

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202832Orig1s000

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: NDA 202,832
Supporting document/s: Vol. 1.1 – 1.2.
Applicant's letter date: January 18, 2011
CDER stamp date: March 7, 2011
Product: Sodium chloride (0.9%) injectables
Indication: Solvent/ vehicle for parental drugs
Applicant: Medefil Inc.
Review Division: Pulmonary, Allergy and Rheumatology
Reviewer: Luqi Pei, Ph.D.
Team Leader: Timothy Robison, Ph.D.
Division Director: Badrul Chowdhury, M.D., Ph.D.,
Project Manager: Eunice Chung-Davis

Template Version: September 1, 2010

Disclaimer

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1 Executive Summary

1.1 Introduction

This application proposes to register saline-filled syringes. The syringes will be used as a vascular access device to deliver parenteral drugs. The syringes will be pre-filled with up to 10-mL normal saline (0.9% sodium chloride) each. The application contained no nonclinical data per agreement between the Agency and the Applicant in a pre-IND meeting held on July 14, 2008 in IND (b) (4)

1.2 Brief Discussion of Nonclinical Findings

Not applicable because no data were submitted.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from nonclinical perspective. The safety evaluation of leachables associated with the device will be done separately if requested by the chemistry discipline.

1.3.2 Additional Nonclinical Recommendations

None.

1.3.3 Labeling

The following is recommended as the nonclinical sections of the label of the proposed products. See Pages 6 – 7 for labeling review.

(b) (4)



13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of fertility

Studies with Sodium Chloride Injection, USP have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 7647-14-5

Generic Name: normal saline (0.9% sodium chloride)

Code Name: None.

Chemical Name: sodium chloride

Molecular Formula/Molecular Weight: NaCl, 58.4

Structure or Biochemical Description: None.

Pharmacologic Class: salt, electrolytes

2.2 Relevant INDs, NDAs, BLAs and DMFs

There are many approved and currently marketed saline products on the market.

The following two are examples:

NDA 21-569, saline filled syringes (50 or 125 mL each).

NDA 06580 (900 mg/100 mL), a standard review drug of 5 approved products.

2.3 Drug Formulation

Normal saline (0.9% sodium chloride) in pre-filled syringes. Two sizes (6 and 12 mL in capacity) of syringes are being proposed. The respective filling volume will be 1, 2, 2.5, 3 or 5 milliliters in a 6-mL syringe and 2, 5 or 10 milliliters in a 12-mL syringe.

2.4 Comments on Novel Excipients

Not applicable because no excipients is present.

2.5 Comments on Impurities/Degradants of Concern

Not applicable.

2.6 Proposed Clinical Population and Dosing Regimen

Not specified. The proposed text in the Recommended Usage section states: "The volume of preparation to be used for diluting or dissolving any drug for injection is dependent on the vehicle concentration, dose and route of administration as recommended by the manufacturer." (b) (4)

The lack of specified dose is not an outstanding issue because very large volumes of normal saline have been used safely in clinical practice. The amount of normal saline that a patient may receive from the proposed device will likely to be a small fraction of the dose that the Agency has found safe.

2.7 Regulatory Background

These saline filled syringe products were developed under IND (b) (4). The Division of Gastrointestinal and Hematology Products (DGHP) and the Medefil Inc. had scheduled a pre-IND/pre-NDA meeting on July 14, 2008 regarding a development program and registration requirements of these saline products (1, 2, 2.5, 3 and 5 mL saline in a (b) (4) ML syringe). Medefil submitted a meeting package on May 14, 2008. DGHP reviewed the package and sent responses to the Medefil's questions on July 11, 2008. Medefil was satisfied with the responses and the meeting was canceled. The pre-meeting response states the following regarding nonclinical developmental program:

"Question 2: No non-clinical studies are planned for the proposed Sodium Chloride Injection, USP, 0.9% in Plastic Syringes. Does the Division concur with this conclusion?"

FDA Response: Yes, the Division concurs."

Medefil submitted the NDA application to the Division of Gastroenterology Products on January 31, 2011. The Center reassigned the application to the Division of Pulmonary, Allergy and Rheumatology Products on March 7, 2011.

3 Studies Submitted

3.1 Studies Reviewed

Not applicable because no study reports were submitted.

3.2 Studies Not Reviewed

Not applicable because no study reports were submitted.

4 Pharmacology

Not applicable because no data were submitted.

5 Pharmacokinetics/ADME/Toxicokinetics

Not applicable because no data were submitted.

6 General Toxicology

Not applicable because no data were submitted.

7 Genetic Toxicology

Not applicable because no data were submitted.

8 Carcinogenicity

Not applicable because no data were submitted.

9 Reproductive and Developmental Toxicology

Not applicable because no data were submitted.

10 Special Toxicology Studies

Not applicable because no data were submitted.

