Summary Basis for Regulatory Action

Date: August 1, 2019

From: Elena Karnaukhova, Ph.D., Review Committee Chair

NDA STN#: BN125695/0

Applicant Name: Fresenius Kabi AG

Date of Submission: September 28, 2018

Goal Date: September 5, 2019

Product: 0.9% Sodium Chloride Injection USP

Proprietary Name/ Established Name: N/A

Indication: A pre-attached subassembly component of an apheresis kit for apheresis kit priming and/or for use as a replenishment fluid to maintain isovolemia in subjects undergoing an apheresis procedure.

Recommended Action: The Review Committee recommends approval

Review Office Signatory Authority: Nicole Verdun, M.D., Director, OBRR

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The table below indicates the material reviewed when developing the SBRA

Document title	**Reviewer name, Document date**
CMC Review(s) • *CMC (product office)* • *Facilities review (OCBQ/DMPQ)* • *Establishment Inspection Report (OCBQ/DMPQ)*	Elena Karnaukhova, July 25, 2019 Lily Koo, July 31, 2019 Not applicable (inspection waiver)

Clinical Review(s) • *Clinical (product office)* • *Postmarketing safety epidemiological review (OBE/DE)* • *BIMO*	Not applicable for this submission
Statistical Review(s) • *Clinical data* • *Non-clinical data*	Not applicable for this submission
Pharmacology/Toxicology Review(s) • *Toxicology (product office)* • *Developmental toxicology (product office)* • *Animal pharmacology*	Jin Hyen Baek, July 19, 2019
Clinical Pharmacology Review(s)	Not applicable for this submission
Labeling Review(s) • *(OBRR)*	Lorraine Wood and Elena Karnaukhova, July 26, 2019.
Other Review(s) • *additional reviews not captured in above categories* • *consult review* (CDRH)	Katherine Vorvolakos, March 3, 2019
Advisory Committee summary	Not applicable for this submission

1. INTRODUCTION

Fresenius Kabi AG submitted a New Drug Application (NDA) for in-sourcing the manufacture of 0.9% Sodium Chloride Injection USP for use in Fresenius Kabi apheresis kits that are separately regulated as medical devices. Fresenius Kabi apheresis kits are cleared as Class II medical devices.

The 0.9% Sodium Chloride Injection USP (also referred to as Saline Solution) will be a pre-attached subassembly component of apheresis kits used on a corresponding apheresis medical device for blood collection and processing. The Saline Solution will be manufactured in the Fresenius Kabi facility located in (b) (4) .

2. BACKGROUND

Meetings with FDA:

Prior to submitting this Original NDA, Fresenius Kabi requested a pre-submission meeting with FDA to discuss the scope of the application and submitted the Meeting Package on December 22, 2017. FDA provided responses to the sponsor questions on February 21, 2018.

0.9% Sodium Chloride Injection USP (General)

0.9% Sodium Chloride Injection USP is a solution containing 900 mg of USP grade Sodium Chloride (NaCl) in Water for Injection (WFI) for every 100 mL of the total solution. Sodium Chloride USP provides an isotonic solution environment. Water for Injection USP serves as a vehicle and is the only excipient used in the manufacture of 0.9% Sodium Chloride Injection USP drug product which meets the requirements of the current USP monograph. There are no other excipients in the drug product formulation.

The Saline Solution is designated as physiological sodium chloride solution (due to its osmolarity of approximately 308 mosmol/L). The cation Na+ and the anion Cl- are the predominant electrolytes in extracellular fluid, thus predetermining the most common indications for Saline Solution in general: isotonic fluid replacement, or as a solvent and vehicle for biologicals, drugs or other electrolytes.

