

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202832Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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NDA/Supporting document no.	202-832
Submission Date	03/07/11
Brand Name	TBD
Generic Name	Sodium Chloride 0.9% USP
Reviewer	Lokesh Jain, Ph.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCP Division	Clinical Pharmacology II
OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Medefil, Inc.
Submission Type; Code	505(b)(2)
Formulation; Strength(s)	Pre-filled syringe <ul style="list-style-type: none"> <li>• 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL Syringe</li> <li>• 2 mL, 5 mL and 10 mL fill in 12 mL Syringe</li> </ul>
Indication	<ul style="list-style-type: none"> <li>• for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injections</li> <li>• <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> for flushing <span style="background-color: #cccccc; padding: 2px;">(b) (4)</span> indwelling access devices to maintain their patency</li> </ul>

<b>1.</b>	<b>Executive Summary</b> .....	<b>2</b>
<b>1.1</b>	<b>Recommendation</b> .....	<b>2</b>
<b>1.2</b>	<b>Phase IV Commitments</b> .....	<b>2</b>
<b>1.3</b>	<b>Summary of Clinical Pharmacology and Biopharmaceutics Findings</b> .....	<b>2</b>
<b>2</b>	<b>General Clinical Pharmacology</b> .....	<b>NA</b>
2.1	What are the design features of the clinical pharmacology Pharmacology and clinical studies used to support dosing or claims.....	NA
2.2	What are the characteristics of the exposure-response relationship for effectiveness and safety? .....	NA
2.3	Does this drug prolong QT/QTc Interval? .....	NA
2.4	What are the PK characteristics of the drug? .....	NA
2.5	What dosage regimen adjustments are recommended for body weight, age, gender, race, renal impairment, and hepatic impairment? .....	NA
2.6	Is there an in vitro basis to suspect in vivo drug-drug interactions? .....	NA
2.7	What are the drug-drug interactions? .....	NA

## 1. Executive Summary

### 1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, NDA 202832 for Sodium Chloride Injection, USP, 0.9% pre-filled syringes is acceptable.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Medefil, Inc. has submitted the NDA 202832 to seek the marketing approval for 0.9% Sodium Chloride Injection, USP (b) (4) supplied in a disposable, single-use plastic syringe. The proposed strengths are:

- 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL Syringe
- 2 mL, 5 mL and 10 mL fill in 12 mL Syringe

The NDA 202832 only consists of three modules consisting of administrative information (module 1), introduction and overall quality summary (module 2), and CMC information (module 3). **No clinical or clinical pharmacology studies are submitted with this NDA.**

## Background and Regulatory History

In Pre-IND meeting with the Division of Gastroenterology Products, Agency has agreed upon waiver of *in vivo* bioavailability requirements (see related excerpts from meeting minutes dated 07/11/2008 below).

Pre-IND (b) (4)

“Clinical Pharmacology:

3. Since the proposed Sodium Chloride Injection, USP, 0.9%, in Plastic Syringes for diluting or dissolving drugs for injection does not raise pharmacokinetic issues, Medefil intends to request a waiver of *in vivo* bioavailability requirements under 21 CFR 320.22. Does the Division concur with this conclusion?

**FDA Response:**

**Yes, we concur.”**

In this NDA, as previously agreed, Sponsor has requested a waiver for *in vivo* bioavailability studies, which is reproduced below:

“In accordance with 21 CFR §320.22 (b)(1), and as concurred by FDA in PIND (b) (4), Medefil, Inc., requests a waiver of *in-vivo* bioavailability / bioequivalence requirements for Sodium Chloride Injection (b) (4), USP Syringes. This request is based on 21 CFR

§320.22 (b) which states that for certain drug products, the in-vivo bioavailability or bioequivalence of the drug product may be self evident. The drug product's self evident bioavailability or bioequivalence is based on the fact that Sodium Chloride Injection (b)(4) USP Syringes is a parenteral solution intended solely for dilution or dissolution of drugs or to maintain patency of the IVAD's, having Sodium Chloride, USP (9 mg/mL) and the same ingredient, in the same concentrations, as a drug product that is the subject of an approved full new drug application.”

Biopharm group in ONDQA will evaluate this request to waive the *in vivo* bioavailability studies.

*Labeling comments pertaining to the general clinical pharmacology information can be found in section 3*

### 3 Detailed Labeling Recommendations

Following are the labeling comments for the sponsor:

- ~~Strikeout text~~ should be removed from labeling and underlined text should be added to labeling.

## 12 CLINICAL PHARMACOLOGY

Sodium chloride in water dissociates to provide sodium (Na<sup>+</sup>) and chloride (Cl<sup>-</sup>) ions. These ions are normal constituents of the body fluids (principally extracellular) and are essential for maintaining electrolyte balance. (b)(4)

(b)(4)

(b)(4)

The small volume of fluid and amount of sodium chloride provided by (b)(4) Sodium Chloride Injection, USP, 0.9% (b)(4) when used only as an isotonic vehicle for parenteral injection of drugs or for flushing of indwelling access devices, is unlikely to exert a significant effect on fluid and electrolyte balance except possibly in neonates and very small infants<sup>†</sup>.

