterile vial containing 10 mL furosemide solution (8 mg/mL, for a total of 80 mg) and a wearable, electrically powered infusor system that is to be placed on the patient's abdomen and is intended to deliver the vial's contents over 5 hours into the abdominal subcutaneous tissue through an injection needle protruding from the device. The intended indication is use "in adult patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome."

The CDRH review team and the DCRP Clinical /Statistical team both recommended a CR based on the failure of the Applicant's PDCV study in patients with heart failure (HF) study to meet its primary endpoint (which was merely an assessment of the rate of successful infusion of a single vial of furosemide over 5 hours). Both CDRH and DCRP were concerned that (b) (4) (b) (4) there was a failure to infuse the vial contents. The CDRH reviewers also described other deficiencies related to the device. In addition, based on the views of the Clinical team that the device failures observed in the PDCV study could have serious, adverse clinical consequences in patients with HF, the DMEPA reviewers also recommended a CR. OPQ recommended a CR because of microbiological deficiencies involving the drug product. Two review disciplines that did not consider the results of the PDCV study concluded that the application was approvable from their standpoint. These included Pharmacology/Toxicology and Clinical Pharmacology. I concur with the review teams that recommended a Complete Response, for the same reasons that were stated by DCRP Clinical/Statistical reviewers. These reasons are described in detail in Sec. 7 of this review and are also mentioned in Sec. 2.1.

2. Background

2.1 Condition

Loop diuretics, including furosemide, are a mainstay of treatment of edema of various etiologies. Furosemide is available as oral tablets or a solution for IV or IM administration. The complete indication statement of the solution is:

> "Parenteral therapy should be reserved for patients unable to take oral medication or for patients in emergency clinical situations.
>
> **Edema:** Furosemide is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. Furosemide is particularly useful when an agent with greater diuretic potential is desired.
>
> Furosemide is indicated as adjunctive therapy in acute pulmonary edema. The intravenous administration of furosemide is indicated when a rapid onset of diuresis is desired, e.g., in acute pulmonary edema.
>
> If gastrointestinal absorption is impaired or oral medication is not practical for any reason, furosemide is indicated by the intravenous or intramuscular route. Parenteral use should be replaced with oral furosemide as soon as practical."

Furosemide oral tablets (Lasix®) have the following indication statement:

> **"Edema**
> LASIX is indicated in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome. LASIX is particularly useful when an agent with greater diuretic potential is desired.
>
> **Hypertension**
> Oral LASIX may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with LASIX alone."

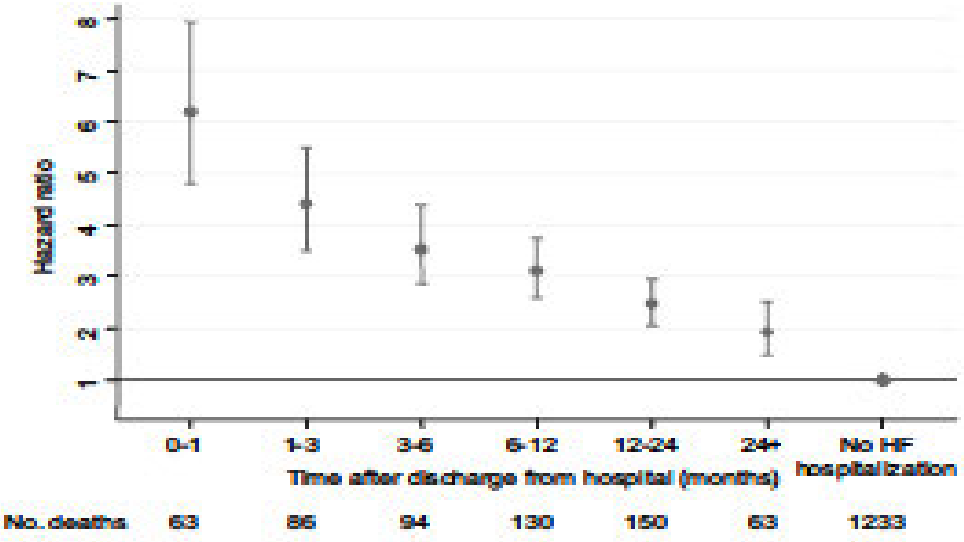
The Applicant's proposed indication for Furoscix is more restricted than the above indications:

(b) (4)

The Furoscix Infusor is programmed to deliver the contents of the 10 mL vial (8 mg furosemide per mL) over 5 hours as follows: 30 mg over the first hour, then 12.5 mg/hour for the next 4 hours. The programming is fixed.

I expect that if this product is approved, most within-indication use of Furoscix will be in patients with HF, based on the Sponsor's clinical trials, an investigator-sponsored trial of Furoscix Infusor in patients with ADHF (b) (4), PI: Adrian Hernandez, DCRI), and one European publication indicating that use of furosemide for HF by GPs dramatically exceeds all other uses except for hypertension, for which Furoscix is not indicated. (1). This is relevant because in patients with HF, edema is more than a nuisance. There appears to be a relationship between fluid overload, of which edema is one manifestation, and mortality. Increased fluid volume due to salt loading and/or failure to take prescribed medications is thought to be a major precipitating factor for hospitalization for acute decompensated HF (ADHF).(2) In a large, multiple community-based observational study, an episode of hospitalization for ADHF was associated with a mortality rate of 10% at 28 days after admission and 30% at 1 year after admission.(3) Also, in 7599 patients in the CHARM program of 3 placebo-controlled trials of candesartan in patients with chronic HF, the rate of mortality was notably elevated for at least 2 years after discharge alive from a hospital admission for HF, compared to patients who were not hospitalized for HF (**Figure 1**). In addition, the second and third hospital admissions for HF serially increased the risk of death, but there was no further increase in risk of death for the fourth or subsequent admissions for HF.(4)

Figure 1 CHARM Program: HR and 95% CI for Death after Discharge Alive from a First Hospitalization for HF Compared to Patients with No Such Hospitalization



Source: Reference (4)

While these data are not conclusive with respect to causation, they certainly raise the concern that an admission for ADHF is associated with a substantial increase in the rate of death. Given that failure to take HF medications is cited as an important cause of ADHF, it seems reasonable to be concerned that unnoticed and unalarmed failure of the device, especially if repeated for several consecutive days, could increase the risk of hospitalization for ADHF and ultimately the risk of death.