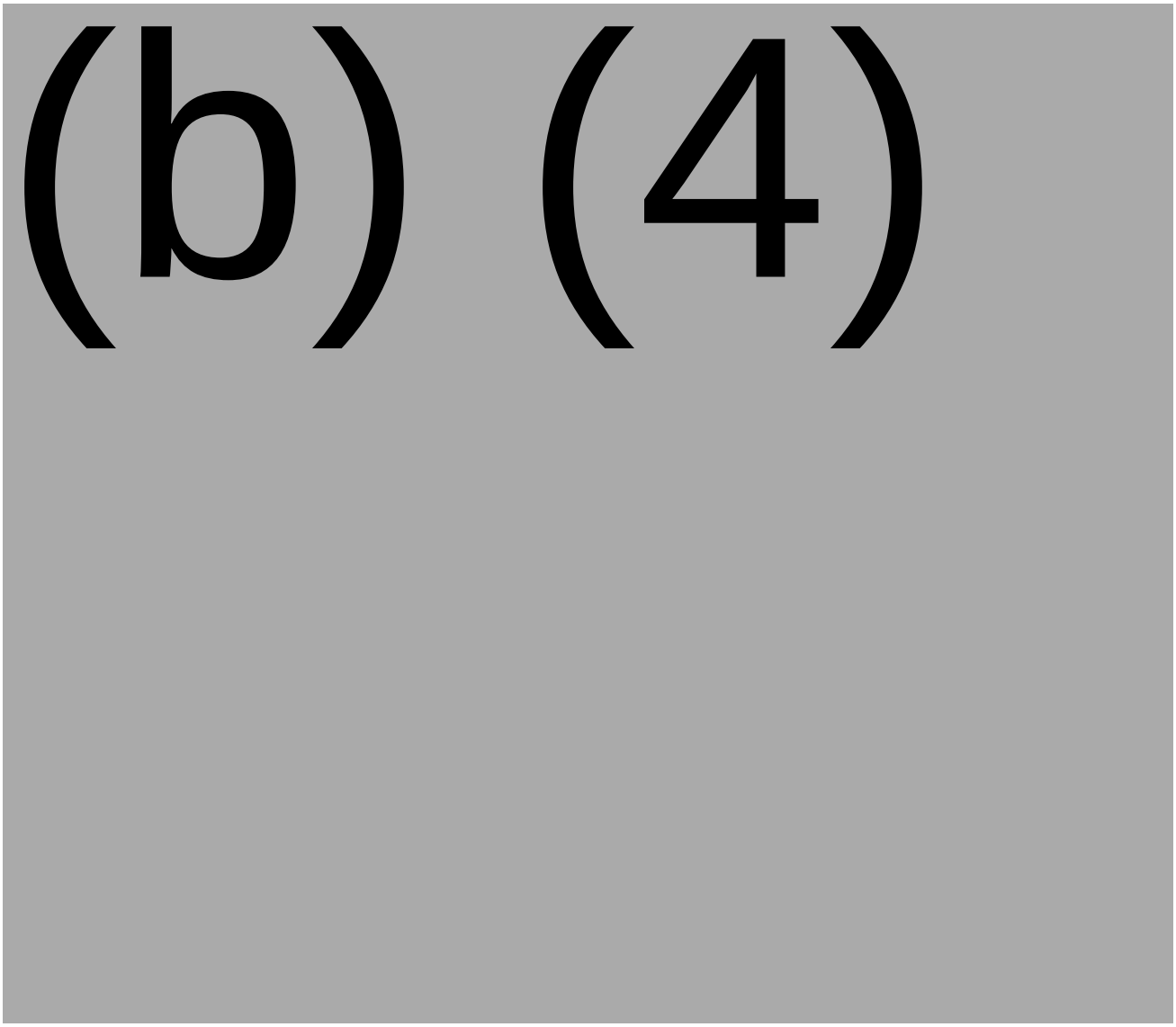
The pH of Saline Solution ranges from (b) (4) . Adjustment to physiological pH of (b) (4) is achieved by adding (b) (4) .