(b)(4)

# Office of Clinical Pharmacology

## New Drug Application Filing and Review Form

### General Information about the Submission

	Information		Information
NDA/BLA Number	202832	Brand Name	(b) (4)
OCP Division (I, II, III, IV, V)	II	Generic Name	Sodium Chloride 0.9% USP
Medical Division	DPARP	Drug Class	Normal Saline
OCP Reviewer	Lokesh Jain, Ph.D.	Indication(s)	Dilution solvent for IV, IM, SC injections
OCP Team Leader	Suresh Doddapaneni, Ph.D.	Dosage Form	Pre-filled syringe
Pharmacometrics Reviewer		Dosing Regimen	
Date of Submission	03/07/2011	Route of Administration	IV, IM, SC
Estimated Due Date of OCP Review		Sponsor	Medefil, Inc.
Medical Division Due Date		Priority Classification	Standard
PDUFA Due Date			

### *Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods				
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Transporter specificity:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				

hepatic impairment:				
<b>PD -</b>				
Phase 2:				
Phase 3:				
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
<b>Population Analyses -</b>				
Data rich:				
Data sparse:				
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		<b>0</b>		

On **initial** review of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>N/A</b>	<b>Comment</b>
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?			X	
5	Has a rationale for dose selection been submitted?			X	
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?			X	
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?			X	
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?			X	It is a paper submission
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>					

<b>Data</b>					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
<b>Studies and Analyses</b>					
11	Is the appropriate pharmacokinetic information submitted?			X	
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
<b>General</b>					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?			X	
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

Yes

If the NDA/BLA is not fileable from the clinical pharmacology 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.

- None

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LOKESH JAIN  
12/08/2011

SURESH DODDAPANENI  
12/08/2011

# Office of Clinical Pharmacology

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Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
- None

Lokesh Jain	03/28/11
Reviewing Clinical Pharmacologist	Date
Suresh Doddapaneni	03/28/11
Team Leader/Supervisor	Date

**Submission in brief:**

***Product and Indication***

Medefil, Inc. has submitted the NDA 202832 to seek the marketing approval for 0.9% Sodium Chloride Injection, USP (b) (4) supplied in a disposable, single-use plastic syringe. The proposed strengths are:

- 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL fill in 6 mL Syringe
- 2 mL, 5 mL and 10 mL fill in 12 mL Syringe

These syringes are to be used: (a) for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injections, and (b) (b) (4) for flushing (b) (4) (b) (4) indwelling access devices to maintain their patency.

***Summary of information submitted***

The NDA 202832 only consists of three modules consisting of administrative information (module 1), introduction and overall quality summary (module 2), and CMC information (module 3). No clinical or clinical pharmacology studies are submitted with this NDA, as agreed upon with the FDA (Division of Gastroenterology Products) in the Pre-IND meeting (see related excerpt from meeting minutes below).

Pre-IND (b) (4)

“Clinical Pharmacology:

3. Since the proposed Sodium Chloride Injection, USP, 0.9%, in Plastic Syringes for diluting or dissolving drugs for injection does not raise pharmacokinetic issues, Medefil intends to request a waiver of *in vivo* bioavailability requirements under 21 CFR 320.22. Does the Division concur with this conclusion?

**FDA Response:**

**Yes, we concur.”**

In this NDA, as previously agreed, Sponsor has requested a waiver for *in vivo* bioavailability studies, which is reproduced below:

“In accordance with 21 CFR §320.22 (b)(1), and as concurred by FDA in PIND (b) (4) Medefil, Inc., requests a waiver of *in-vivo* bioavailability / bioequivalence requirements for Sodium Chloride Injection (b) (4), USP Syringes. This request is based on 21 CFR §320.22 (b) which states that for certain drug products, the *in-vivo* bioavailability or bioequivalence of the drug product may be self evident. The drug product's self evident bioavailability or bioequivalence is based on the fact that Sodium Chloride Injection (b) (4) USP Syringes is a parenteral solution intended solely for dilution or dissolution of drugs or to maintain patency of the IVAD's, having Sodium Chloride, USP (9 mg/mL) and the same ingredient, in the same concentrations, as a drug product that is the subject of an approved full new drug application.”

Biopharm group in ONDQA will evaluate this request to waive the *in vivo* bioavailability studies.

**Focus of clinical pharmacology review:**

Clinical pharmacology review will only include reviewing the labeling information.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LOKESH JAIN  
04/14/2011

SURESH DODDAPANENI  
04/14/2011