

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202832Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: December 15, 2011
FROM: Edwin Jao, Ph.D., Review Chemist, Branch VIII, ONDQA III/ONDQA
THROUGH: Prasad Peri, Ph.D., Branch Chief, Branch VIII, ONDQA III /ONDQA
SUBJECT: Addendum to CMC Review #1 for NDA 202-832
TO: NDA 202-832

In my CMC Review #1, dated 12-9-11, this NDA was recommended for approval pending on the final recommendation from the Office of Compliance.

The Office of Compliance issued an overall acceptable recommendation for this NDA on 12/15/2011.

(b) (4)



Therefore, this NDA is recommended for approval from the ONDQA perspective.

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/s/

EDWIN JAO
12/15/2011

PRASAD PERI
12/15/2011
I concur

NDA 202832

Sodium Chloride Injection, USP, 0.9%

Medefil, Inc.

Chemistry Review #1

December 9, 2011

Recommendation: Approval

Edwin Jao, Ph.D.

ONDQA/Division III/Branch VIII

for

Division of Pulmonary, Allergy, and Rheumatology Product

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Chemistry Review Data Sheet

1. NDA 202-832
2. REVIEW #:1
3. REVIEW DATE: December 9, 2011
4. REVIEWER: Edwin Jao, Ph.D.
5. Related DOCUMENTS:

Previous DocumentsDocument Date

Original NDA	01-31-2011 *
Amendment	07-05-2011
Amendment	10-12-2011
Amendment	11-21-2011

*the submission date is 1/31/2011; the PDUFA clock starts on 3/7/2011

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA dated 1-31-2011*

Amendment dated 05-07-2011

Amendment dated 10-12-2011

Amendment dated 11-21-2011

*the submission date is 1/31/2011; the PDUFA clock starts on 3/7/2011

7. NAME & ADDRESS OF APPLICANT:

Name:	Medefil, INC.
Address:	250 Windy Point Drive Glendale Height, IL 60139
Representative:	Pradeep Aggarwal
Telephone:	630-682-4600

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:

b) Non-Proprietary Name (USAN): Sodium Chloride Injection, USP, 0.9%

c) Code Name/# none provided

d) Chem. Type/Submission Priority:

- Chem. Type: 5 (new manufacturer)
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

10. PHARMACOL. CATEGORY:

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY:

9 mg/mL (0.9%)

13. ROUTE OF ADMINISTRATION: Intravenous, Subcutaneous, Intramuscular

14. Rx/OTC DISPENSED: x Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

 SPOTS product

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sodium Chloride Injection, USP

NaCl=58.5

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYP E	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENT S
(b) (4)	III	(b) (4)	(b) (4)	1, 4	adequate	8/5/2011	By Lt Keith Marin of CDRH (b) (4)
	III			1, 4	adequate	8/5/2011	By Lt Keith Marin of CDRH (b) (4)
	III			1, 4	adequate	8/5/2011	By Lt Keith Marin of CDRH

							(b) (4)
(b) (4)	III	(b) (4)		1, 4	adequate	8/5/2011	<i>By Lt Keith Marin of CDRH</i> (b) (4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
510(k)	K020999	Normal Saline IV Flush Syringes
510(k)	K091583	

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Biometrics	approval	Ms. Feng Zhou	10/4/2011
EES	pending		
Pharm/Tox	Approval	5/23/2011	Dr. Luqi Pei
Clinpharm	Approval	12/8/2011	Dr. Lokesh Jain
LNC	N.A.		
Methods Validation	Not necessary		
EA	acceptable	12/2/2011	Dr. Edwin Jao
Microbiology	Approval	10/31/2011	Dr. Stephen Langille
CDRH	No device performance and DMF related issues	8/5/2011	LT Keith Marin

Executive Summary Section

The Chemistry Review for NDA 22-472

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

The applicant of the NDA has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

Labels/labeling have been evaluated and required information has been communicated. However, all information referenced to the device should be removed from the labeling.

The recommendation from the Office of Compliance for this NDA is pending.

Therefore, from the **ONDQA** perspective, this NDA is recommended for Approval.

However, since the facility inspection is still outstanding the CMC recommendation does not incorporate any potential facility inspection issues.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

The drug substance is Sodium Chloride, USP. It is a naturally occurring salt found in the earth. The manufacturing process (b) (4)

Sodium Chloride, USP bulk drug substance is manufactured, packaged, tested (release and stability), and supplied by (b) (4). *The manufacturing of sodium chloride, USP is straight forward. No organic chemical transformations are involved. The proposed in-progress controls and drug substance specification are adequate to ensure the quality and batch to batch consistency of sodium chloride production. The quality and stability of the registration batches of the drug substance sodium chloride, USP are adequately demonstrated by release and stability data (three years). Most of the attributes in the stability specification are not considered stability correlated. Therefore, it is acceptable not to assign a retest period for this drug*

Executive Summary Section

substance. Sodium Chloride, USP is available from [REDACTED] (b) (4)

The drug products submitted in this NDA is a sodium chloride injection, USP, 0.9%, supplied in a disposable, single-use plastic syringe, for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection. The drug product is available in 1 mL, 2 mL, 2.5 mL, 3 mL, 5 mL, and 10 mL dosage units. The drug product contains sodium chloride, USP and water for injection, USP. No other excipients are used. The drug product is currently marketed in USA as Normal Saline I. V. Flush Syringes under two 510(k). 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, which was recommended by the Agency in response to the pre-NDA meeting. Normal Saline I. V. Flush Syringes are indicated for use in maintaining patency of in-dwelling intravenous access devices (IVAD). The drug product submitted in this NDA is identical in composition, strengths, packaging, and manufacturing process to the ones that are currently marketed under 510(k), except for the color of the labels and tip caps. LT Keith Marin of CDRH has conducted a consult review per OND's request for this NDA and related DMFs for all components of the container/closure system. He has found no questions in drug product performance and referenced DMFs.