The container closure system used in (b) (4) for the 0.9% Sodium Chloride Injection USP subassembly product is (b) (4) material which is qualified for use in storage of pharmaceutical goods. Fenwal receives the fully-formed empty containers with integrated port tube from (b) (4) , an approved external supplier that fabricates them. The closure system consists of a polycarbonate frangible molded from (b) (4) sourced from (b) (4) .

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

Manufacturing steps for 0.9% Sodium Chloride Injection USP includes manufacturing of the solution, thermal printing of the containers, solution filling, sterilization operations, quality control testing, final product release testing, packaging and shipping. The flow diagram below shows manufacturing operations, solution formulation ingredients and container component

Figure 1. Manufacturing Flow Diagram



Container/ Closure

The drug product is filled into 500 mL polypropylene containers ((b) (4)), which includes one port assembly as the closure. The closure assembly is composed of a molded polycarbonate frangible and a molded (b) (4) frangible housing of (b) (4) construction. Fresenius Kabi performed container closure integrity testing employing an (b) (4) test; the acceptance criterion was met.

Water for Injection System

Water for Injection (WFI) at the Fenwal facility in (b) (4) is supplied from an in-house water system and used for (b) (4) preparation of the product solution. The supply system is qualified to meet USP requirements. The facility has monitoring and maintenance systems in place.

a) Product Quality

The manufacturer performed quality control for 0.9% Sodium Chloride Injection USP drug substance in accordance with USP and by using compendial analytical methods. Prior to implementation, the compendial methods have been verified according USP (b) (4) .

Table 1 lists final release specification for 0.9% Sodium Chloride USP, including analytical methods used for testing. The acceptance criteria limits match the requirements of the current USP monograph.

Table 1. Sodium Chloride USP Specification

Test	Method	Acceptance Criteria
Sodium Identification	(b) (4)	Positive
Sodium Identification		Positive
Chloride Identification		Positive
Appearance of Solution	Clear and colorless	Pass
Acidity or alkalinity	(b) (4)	Pass
(b) (4)		(b) (4)
		Pass
		Pass
		(b) (4)
		Pass
		(b) (4)
		Pass
Bacterial Endotoxins		(b) (4)

NMT=Not More Than

To assure the consistency of manufacturing procedures, the manufacturer provided batch analysis data for three consecutive lots of Sodium Chloride USP.

All test results for the conformance lots met the specification acceptance criteria, thus supporting the conclusion that 0.9% Sodium Chloride Injection USP drug product meets the requirements of the current USP monograph.

The manufacturing process for 0.9% Sodium Chloride Injection USP includes several Critical Control Points to ensure that the product is free from impurities. The manufacturing process controls are fully described in the Plant HACCP (Hazard Analysis Critical Control Points) Manual.

b) CBER Lot Release (only applicable for BLAs)

Not applicable for this submission.

c) Facilities review/inspection

The facilities involved in the manufacture of 0.9% Sodium Chloride Injection USP are listed in the table below. The activities performed and inspectional histories are noted in the Table 2.

Table 2: Facility Information and Inspectional History

Name/Address	FEI number	DUNS number	Inspection/ waiver	Justification /Results
Drug Substance, Drug Product, Terminal Sterilization, Release Testing Fenwal International, Inc. (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI
Release Testing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI

Active Pharmaceutical Ingredient (Sodium Chloride, USP) Manufacturing (b) (4)	(b) (4)	(b) (4)	Waived	ORA (b) (4) NAI

ORA conducted a surveillance inspection at Fenwal International, Inc. in (b) (4) and a Form FDA 483 was issued at the end of the inspection. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved and the inspection was classified as voluntary action indicated (VAI).

ORA performed a surveillance inspection of the (b) (4) from (b) (4). A Form FDA 483 was issued at the end of the inspection. The firm has responded to the observations and the corrective actions were reviewed and found to be adequate. All inspectional issues were resolved and the inspection was classified as VAI.