2.2 Regulatory Considerations

Prior to submission of this application, we reached agreement with the Applicant on the following: a Sec. 505(b)(2) application for a drug/device combination product designed to infuse the contents of a vial containing 80 mg furosemide subcutaneously over 5 hours and with the Applicant's proposed indication could be supported by the following clinical information:

1. A study showing biosimilarity of bolus IV injection of 80 mg furosemide for injection to a subcutaneous infusion of 80 mg furosemide. A commercially available pump could be used in this study in lieu of the Furoscix pump.
2. An open label study in patients with HF to examine the reliability of the Furoscix Infusor in delivering the planned volume of furosemide solution.

Of note, the major clinical issues in this application relate to study 2.

3. Product Quality

Because Furoscix is a drug-device combination, this section has two parts: the first is the discussion of issues related to the drug component, followed by those related to the device component.

3.1 Drug-related Issues

The CDER OPQ reviewers (see table at the end of this section for names and roles) recommend a complete response from the standpoint of their discipline, based on inadequate controls for microbiological quality for the drug product. This was due to "… insufficient data included in the submission to demonstrate container closure integrity as well as the lack of a bioburden control (b) (4) See below for details.

There are no deficiencies associated with the furosemide drug substance (DMF (b) (4), which is manufactured by (b) (4) The drug is compliant with USP and EP specifications.

The drug product component of this drug-device combination product is a 10 mL, (b) (4) (b) (4) vial containing 10 mL of an aqueous solution of furosemide at a concentration of 8 mg/mL (80 mg/vial). The vial has a (b) (4) stopper and is sealed with an aluminum flip seal. It is co-packaged with (b) (4) patient-contacting or drug-contacting single use components. Prior to administration of Furoscix, the vial of drug product is inserted into the cartridge. The vial and cartridge may be co-packaged with the "activator," a reusable, electrically powered piston pump. The ready-to-use product includes the vial, cartridge, and activator, and is termed the "infusor." The infusor is applied to the patient's abdomen, and delivers the contents of the vial over 5 hours. Delivery is through a needle that protrudes from the cartridge. The needle is intended to deliver the drug into the abdominal subcutaneous tissue.

Excipients are listed in the table below. All are compendial except for Tris HCl, which does not have a compendial monograph. However, the OPQ reviewers found this component acceptable.

Composition of the Drug Product

Ingredients	Quantity	Function	Reference to Standard
Furosemide	80.0 mg	Active ingredient	USP/Ph. Eur.
Tris HCl	78.8 mg	(b) (4)	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 to 1 (b) (4) mL	(b) (4)	USP/NF, Ph. Eur., JP

Source: OPQ review, Table 3.2.P.1-1

Deficiencies and quality-related labeling issues described in the review are discussed below.

pH issue:

The drug product is adjusted to pH 7.4 to reduce tissue irritation. However, the pH range in the USP monograph for furosemide injection (now approved only for IV and IM administration) is 8.0 – 9.3. Despite suggestions from OPQ reviewers, the Applicant has refused to approach USP to change the monograph for furosemide injection to include the pH of its product in the allowable range, but the reviewers state that the pH discrepancy between the Furoscix drug product and

the USP monograph could be described in the container label if this product is approved. They have provided appropriate language for labeling.

Microbiology issues:

There are two:

(1) Assessment of (b) (4) bioburden: The applicant's (b) (4) (b) (4) (b) (4) process does not include assessment of bioburden (b) (4) which the microbiology teams views as important (b) (4) (b) (4) The Applicant responded by stating that they are willing to commit to assessing bioburden (b) (4) and reporting the result in the batch record, but they have not specified an action limit for this assessment. The reviewers state that the specification of such a limit "…is necessary for review of [the] application."

(2) Container closure integrity: The Applicant's methodology for assessing this parameter is considered insufficient. While integrity was shown by success using two methods, the reviewers considered each method to be flawed, and thus unacceptable (b) (4) (b) (4)

Note that both of these appear to be classified as "minor" deficiencies, but OPQ thinks they justify a CR.

Facilities:

All facilities involved in the manufacture of the drug substance and drug product were considered acceptable.

OPQ 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

3.2 Device-related Issues

The CDRH reviewers of the device component recommend a CR based on "… unacceptable risk analysis, insufficient Human Factors testing, clinical use errors and lacking performance testing " of the device component of Furoscix. A table identifying the staff involved in the review and their roles is at the end of this section. Their 272-page review includes a list of 22 "letter-ready" major deficiencies for inclusion in a CR letter (CRL), most of which describe several related problems. Selected highlights from this list are set forth below. Note that Human Factors testing deficiencies are discussed in Sec. **11 below**.

- Deficiency 1: Review staff were unable to find descriptions of several alarms consistent with the FDA Guidance, Infusion Pumps Total Product Life Cycle, within the device description. (b) (4) (b) (4)
- Deficiency 2: It is unclear how dose accuracy was determined in the Product Design Clinical Validation (PDCV) Study, CP-00001, which is described further immediately below and in section 7, Clinical/Statistical- Efficacy, **below**.
- Deficiency 3: The PDCV Study failed to meet its primary endpoint of freedom from major system-related failures. This was an open label study of SC injection of the Furoscix Infusor in patients with heart failure, and was the primary test of the reliability of the to-be-marketed device. Device failures occurred in 4 of the 67 patients who completed the planned 5-hour infusion of furosemide. (b) (4) (b) (4)
- Deficiency 4: Risk and hazard analyses presented by the Applicant are inconsistent with RA-0002, the scPharmaceuticals Risk Management Plan. (b) (4) (b) (4) The severity of these should be upgraded (b) (4).
- Deficiency 5 d: The Applicant should "… conduct adequate root cause analysis for all use errors that could lead to serious harm, implement adequate risk mitigation measures, and sufficiently test the robustness of your mitigations in a new validation study or

provide justification for not doing so." Text not quoted here explicitly indicates concern that underdosing is a use error that could lead to serious harm.

- Deficiency 10: The Applicant provided Study scP-00-02 as validation for the effectiveness of the adhesive for the device. However, the study was not designed to validate the adhesive (b) (4). The adhesive is part of the essential performance for the device and therefore should be defined, verified and validated.
- Deficiency 18: The Applicant has provided a comparison of the extractable/leachable chemicals from the to-be marketed pump and the original version of the pump included in the biocompatibility studies. However, they did not provide an evaluation of how any new compounds or increased amounts of compounds would impact the following endpoints: cytotoxicity, irritation, sensitization, hemolysis, and pyrogenicity. Such an evaluation should be provided.
- Deficiency 21: The Applicant did not include an evaluation of the particulates that are present within the device fluid-contacting components of the device. Such an evaluation should be included in the Application.