11 Integrated Summary and Safety Evaluation

The available nonclinical data support the approval of the proposed use of normal saline as a diluent or vehicle for parental injection of appropriate drugs, from the nonclinical perspective. The safety evaluation of leachables associated with the pre-filled syringes will be addressed in a separate review in consultation with the chemistry discipline when relevant information is submitted or collected. Approval of the application is recommended, from the nonclinical perspective.

(b) (4)

These syringes will be pre-filled with normal saline (0.9% sodium chloride). Medefil proposes to types of syringes with the maximum capacity of 6 and 12-mL. The filling volume will be 1, 2, 2.5, 3 or 5 milliliters in a 6-mL syringe or 2, 5, 10 milliliters in a 12-mL syringe.

The following evaluates the safety of the active pharmaceutical ingredient (API), leachables, impurities and the proposed label.

API (sodium chloride or normal saline): Normal saline has been approved and marketed as a volume replacement or diluent. There are numerous parenteral saline products on the market. The Agency's website www.drugs@FDA states that there are 5 approved products of 100 ml saline in each package (NDA 006580, a standard review drug). There is essentially no limit on acceptable daily use of normal saline.

The Agency has also approved saline-filled syringes. These syringes are filled with 50 and 125-mL saline for intravascular delivery of drugs (NDA 21-569, approved in 2006). The expected daily use of normal saline from the Medefil's pre-filled syringe is a small fraction of NDA 21-569. The nonclinical safety of the parenteral use of normal saline has been established.

Also, the Agency's pre-meeting responses to questions in the 14-JUL-2008 pre-NDA meeting in IND (b) (4) states that nonclinical data of sodium chloride is needed. The response was issued on July 11, 2008. Approval of the normal saline is recommended from the nonclinical perspective.

Leachables: These products need to be evaluated for the safety of potential leachables in saline at the end of shelf life of the device. The leachable concentrations may increase over the shelf life of the device, but the leachable profile of the device at the end of shelf-life is

unknown at the present time. Nonclinical safety evaluations of the leachables should be conducted when appropriate leachable data are collected and submitted.

Impurities: No impurity issues have been identified by the applicant or the chemistry review discipline.

Labeling: It is unclear at the present time what labeling format and content would be accepted for the proposed product at the present time. Medefil proposed a draft label that is generally compliant with the product labeling rules. Sections 8.1 and 13 are most relevant to the nonclinical discipline. Medefil proposed Section 8.1 but not Section 13. The proposed text for Section 8.1 – Pregnancy is as the following:

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The above text was adopted from the label of an approved and currently marketed normal saline product that is supplied by Hospira. The reference product is 100-mL normal saline as diluent in a plastic bag (<http://products.hospira.com/assets/pdfs/EN-2087.pdf>, 2009 revision).

(b) (4)



(b) (4)



There is no apparent difference in the interpretation of nonclinical data of sodium chloride between the proposed and approved versions of the label. The proposed modification, therefore, may be granted.

Section 13.1: The label of Hospira product (NDA 21-259) also contains the following nonclinical information.

“Carcinogenesis, Mutagenesis and Impairment of fertility: Studies with Sodium Chloride Injection, USP have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.”

The above information should be included Section 13.1 - **Carcinogenesis, Mutagenesis and Impairment of fertility** of the label if the length of the approved label is not a critical factor.

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

LUQI PEI
05/23/2011

TIMOTHY W ROBISON
05/23/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202,832 **Applicant:** Medefil Inc.

Stamp Date: Feb. 2, 2011

Drug Name: 0.9% HCl syringe **NDA/BLA Type:** Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. No nonclinical information was submitted, as the Agency agreed previously. See the Agency's pre-meeting response to the 14-JUL-2008 pre-NDA meeting in IND (b)(4). The response was issued on July 11, 2008.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. See comments in Item 1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant <u>submitted</u> a rationale to justify the alternative route?			Not applicable.
7	Has the applicant <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations?			Not applicable.
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.

**PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR
NDA/BLA or Supplement**

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			The proposal labeling is in the PLR format. It has no description of nonclinical toxicity findings or dose ratios in the proposed labeling; such information may not be needed for saline injectables used as a vehicle for drug delivery.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?		x	The drug is approved and currently marketed for the same route of the administration and same patient demographics.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable. There appears no need for injectable OTC saline.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES.

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

The safety evaluation of leachables could potentially be an issue. The application does not appear to have addressed the leachable issue or have evaluated the safety of the leachables. The issue will be discussed with the chemistry discipline.

Luqi Pei, Ph.D.

March 18, 2011

Reviewing Pharmacologist

Date

Timothy Robison, Ph.D.

March 20, 2010

Team Leader

Date

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

/s/

LUQI PEI
03/31/2011

TIMOTHY W ROBISON
03/31/2011