ORA performed a surveillance inspection of the (b) (4) from (b) (4). No Form FDA 483 was issued at the end of the inspection. The inspection was classified as no action indicated (NAI).

d) Stability

Stability testing is performed at (b) (4). The most recent inspection of the (b) (4) testing facility was conducted by ORA in (b) (4) (from (b) (4)) and classified as VAI.

To support a proposed shelf-life of 18 months, (b) (4) pre-market stability batches were subjected to stability monitoring at 25±2 °C/(b) (4). The results obtained support the recommended storage conditions. In addition, Fresenius Kabi will conduct stability testing on the (b) (4) commercial batches through the assigned shelf life of the product. Subsequently, the product will be monitored on an (b) (4) basis by using selected samples from regular production batches, and the results will be communicated to the FDA in annual reporting.

e) Environmental Assessment

The NDA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution

of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

f) Product Comparability

The 0.9% Sodium Chloride Injection USP drug product manufactured by Fresenius Kabi meets the requirements of the current USP monograph and is identical to the other approved 0.9% Sodium Chloride USP solutions.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There were no new nonclinical toxicology studies conducted with the 0.9% Sodium Chloride Injection USP. The safety of the container closure system was qualified based on biocompatibility analysis and the analysis and safety assessment of the extractables and leachables. Biocompatibility findings were within acceptable limits, and in keeping with ISO-10993 standards. The container closure system produced minimal extractables and leachables components under the proposed conditions and duration of clinical use. The amounts of the identified materials were within the safety limit based on the toxicological safety assessment.

5. CLINICAL PHARMACOLOGY

Not applicable for this submission.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

Not applicable for this submission.

7. SAFETY

Since first approved in 1970 (Baxter, NDA 016677, approved 12/09/1970), 0.9% Sodium Chloride Injection USP (Saline Solution) has a long-term record of safety. The Saline Solution under current application is identical to 0.9% Sodium Chloride Injection USP except for some differences in the container material. Fresenius Kabi is seeking approval for 0.9% Sodium Chloride Injection USP that will be used exclusively as a subassembly solution to the Alyx Apheresis Kit. The safety of the container closure system was qualified based on biocompatibility analysis and the analysis and safety assessment of the extractables and leachables with all findings within acceptable limits and in accordance with ISO-10993 standards.

8. ADVISORY COMMITTEE MEETING

OBRR reviewed information provided in this application and determined that referral to the Blood Products Advisory Committee (BPAC) prior to licensure was not needed.

9. OTHER RELEVANT REGULATORY ISSUES

None.

10. LABELING

The Saline Solution described in this application is a pre-attached subassembly to Fresenius Kabi apheresis kits. Under this application, it is not intended for any direct intravenous infusion and must be used on apheresis devices only. As such, the primary container label is the only level of labeling for this subassembly product. The proposed primary label for 0.9% Sodium Chloride Injection USP, a subassembly component, is considered acceptable.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee members, representing the necessary review disciplines recommend approval. These were independent conclusions based on content of the NDA application. No internal or external disagreements were brought to the attention of the chairperson.

b) Risk/ Benefit Assessment

The product, 0.9% Sodium Chloride Injection USP, has a long-term safety record. It has been used for widespread clinical indications, as well as an ingredient/excipient of numerous approved protein therapeutic solutions, and as a subassembly component of an apheresis kit. Saline solutions are commonly used for priming the apheresis device and as a replenishment fluid to maintain isovolemia in subjects undergoing an apheresis procedure. These activities ensure the safety of blood donors undergoing apheresis procedures.

c) Recommendation for Postmarketing Activities

The FDA agreed to Fresenius Kabi commitments to complete stability monitoring of (b) (4) pre-market stability batches through the assigned shelf life of the product (18 months) and to conduct stability testing on the (b) (4) commercial batches of 0.9% Sodium Chloride Injection USP to comply with the requirements of ICH Q1A(R2), “Stability Testing of New Drugs and Products.” Further, the product will be monitored on an (b) (4) basis

as part of Fresenius Kabi QC Stability Program, and the results will be communicated to FDA in annual reporting.