All facilities involved in the manufacture of the device component were considered to be acceptable.

CDRH Review Team	
Lead Device Reviewer	Carolyn Dorgan
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**
Software	Marc Neubauer CDRH/ODE/DAGRID/GHDB
Clinical	Jodi Savitz CDRH/ODE/DAGRID/GHDB
HF	Rita Lin CDRH/ODE/DAGRID/HFPMET
Biocompatibility	Sarah Mollo CDRH/ODE/DAGRID/GHDB
Sterility	Steven Elliott CDRH/ODE/DAGRID/INCB

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was performed by Drs. Belay Tesfamariam and Jean Wu. They found no information that precludes approval, and stated that, “Furoscix administered subcutaneously is considered to be sufficiently tolerable.”

With the exception of the items described below, the Applicant relied upon either published studies or information for the reference listed drug, furosemide injection, NDA 18667, to satisfy the NDA requirements for pharmacology/toxicology information.

The Applicant’s leachables/extractables studies found no chemicals that were above applicable thresholds in the drug product or in the infusor device. The Applicant also performed various bioassays of extractables from various components of the infusor device, including cytotoxicity (mouse fibroblast cells), sensitization (guinea pig maximization), irritation (intracutaneous in

rabbits), primary skin irritation (shaved skin rabbit), systemic toxicity (IV, IP mice), hemocompatibility (hemolysis assay), and pyrogenicity (febrile response in rabbits). None of these studies provided evidence of toxicity. The reviewers concluded that, "The results of the total extractables provide additional evidence in support of the ICH M7 qualification for impurities." However, the CDRH reviewers had concerns regarding differences in extractable/leachable compounds between the original version of the Furoscix pump and the to-be marketed version (see discussion of CDRH deficiency 18, **above**).

The Applicant performed Phase I and II studies of SC furosemide in rabbits. In the Phase I study (single escalating doses, 5 to 60 mg/kg, followed by observation for 24 hours and euthanization), "local" erythema was observed across the range of administered doses, but not in all treated animals. In the Phase 2 study, in which animals received one dose of SC furosemide 60 mg/kg or vehicle control, were observed for 14 days and then euthanized, findings suggesting infection at the injection catheter site were observed in one rabbit in each of the furosemide and vehicle arms, respectively. Microscopic findings at the infusion site were similar in animals given Furoscix and those given the vehicle. Blood chemistry and hematology tests were consistent with diuresis in animals who received furosemide. No repeat dose studies were performed.

5. Clinical Pharmacology

The Clinical Pharmacology reviewers, Drs. Girish Bende and Sudharshan Hariharan, reached the following conclusion:

> "The Office of Clinical Pharmacology (OCP) has reviewed the information submitted under NDA-209988 and considers the bridge between Furosemide Injection and to-be-marketed drug device combination product (Furoscix-Infusor) is acceptable. Although the PK/PD bridge is acceptable, the OCP relies on the Center for Devices and Radiological Health (CDRH), the Division of Medication Error Prevention and Analysis (DMEPA), and joint clinical and statistical reviews for assessment of the performance of to-be-marketed infusion pump including performance validation of infusion pump and review of the human factor study. Please refer to the respective discipline reviews for approvability issues pertaining to this application."

The Applicant's "PK/PD" study (scP-01-002) was a critical part of the development program for Furoscix. It was a proof-of-principle study to determine whether subcutaneous administration of furosemide could produce drug blood levels and pharmacodynamic effects similar to those of IV furosemide. This was an open-label, 2 period, random-sequence, cross-over trial performed in 16 adults with compensated NYHA Class II/III chronic heart failure undergoing chronic treatment with oral furosemide at a dose of at least 40 mg daily. The washout between treatment periods arms was one week.

In each period, previously screened subjects were admitted to a clinical research unit. Oral furosemide dosing was interrupted at least 24 hours prior to the planned infusion. Subjects were observed in the unit for at least 24 hours prior to and after their infusions. Subjects were randomized to receive either one of these infusion regimens during the first period and the other regimen in the second period:

- SC furosemide 80 mg over 5 hours, with 30 mg infused over the first hour and then 12.5 mg/hr for the next 4 hours.
- IV furosemide 80 mg given as two 40 mg boluses, each infused over two minutes, administered two hours apart.

The furosemide given IV is marketed by Hospira (Furosemide Injection, 10 mg/mL, NDA 18667). The furosemide given SC was also a solution (10 mg/mL), apparently manufactured for this study by (b) (4) under "GMP conditions." It contained sodium chloride, TRIS hydrochloride, and could also contain HCl or NaOH to control pH in the range 7.0 to 7.8, like Furoscix (see Sec. 3 for a discussion of the pH of the Furoscix product).

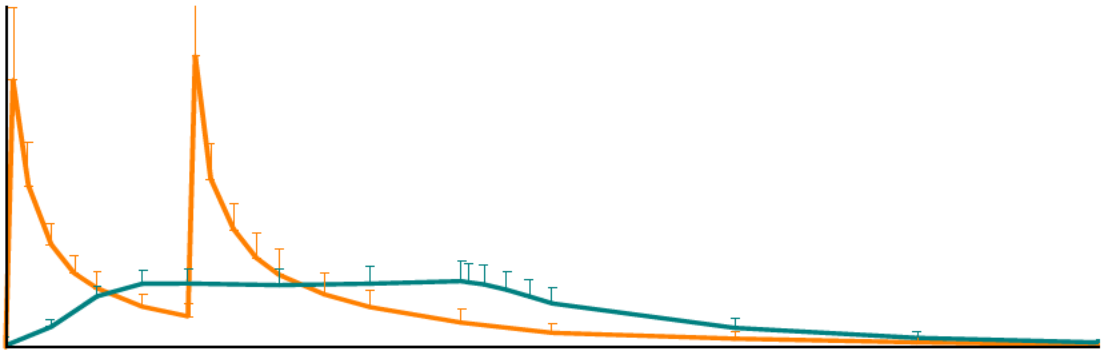
Of note, the pump used to deliver SC furosemide in this study was not the Furoscix activator. Instead, a marketed pump was used: the B. Braun Perfusor® Pump, which is CDRH cleared for subcutaneous infusion.

