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RESEARCH**

APPLICATION NUMBER:

202832Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	December 20, 2011
From	Alan C. Schroeder, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 202832
Applicant	Medefil, Inc.
Date of Submission	January 31, 2011; clock started March 7, 2011
PDUFA Goal Date	January 7, 2012
Proprietary Name / Established (USAN) names	none currently proposed sodium chloride
Dosage forms / Strength	injection/0.9%
Proposed Indication(s)	1. diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered.
Recommended:	Approval

1. Introduction

This memorandum provides an overview of the review of the original submission and its amendments. See the “background” section below.

2. Background

The following background information was provided in the clinical review by Xu Wang, M.D., Ph.D.

“This is a 505(b)(2) application for sodium chloride injection, USP, 0.9% in plastic syringes submitted by Medefil, Inc. The Applicant cites 2 products of 0.9% sodium chloride injection manufactured by Hospira and (b) (4) (NDA 19-217 and ANDA 88-912) as the reference products. The originally proposed trade name for the product was (b) (4) however, on July 11, 2011, the Applicant withdrew the proposed name. At the time of finalization of this review, no new trade name has been proposed for the product. The proposed indication is for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection.. The dosage forms of the product are 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL syringes and 3 mL, 5 mL and 10 mL fill in 12 mL syringes for single use.”

“This product has also been evaluated by CDRH under the 510(k) process and it was determined to be “substantially equivalent to legally marketed predicate devices”, and,

thus, could be marketed as a device with the intention for use of flushing compatible intravenous tubing and/or indwelling intravenous access devices.”

“Medefil submitted the NDA application to the Division of Gastroenterology Products on January 31, 2011 and it was received on February 1, 2011. However, the submission was incomplete and was not accepted for filing since the appropriate user fee was not received at the time of the submission. Subsequently, the user fee for this application was waived on March 7, 2011. Therefore, the application has been accepted as of March 7, 2011. The PDUFA action date is January 7, 2012. In addition, CDER reassigned the application to the Division of Pulmonary, Allergy, and Rheumatology Products on March 7, 2011.”

The proposed drug products were previously submitted in IND (b) (4) to The Division of Gastrointestinal and Hematology Products (DGHP). The sponsor had requested a meeting and submitted a premeeting package dated May 14, 2008. The sponsor was granted a meeting on July 14, 2008. DGHP sent responses to the sponsor’s questions in advance of the meeting and it was subsequently cancelled. DGHP provided comments from the OPS microbiology reviewer, Anastasia G. Lolas, and DGHP agreed that non-clinical studies, in vivo bioavailability requirements, and clinical studies would not be required for the proposed products. In addition, DGHP agreed that the products may be submitted under section 505(b)(2) of the Act.

Subsequent to the clinical review, referenced above, it was determined by the Division of Pulmonary, Allergy and Rheumatology Products and by Beth Duvall, Associate Director of Regulatory Affairs, CDER, that this 505(b)(2) NDA only relies on NDA 18803 as the listed drug. NDA 18803 is for Hospira Worldwide, Inc.’s sodium chloride injection, 0.9%,

3. CMC/Device

The recommended action from the CMC perspective is Approval. No other CMC issues remain outstanding.

- **General product quality considerations**

The drug substance, sodium chloride, USP, is an inorganic salt. Stability data (b) (4) have been provided to ensure its stability and quality on storage. The sodium chloride is provided in (b) (4)

The drug product is sodium chloride injection, USP, 0.9%. It is contained in a disposable, single-use plastic syringe and it is to be used for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection. The drug formulation only contains sodium chloride, USP and water for injection, USP. The drug product presentations are as follows: 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL, each in a 6 mL syringe, and, 3 mL, 5 mL and 10 mL, each in a 12 mL syringe.

The following information is from the chemist's review (Dr. Edwin Jao): "The drug product is currently marketed in USA as Normal Saline I. V. Flush Syringes under two 510(k)s. It was approved by CDRH first as K020999 on 6/20/2002, then as K091583 on 1/28/2010. The two 510(k)s differ only in the sterilization method used: the first one used aseptic fill while the second one used terminal sterilization." This product was approved as a device for use in maintaining patency of in-dwelling intravenous access devices (IVAD). "The drug product submitted in this NDA is identical in composition, strength, packaging, and manufacturing process to the ones that are currently marketed under 510(k), except for the color of the labels and tip caps. [from the primary CMC review]

The syringe is made of (b) (4) it contains a luer-lock (b) (4). The tip caps are (b) (4) "peach/white" in color. The plunger stoppers are (b) (4) black (b) (4). The plunger rods are (b) (4). Finished syringes are individually placed into a (b) (4) overwrap for protection from dust, and sixty filled syringes are packaged in each dispensing box.