Study assessments included: Blood collections for furosemide PK (see Figure 1 for the timing of collections) and serum and urine electrolytes (urine was collected from spontaneous voids for 24 hours after dosing). Water intake was controlled at 100 mL/hour from 2 hours before the infusion start to 12 hours "after dosing" in each period. It is not stated precisely when the 12-hour period after dosing started in each of the treatment periods.

Seventeen subjects were randomized, but the main analysis of PK parameters included 15 subjects. One subject was withdrawn from the study by the investigator and not treated because of an elevated INR at baseline. Another subject was treated but excluded from the main analysis because the subject's baseline furosemide plasma concentration was considered to be too high. A sensitivity analysis of AUClast and AUCinf that included this subject had AUC values nearly identical to those of the main analysis and well within the traditional 80% to 125% bioequivalence boundary (data not shown).

Furosemide drug concentrations over time are plotted in in **Figure 2** for IV and SC administration for 15 subjects. Furosemide pharmacokinetic parameters during the two treatment periods are shown in **Table 1**.

Figure 2 Plasma Furosemide Concentration (Mean ± SE) vs. Time Profiles



Source: Clinical Pharmacology Review, Figure 2-1.

Table 1 Plasma Furosemide Pharmacokinetic Parameters

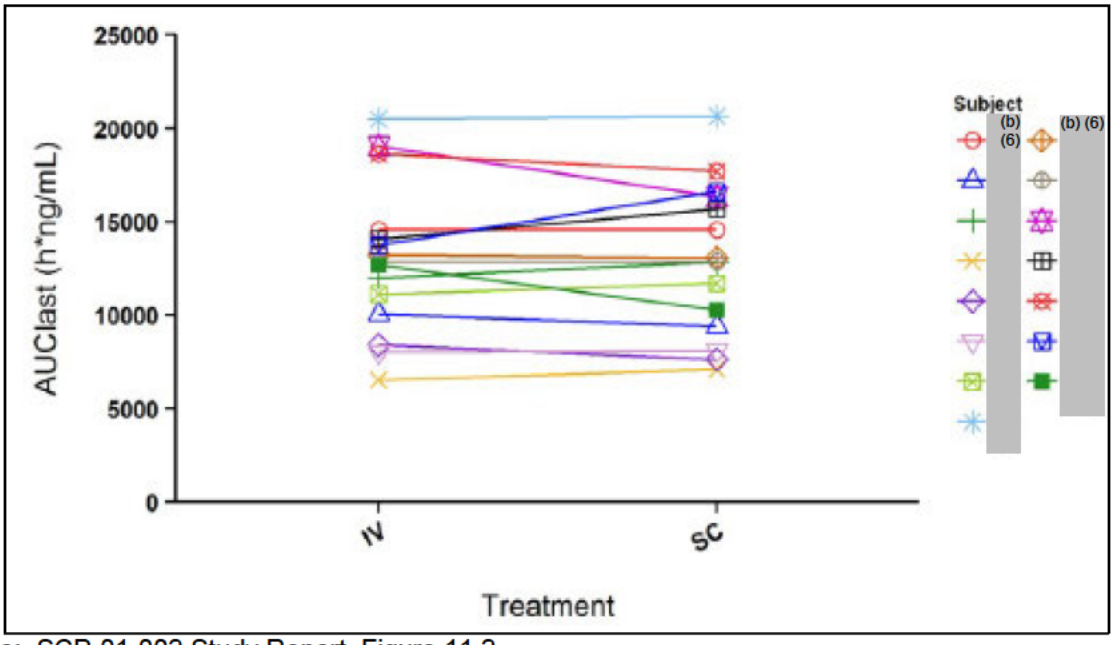
Route	Cmax (ng/mL)	AUClast (ng.h/ mL)	AUCinf (ng.h/mL)	Half-Life (h)
IV (80 mg) (n=15/16)	8,580 ±2,540 (29.5%)	13,000 ±4,050 (31.1%)	13,200 ±4,170 (31.6%)	2.55 ±0.339 (13.3%)
SC (80 mg) (n=15/16)	2,040 ±449 (22.0%)	13,000 ±4,000 (30.8%)	13,100 ±4,010 (30.6%)	3.16 ±0.911 (28.8%)
GMR (90% CIs)	-	99.50 (94.77, 104.46)	99.65 (94.79, 104.75)	-

Data presented as Mean ± Std Dev. (CV%); GMR: Geometric Mean Ratio with (90% CI)
Source: Clinical Pharmacology Review, Table 2-2.

The data indicate that the C_{max} is several-fold higher with IV administration compared to a 5-hour SC infusion. However, AUClast and AUCinf are similar for the two routes.

Matchstick plots showing AUClast with IV and SC administration of furosemide are shown for each of 15 study patients in **Figure 3**. The data show a high degree of similarity of exposure with the two routes of administration for individuals.

Figure 3 Study 01-002 - Matchstick Plot of AUClast for Individual Patients



Source: SCP-01-002 Study Report, Figure 11.2

In addition, the PD parameters of urine output and urinary sodium excretion were similar for the two routes over two analyzed time periods: hours 0-8 and hours 0-24 (**Table 2**).

Table 2 Pharmacodynamic Parameters

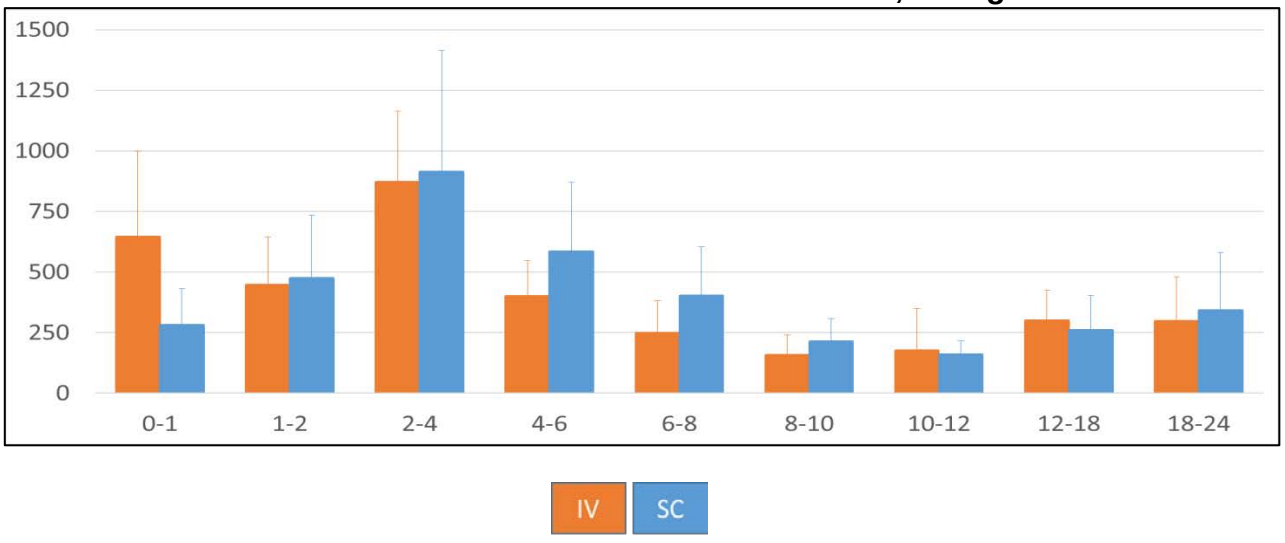
Route (80 mg)	Total Urine Output (mL)		Total Urinary Sodium Excretion (mmol)	
	(0-8h)	(0-24h)	(0-8h)	(0-24h)
IV (80 mg) (n=16/16)	2610 ±766 (29.4%)	3538 ±893 (25.2%)	292 ±111 (38.0%)	350 ±135 (38.6%)
SC (80 mg) (n=16/16)	2654 ±987 (37.2%)	3630 ±1011 (27.9%)	284 ±126 (44.4%)	341 ±121 (35.5%)
Difference (95% CIs)	-44.4 (-488, 399)	-91.4 (-603, 420)	8.39 (-53.4, 70.2)	8.43 (-60.1, 77.0)

Source: Clinical Pharmacology Review, Table 2-3.

Taken as a whole, the data from Study 01-002 indicate that delivery of furosemide by the SC route over 5 hours is feasible and provides exposure (as assessed by AUC parameters over at least 8 hours) and PD effects similar to those obtained with IV bolus administration of the same total dose.

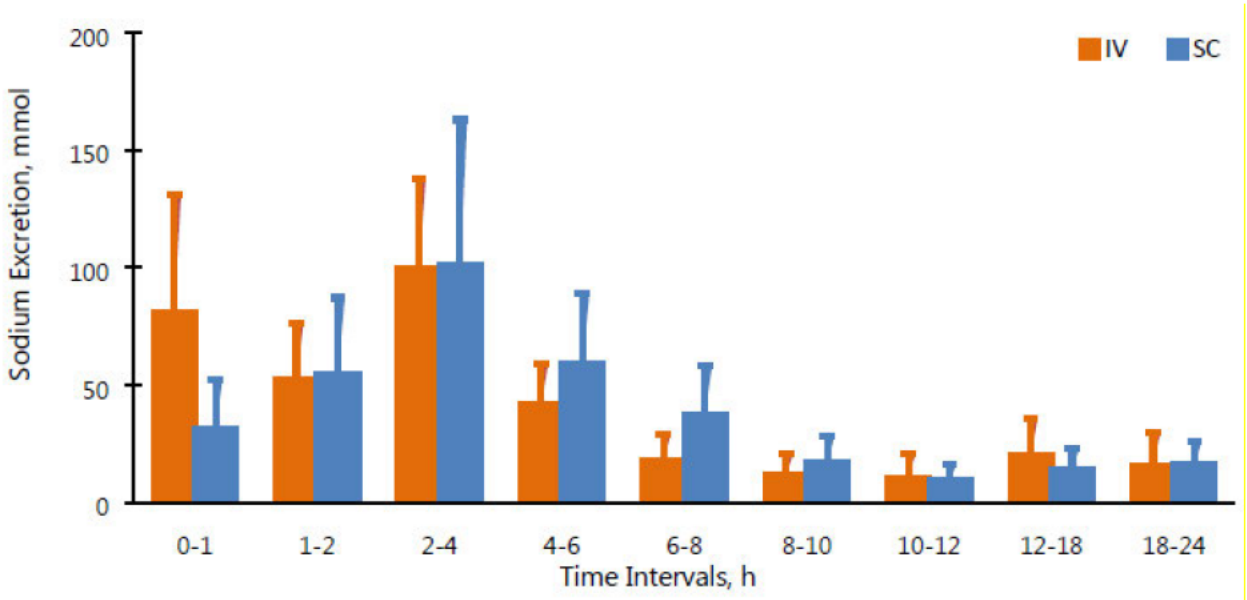
However, as one might expect, when different time cut points are used, the pharmacodynamic advantage of IV administration for excretion of fluid and sodium in the first hour after the start of treatment is clear. The data indicate that IV infusion of furosemide would be preferable to SC infusion when a rapid diuresis is desired, such as in patients with acute pulmonary edema (**Figure 4**, **Figure 5**).

Figure 4 Urine volume (Mean ± SE) in Discrete Time Periods following Subcutaneous or Intravenous Furosemide, 80 mg



Source: Clinical Pharmacology Review, Figure 2-2

Figure 5 Sodium Excretion (Mean ± SE) in Discrete Time Periods following Subcutaneous or Intravenous Furosemide, 80 mg



Source: Clinical Pharmacology Review, Figure 2-4

In addition, the reviewers evaluated the "bridge" between the SC infusion data from the PK/PD study (using the Braun pump) and the Product Design Clinical Validation (PDCV) study, CP-00001. This study was performed in 66 patients with heart failure treated with Furoscix 80 mg, administered SC using the Furoscix infusor. Only the PK data from the PDCV study are discussed here. The study is discussed in greater depth below in Sec. 7.