(b) (4)
Container closure integrity was tested and found to be adequate. The process validation of the (b) (4) of container closure components was found to be adequate. Specifications and methods for control of the sterility and endotoxins are adequate. This is all addressed in the microbiology review. All components of the syringe (container closure system) in contact with the drug formulation meet USP <87> and <88> requirements, and no leachable concerns were identified.

The (b) (4) impurities controlled by the specifications are limited to (b) (4). Heavy metals are limited to NMT (b) (4). Drug product is controlled by specifications for assay (concentration), pH, bacterial endotoxins, sterility, (b) (4) appearance, weight, volume, (b) (4). An expiration dating period of 2 years was requested by the applicant, and it is acceptable based upon full shelf life stability data. The drug product is labeled for storage at 25°C (77°F) with excursions permitted to 15°-30°C (59°-86°F).

The CMC reviewer has not recommended any post-marketing commitments or risk management steps.

- **Facilities review/inspection**

The drug substance is manufactured by (b) (4). Sodium chloride, USP is manufactured, packaged, tested (release and stability) (b) (4). Primary container closure components are (b) (4). The drug product

manufacturing, filling, labeling and release testing are conducted at Medefil, Inc., Glendale Heights, IL. Stability storage and testing of the drug product are performed by (b) (4). The Establishment Evaluation System (EES) shows that all the above facilities are acceptable as of December 15, 2011, and the overall compliance recommendation for this application is “acceptable” as of December 15, 2011. This has been accepted by the Office of New Drug Quality Assessment.

- **Other notable issues (resolved or outstanding)**

A consult request was submitted to CDRH for evaluation of “the performance, robustness and manufacturability of the device as appropriate” and for a human factors evaluation. The resulting consult review by Keith G. Marin of the General Hospital Devices Branch, CDRH was completed on August 5, 2011 and it recommended that the applicant indicate why there is no mention of heparin in the submission, since two pre-filled heparin syringes are referenced in this submission. Heparin is not an issue in this NDA as the NDA does not propose a heparin product. The CDRH consult review also recommended that a human factors/usability validation study be performed or else that justification be provided for its absence. The CDRH reviewer did not identify any concerns with any of the supporting Drug Master Files for the syringe device.

The CDRH reviewer’s recommendations for a human factors study were discussed in the mid-cycle review team meeting on August 10, 2010. Dr. Xu Wang’s clinical review describes the consensus of the review team with respect to these recommendations. It was decided that the human factors study would not be necessary for the drug labeling indication. The rationale was that the patient would have received needed training and would have obtained skills to correctly use the drug product if the patient was directed to use it according to the labeling. Therefore a human factors study would have no significant impact on user performance and on risk to the user. In addition, it was noted that there are many approved and marketed sodium chloride injections products; human factors studies were not required for approval of these products.

The CDRH reviewer, LT Keith Marin reviewed the NDA and the related DMFs for the container closure system and this review found no performance concerns.

There are no other outstanding concerns pertaining to this drug product.

4. Nonclinical Pharmacology/Toxicology

The application is recommended for approval from a nonclinical pharmacology perspective. The pharmacology/toxicology reviewer (Dr. Luqi Pei) has stated that “the available nonclinical data support the approval of the proposed use of normal saline as a diluent or vehicle for parenteral injection of appropriate drugs, from the nonclinical perspective.” The reviewer commented that “the safety evaluation of leachables associated with the device would be performed separately if requested by the chemistry discipline.” The chemistry reviewer has determined that such a consult review was not necessary. No pharmacology/toxicology

studies were submitted to this NDA, nor were any pharmacology/toxicology data submitted to this NDA. The pharmacology/toxicology reviewer notes that normal saline for a volume diluent or replacement has been approved.

5. Clinical Pharmacology/Biopharmaceutics

The application is recommended for Approval from a Clinical Pharmacology perspective, and there are no outstanding clinical pharmacology issues. There are no clinical pharmacology or clinical studies submitted with this NDA. The clinical pharmacology reviewer (Dr. Lokesh Jain) has noted that “in a pre-IND meeting with the Division of Gastroenterology Products, Agency has agreed upon waiver of in vivo bioavailability requirements.” The meeting minutes were dated July 11, 2008. The reason for the waiver request given by the sponsor is that the proposed product, sodium chloride injection, does not raise pharmacokinetic issues. The clinical pharmacology review states that the Biopharmaceutics group in ONDQA shall review the NDA request for a waiver of in-vivo bioavailability/bioequivalence requirements. The request for a waiver is based on 21 CFR 320.22(b).