As described earlier, the PK/PD study establishes a bridge from bolus IV infusion of furosemide to SC infusion with the Braun pump. The bridge between the Braun pump and the Furoscix pump is based on data from the PK/PD study and the PDCV study for (1) mean furosemide plasma concentrations at baseline (resulting from the patients' prior oral furosemide use) and (2) mean furosemide plasma concentrations during the 1 to 5 hour plateau period of the SC infusion, when the infusion rate of each pump was 12.5 mg furosemide/hr (**Table 3**). The data show a small absolute difference between studies at baseline (~20 ng/mL) and a larger absolute difference during the plateau phase (~400 ng/mL), with higher mean concentrations observed with the Furoscix pump at each time. Variance of the mean concentration is somewhat higher with the Furoscix pump that with the Braun Pump during the plateau phase. However, the mean plateau levels with either pump (roughly 2000 ng/mL) are well below the mean Cmax of furosemide 80 mg IV in the PK/PD study (~ 8000 ng/mL), suggesting adequate safety with the Furoscix pump based on Cmax. Also, current labeling of furosemide injection supports continuous IV infusion at a rate as high as 4 mg/min (240 mg/hr, 19.2 X the plateau infusion rate of 12.5 mg/min), which ought to be associated with plasma furosemide levels far above those observed during the plateau phase of either of the two pump studies. Thus, the somewhat higher plateau plasma concentrations levels observed with the Furoscix pump compared to the Braun pump are not worrisome. I agree with the OCP reviewers that the bridging data from this study are adequate to support approval, but they do not account for the possibility that underdosing due to occasional or repeated device failure could lead to fluid accumulation and hospitalization for ADHF, potentially leading to an increased risk of death.

Table 3 Comparison of Furosemide Concentrations Observed during Plateau Phase (1 to 5h) of Subcutaneous Infusion (PDCV Versus PK/PD Study).

Products	Pump	Pre-dose (baseline; ng/mL)	Post-dose (1-5h plateau; ng/mL)
PDCV Study (SC; n=66)	Infusor (to-be marketed*)	87.9 ±95.9 (109%)	2160 ±766 (35.5%)
PK/PD Study (SC; n=16)	Braun (Commercial pump)	66.7 ±230 (345%)	1780 ±405 (22.8%)

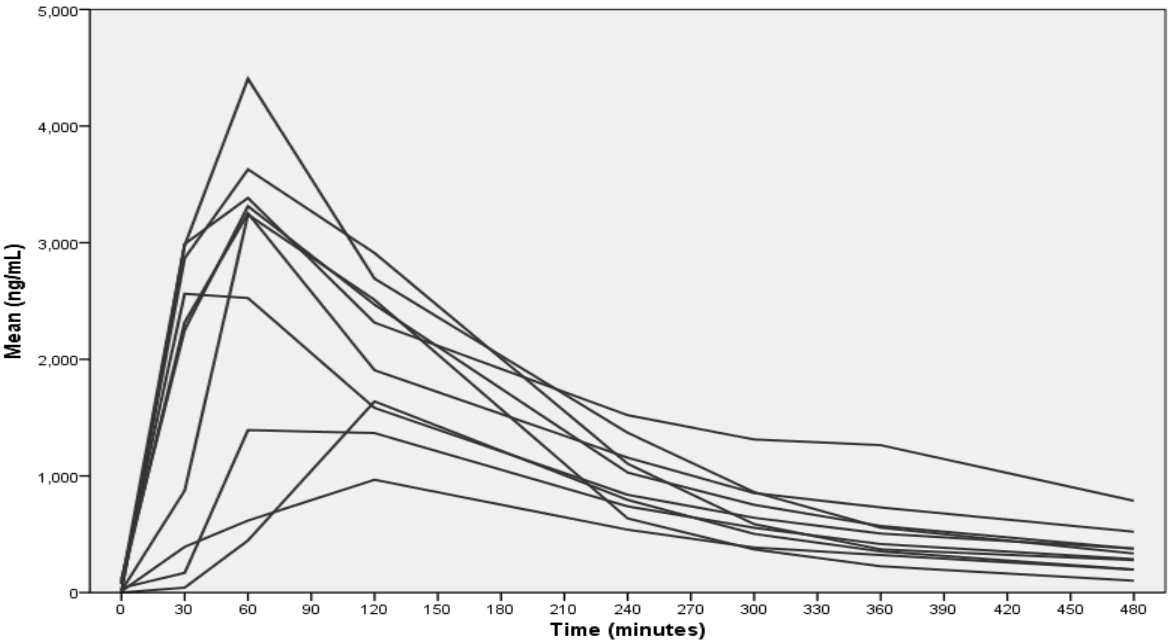
Source: Clinical Pharmacology Review, Table 2-4

There was one clinical pharmacology study that was not reviewed by the OCP reviewers. This was study SCP-01-001, a single center, random sequence, two-period crossover PK/PD trial in patients with HF, with evidence of fluid overload and also elevated NT-proBNP. Subjects received a single dose of 80 mg furosemide by two routes, separated by 14 +- 7 days. The two treatments were and an 80 mg Lasix oral tablet and 10 mL SCP 101, a novel furosemide solution, 8 mg/mL, infused SC in the abdominal area with a marketed Braun infusion pump,. Subjects were confined for 8 hours after each treatment. Assessments included urine output, urinary sodium, and serum furosemide levels at 0, 30, 60, 120, 240, 300, 360 and 480 minutes post-dose, using a "validated LC-MS/MS analytical method." However, urine output assessments were confounded by a misunderstanding of the protocol, which resulted in a lack of standardization of fluid intake.

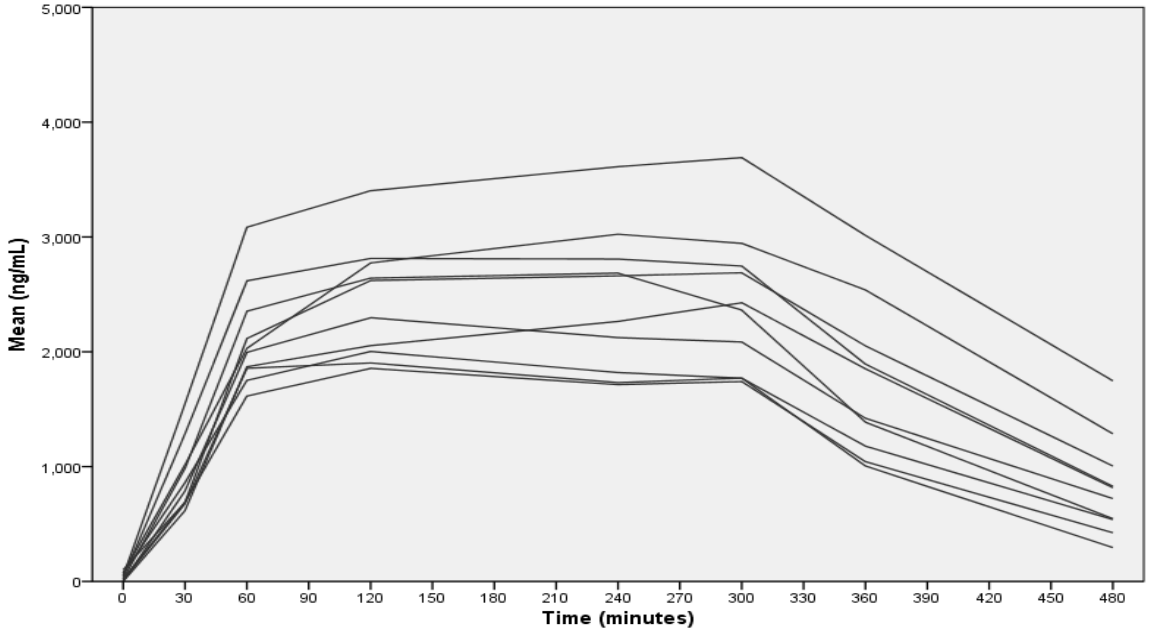
PK data from the two periods are shown in **Figure 6**. Graphics A and B provide data for the oral and SC periods, respectively (N=10 for each).

Figure 6 Mean Furosemide Concentration (ng/mL)

A. Oral Period



B. SC Period



I could find no summary statistics for the PK parameters, but visual inspection of the two plots indicates that there was less inter-subject variability in C_{max} and in apparent AUClast during the SC infusion period than the oral tablet period. Unfortunately, the Applicant did not perform a similar study comparing the Furoscix Infusor to oral furosemide.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

The joint Clinical/Statistical review was performed by Drs. Melanie Blank and Steven Bai. They recommend a Complete Response on the basis of lack of substantial evidence of effectiveness. Their conclusion is based on the failure of the infusor to meet its pre-specified performance goals with respect to reliable delivery of furosemide to study patients in the PDCV study in patients with heart failure (HF). They argue that failure of the device to deliver the entire planned 80 mg dose of furosemide to a patient with HF, (b) (4) (b) (4) could result in an unacceptable rate of under-diuresis and fluid overload. In a patient with chronic stable HF, fluid overload could trigger a hospitalization for acute decompensated HF (ADHF), which is associated with a notably increased risk of death during hospitalization and for over a year after discharge (see Section 2.1, **above**).

I agree with Drs. Blank and Bai regarding the above. To cure these performance defects, the Applicant should redesign the pump so that it (1) meets its performance criteria when used by patients or lay caregivers (b) (4) (b) (4)

I agree with the OCP reviewers that biosimilarity of an SC infusion of a novel furosemide solution using the Braun pump to IV bolus infusion of the furosemide injection (Hospira, NDA 18667) was established in the PK/PD study.

The remainder of this section of the review will focus primarily on the PDCV study, CP-00001. This was an open label, single-arm, single-dose study at 5 US centers to evaluate the clinical performance of the to-be-marketed drug-device combination product in up to 70 adult male and female subjects previously diagnosed with HF. The objectives of the study were:

- To demonstrate that the Furoscix + Infusor combination product performs as intended and delivers 80 mg of furosemide subcutaneously in the abdominal area
- To assess safety and local tolerance of the combination product.

Subjects had NYHA Class II-IV HF, without regard to ejection fraction. Exclusions included contraindication to furosemide, skin reactions to adhesives, serum K < 3.6 mEq/L, SBP < 90 mmHg, pregnancy, or lactation.

On the study day, subjects could not ingest an oral diuretic within 8 hours of the planned study treatment. The study treatment was a 5 hour infusion of Furoscix (total of 80 mg) into the subcutaneous tissue of the abdomen, using the Furoscix infusor. The infusion was similar to the one in the PK/PD study: 30 mg in the first hour, then 4 hours at 12.5 mg/hr. Blood samples were drawn for plasma drug levels at Hour 0 (pre-dose) and then once at some point during the plateau phase (Hours 1 to 5).

The primary endpoint was "Absence of Major Product Failures" including evidence of ineffective drug delivery as intended:

- Failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements), OR
- a combination of obvious leakage AND failure to achieve furosemide plasma levels >250 ng/mL during plateau phase of delivery (1-5 hours following activation).

  *Note: In the PK/PD study, the mean furosemide concentration during the plateau period of SC infusion, using the Braun pump, was near 2000 ng/mL (**Figure 2**). Thus, a plasma level less of 250 ng/mL or less might suggest very substantial leakage or some other failure to deliver furosemide.*

The specified analysis of this endpoint was stated as "The rate of successful infusion is compared to a minimum 95% success rate using a one-tailed binomial test." The MITT population was to be used for the primary endpoint analysis. Subject who did not complete the full 5 hour infusion were excluded from this analysis.

Results: A total of 74 subjects received study treatment; 67 of these completed 5 hours of treatment and comprised the MITT population. Of the 7 who did not complete the infusion, 5 had pumps with software failures that triggered an alarm and one was due to disconnection of the cartridge from the activator, which also triggered the alarm. The 1 remaining non-completer was a subject who asked to discontinue the infusion 15 minutes before the planned end of the infusion because of discomfort.

Of these 67 subjects in the MITT population, 63 met the Applicant's success criteria (94.0%, 95% CI: (b) (4)) (per Dr. Bai). The Applicant reports the CI as 85 (b) (4)%, 98 (b) (4)%. Neither calculation meets the pre-specified success criteria for the trial -- a lower limit of the 95% CI not less than 95%. I agree with the clinical and statistical reviewers that these results do not satisfy the prespecified success criteria for the study.

All 4 of the failures in the MITT had drug delivery less than 10 mL ± 10%. Three of these were due to filling errors and one to a dispensing error (b) (4) (b) (4). None of these failures produced any sort of alarm.

The Applicant notes that all 4 failures had plateau period plasma furosemide levels above the 250 ng/mL level that would indicate failure if associated with leakage. The mean plasma level of the 4 was 1319 ng/mL (range 763 - 1993). While these levels may have produced an adequate diuresis, we don't know because urine volume was not measured.

We do know, however, of the subjects in the MITT population (all of whom had 5-hour infusions), 6% had filling or dispensing errors. It is noteworthy that the site staff set up the infusor for each subject, not the subject or a lay caregiver. We don't know how many more subjects might have had failures if the patients or a family member had been required to set up the infusors. I agree with Dr. Blank that this is a critical deficiency in the study data, because we expect that many patient or their family members will be setting up the infusors if this product is marketed.