This pertains to this Biopharmaceutics issue. The ONDQA Biopharmaceutics reviewer sent an e-mail on December 16, 2011 with the following comment about this issue:

The ONDQA Biopharmaceutics reviewer, Dr. Akm Khairuzzaman is in agreement that the drug product under the NDA 202832, Sodium Chloride Injection does not have any pharmacokinetic issues (e.g. C_{max} , T_{max} , AUC) since the product is just a 0.9% saline to be used as a vehicle. In a pre-IND meeting with the Division of Gastroenterology Products, Agency has agreed upon waiver of in vivo bioavailability requirements based on 21 CFR 320.22(b), i.e., “For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident.” There are no other quality attributes of this product that is necessary to be evaluated from biopharmaceutics point of view and therefore no separate biopharmaceutics review is necessary.

6. Clinical Microbiology

Sodium chloride injection, USP 0.9% is not an antimicrobial product, and the application does not contain any clinical microbiology data.

7. Clinical/Statistical- Efficacy

The clinical review recommends an approval action. There are no clinical data in this application for efficacy. The “drug substance” is sodium chloride which is not an active ingredient. The drug labeling indication is for diluting or dissolving drugs which are compatible with the 0.9% saline.

The statistical review does not actually make a recommendation, but it states that there is no need for a statistical review since as previously agreed, no clinical information was submitted in the NDA. The Agency's premeeting response issued on July 11, 2008 for IND (b) (4) is referenced by the statistical review.

8. Safety

No clinical safety studies have been submitted in the NDA. The applicant has relied for their proposed product, on the Agency's previous finding of safety for the reference product 0.9% sodium chloride injection.

The clinical reviewer (Dr. Xu Wang) has stated that "as a physiologic solution, there is minimal risk to patients who receive small quantities of 0.9% sodium chloride. Thus, the risk and benefit in clinical usage of the proposed product will be determined by the specific drug to be diluted or dissolved. There are many approved and currently marketed saline products on the market. No new safety concerns are apparent for the use of the proposed normal saline solution in pre-filled plastic syringes for single use."

When the applicant was asked, in the 74 day letter, to "submit a summary and update of safety information of the proposed product per regulation 21 CFR 314.50(d)(5)(vi)," the applicant responded that "safety information and clinical evaluation of the 0.9% Normal Saline Injection is equivalent in terms of intended use as other normal saline IV flush syringe devices regularly placed on the market." (This information is from the clinical review.)

See under section 2 of this review for the discussion of the lack of a need for human factors studies for this product, in connection with the consult review received from CDRH.

9. Advisory Committee Meeting

There will be no Advisory Committee meeting for this NDA.

10. Pediatrics

Discussions with the PREA team indicated that this NDA does not trigger PREA. The clinical reviewer has indicated that he sees no pediatric issues for the small amount of saline used to dilute or dissolve other drugs.

11. Other Relevant Regulatory Issues

None.

12. Labeling

The proposed drug product is sodium chloride injection, USP, 0.9%.

The history of the labeling evaluation is addressed in the clinical review (Section 9.2).

The last significant labeling issue is that the labeling is proposed for both drug and device indications. The Study Endpoints and Labeling Development (SEALD) Review Team advised DPARP that the dual drug device labeling which was proposed, was inappropriate. The Division of Pulmonary, Allergy and Rheumatology Products concurs with this assessment. In a telephone conference on December 14, 2011, the sponsor indicated that (b) (4)

(b) (4) In addition, the reference product for the proposed product (Hospira's sodium chloride injection, NDA 18-803) does not have a "flush IV catheter" indication. The applicant will be asked to remove device indications from the labeling.

Final labeling is pending at the time of this memorandum. Draft labeling is comprised of the package insert in PLR format, syringe and carton labels. There are no patient's instructions for use. There is currently no tradename proposed. The originally proposed tradename was (b) (4) which has been withdrawn by the applicant in correspondence dated July 11, 2011 after it was found unacceptable by DMEPA.

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval. The NDA does not contain efficacy and safety data for this drug product, which consists only of 0.9% sodium chloride in pre-filled syringes. Sufficient CMC data were provided in the application to support the identity, strength, quality, purity and stability of the drug product.

- **Risk Benefit Assessment**

The clinical reviewer has noted that there is minimal risk to the patients in the use of this physiologic solution and the small amount of sodium chloride that it contains. The risk and benefit to the patient will be determined by the specific drug to be used with this drug product.

None of the other review disciplines have indicated any specific safety concerns with this drug product. In a consult review, CDRH had recommended a human factors study, but discussion by the review team concluded that for this particular drug product, a human factors study "would have no significant impact on user performance and on risk to the user." (from the clinical review: see the discussion earlier in this review)

There are no outstanding issues from a CMC, nonclinical, clinical pharmacology, or clinical perspective.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No postmarketing risk evaluation and management strategies are recommended.

- **Recommendation for other Postmarketing Requirements and Commitments**

No postmarketing requirements and commitments are requested by the Agency.

- Recommended Comments to Applicant

There are no comments.

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/s/

ALAN C SCHROEDER
12/22/2011