The Applicant's analysis and all the statistics described above do not include the 7 patients who were treated but not included in the MITT population.

See Sec. 14 for a discussion of benefits and risks.

8. Safety

The systemic risks of furosemide are well-established. Because furosemide AUC with 80 mg delivered over 5 hours is similar to that obtained with 80 mg furosemide given IV, and C_{max} is less with SC infusion, we can assume that the systemic risks of Furoscix will be no greater than those of IV furosemide. While total human exposure to SC furosemide in this development program has been modest (N=xx), it seems sufficient. There have been no demonstrated device-related safety risks, and no important risks that appear to be peculiar to SC administration of furosemide. Application site risks related to irritation, allergy or infection were not common and were manageable in the clinical experience. The only risk that seems important is the risk of underdosing due to unappreciated device failure, which is discussed in Sec. 7. See Sec. 14 for a discussion of benefits and risks.

9. Advisory Committee Meeting

Both disciplines that reviewed the Applicant's confirmatory PDCV study, CDRH and DCRP Clinical/Statistical, recommended a CR because the study did not meet its primary endpoint, infusion of 10 mL $\pm$ 10% of furosemide solution in at least 95% of presumably completed infusions. In addition, the DMEPA reviewers also recommended a CR because of the Clinical reviewer's belief that unrecognized failure to deliver the full dose of furosemide could increase the risk of hospitalization for ADHF, leading to increased risk of death. Thus, all the disciplines that focused on clinical outcomes recommended a CR, and there are no disputed issues that require input from an Advisory Committee (AC). Accordingly, I recommend that we not convene an AC meeting for this application.

10. Pediatrics

The clinical/statistical review indicates that:

> "Similar PK/PD relationships in children provide evidence of extrapolatable efficacy for children who are large enough to accommodate the device on their abdomens and weigh enough so that the dose of 80 mg is appropriate (42.5 kg and above). Because of the fixed size of the device, the product will be contraindicated in younger/smaller children because it would be too cumbersome for young children and unsafe for children who weigh < 42.5 kg because of the fixed dose."

I concur, and recommend that no pediatric studies should be required.

11. Other Relevant Regulatory Issues

DMEPA has completed an extensive review of human factors validation information (including 4 human factors studies), labels, labeling and training information, including videos. The primary and secondary reviewers were Sarah Thomas and Chi-Ming (Alice) Tu, respectively. They conclude that,

> "The Human Factors Validation Studies identified use errors that could result in delay in treatment, partial treatment, or treatment omission. If patients do not receive the full intended treatment, or treatment is delayed, they would experience a continuation of symptoms. We acknowledge that the applicant did not consider these use errors to be critical to the safe and

effective use of the product because the product is not intended for use in emergency situations (i.e., for the treatment of acute heart failure symptoms or pulmonary edema).

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

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

The review includes a list of recommendations for labeling, labels and IFU. More importantly, it includes recommendations for the Applicant regarding their use-related risk analysis and human factors protocol methodology. These are set forth below. Note that here, "HF" refers to human factors, not heart failure:

1. "Use errors that can cause potential serious harm (including compromised medical treatment, contamination, and infection) should be evaluated as critical tasks.
2. Hazards that can cause potential damage to the device (i.e., disengaging the device by force) may not be detected and may result in delay of treatment or treatment omission with subsequent treatments. Implement additional mitigation strategies to communicate hazardous situations to the users, and ensure your use-related risk analysis and HF protocol evaluate such hazards and associated mitigations accordingly.
3. Ensure the training methodology employed in your future HF testing (including trainers, training materials, and training decay periods) reflect the training that intended users would receive in real-world, and include justification for the training methodology.
4. We expect your HF study report to document subjective feedback collected from study participants for all use errors, difficulties, and close calls (including participant's feedback on potential root cause of the use errors, difficulties, and close calls).
5. We expect your HF study to test the final intend-to-market user interface or provide justification for not testing alterations. Alterations to the device in your HF studies (b) (4) (b) (4)) may have limited testing of the full functionality of the device and effectiveness of the user interface in the simulated studies (b) (4) and confounds the interpretation of the study results. Furthermore, because you made changes (b) (4) (b) (4) after HF studies 123 and 133, you may not have adequately validated your final user interface (b) (4) in the intended user populations.
6. We expect your HF study to evaluate user ability to understand all warnings, alerts, and troubleshooting the device. We consider user's understanding of critical warnings, alerts,

and ability to troubleshoot the device to be critical tasks and should be evaluated in HF validation testing."

12. Labeling

Deferred.

13. Postmarketing Recommendations

Not applicable.

14. Risk-Benefit Analysis and Recommendations

The analysis of benefits and risk is greatly complicated by the nature of the efficacy data. The only endpoints were pharmacokinetic, pharmacodynamic (urine volume or urinary sodium excretion), or the rate of successful infusion of the contents of a Furoscix vial using the Furoscix Infusor. None of these are suitable for a comparison to the rate of observed adverse events. It should be noted that observed toxicity was quite modest.

However, as noted in Sections 2 and 7, the Furoscix Infusor failed to meet its primary endpoint in the PDCV study, which involved the rate of successful infusion of the vial contents. It is notable that in this study, the device was set up by trained site staff, not patients or their caregivers. One might expect a higher rate of failure in the postmarketing setting when setup is performed by patients or family caregivers. Failure to infuse the entire contents of the vial, especially if repeated over several days, could lead to inadequate diuresis and hospitalization for ADHF, leading to an increased risk of death. Although all use in the PDCV study was single-dose, one might expect multiple failures in the postmarketing setting, given that (b) (4) setup failures might be repeated by an inadequately trained or inattentive patient or caregiver. While this scenario of device failure leading to ADHF and hospitalization has not been proven to occur, it seems possible and its true rate if the device is marketed as-is may not be trivially small. Moreover, the likelihood of the occurrence of this scenario could probably be reduced by re-engineering the device (b) (4) (b) (4).

Accordingly, I believe a CR is appropriate here to protect patients from the risk of device failure, as well as other deficiencies described by OPQ, CDRH and DMEPA. A CRL with an extensive list of deficiencies from DCRP clinical staff and the three review disciplines named in the previous sentence has been drafted. Some are described in the text of this review.

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/s/

MARTIN ROSE
06/08/2018