Sodium chloride injection, USP, 0.9% in prefilled syringes, is manufactured [REDACTED] (b) (4)

The terminal sterilization process is considered adequate to ensure sterility of the drug product by microbiologist Dr. Stephen Langille. The proposed in-process controls and drug product specification are adequate to ensure the quality and batch to batch consistency of the drug product production. The quality and stability of the registration batches of the drug product, sodium chloride injection, USP, 0.9% in prefilled syringes are adequately demonstrated by the release and stability data. The proposed expiry dating of two years for the drug product is supported by full shelf life stability data and is granted.

All formulation contacting components of the container/closure system met the safety requirements listed in the pertinent sections of USP <87> and <88>. Controlled extraction study for formulation contacting components and preliminary leachable study for the drug product during storage reveal no safety concerns.

B. Description of How the Drug Product is Intended to be Used

Sodium chloride injection, USP, 0.9%, supplied in a disposable, single-use plastic syringe, for diluting or dissolving drugs for intravenous, intramuscular or subcutaneous injection.

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

1. *The applicant has provided sufficient information on raw material controls, manufacturing processes, process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. Also sufficient stability information is provided on the drug product in the NDA to assure strength, purity, and quality of the drug product during the expiration dating period of 24 months.*
2. *The recommendation from the Office of Compliance for this NDA is still Pending.*
3. *All labels/labeling have the required information. However, all information referenced to the device should be removed from the labeling.*

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

Edwin Jao, Ph.D./Date: 12/2/2011

Prasad Peri, Ph.D.

C. CC Block

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/s/

EDWIN JAO
12/09/2011

PRASAD PERI
12/09/2011
I concur

**ONDQA Review for
OND Division of Pulmonary Allergy and Rheumatology Products
Initial Quality Assessment
Date: April 8, 2011**

NDA 202,832

Product Name: (b) (4) (sodium chloride) injection 0.9%

Applicant: Medefil, Inc.

“Stamp Date:” March 7, 2011 (date user fee waiver was granted; this starts the clock)

PDUFA Date: January 7, 2012

ONDQA 5 month date: August 7, 2011

Proposed Proprietary Name: (b) (4)

Established Name: sodium chloride injection 0.9%

Dosage form and strength: injection, 0.9%

Indications and Route of Administration: “to dilute or dissolve drugs for intravenous, intramuscular, or subcutaneous injection and to maintain patency of” intravenous access devices.

CMC Lead (acting): Alan C. Schroeder, Ph.D. /DNDQA III/ONDQA

Filability recommendation: fileable

Review team recommendation: Single primary reviewer (Dr. Edwin Jao)

Time goals:

- Initial Quality Assessment in DFS: May 7, 2011
- Filing decision “Day 45”: April 21, 2011
- Filing review issues “Day 74”: May 20, 2011
- **Initial Chemistry Review (DR/IR) letter: by month 5 (August 7, 2011)**
- Mid-cycle meeting “Month 5”: TBA
- Wrap Up: TBA
- **Final Chemistry Review “Month 8” in DFS:** November 7, 2011
- PDUFA: January 7, 2012

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharmaceutics	Applicant has requested a biowaiver - Akm Khairuzzaman is the assigned Biopharmaceutics reviewer
CDRH	May not be needed if only difference in the drug product from the approved 510(k) device is in the terminal sterilization; as long as that sterilization process doesn't adversely affect the device components and their function. To be determined by reviewer's discussion with branch chief.
EA	To be assessed by Primary Reviewer
EES	EER was sent to Office of Compliance on April 1, 2011
DMETS	Labeling consult request will be sent as part of DPARP's request.
Methods Validation	Methods validation for non-compendial methods may be requested of FDA laboratories if deemed necessary by the reviewer after test methods are finalized.

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Microbiology	Consult needed: drug product is sterile. Consult request was sent through DARRTS on 3/21/2011.
Pharm/Tox	DS and DP impurities/degradants/leachables to be evaluated for safety.

Review Notes:

Background: The applicant previously requested a pIND/pNDA meeting of DGP in OND, and based on FDA’s written responses to their questions, they cancelled the meeting. See DARRTS for our letter sent on July 11, 2008 for pIND (b) (4); this letter acknowledged cancellation of the meeting and provided written responses to the sponsor’s questions. For convenience of the reviewer, the CMC comments sent to the sponsor in that letter are reproduced below:

The information that you plan to submit in the NDA appears generally acceptable, but you will also need to submit data to demonstrate that the syringes conform to USP <661> for plastic containers and a more detailed description of the manufacturing process, describing any in-process testing that will be done, as well as sterile process validation data. In addition, when you submit your batch analysis and stability data, please report actual test results; do not report your results as “conforms”. Please refer to the FDA Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (<http://www.fda.gov/cder/guidance/cmc2.pdf>) for specific information to be included in the NDA submission. It is strongly recommended that you explore terminal sterilization for the product as a sterilization process which provides a greater sterility assurance level.

Module 1 of this application includes information relating to the applicant’s 510(k) approved device (Medefil’s Normal Saline I.V. Flush Syringe). This pertains to K091583 (terminally sterilized; see CDRH letter dated 1/28/2010) and K020996 (see CDRH letter dated 6/24/2002). K020999 and K092491 are also referenced.

Note that DARRTS lists the sponsor for IND (b) (4) (see pIND meeting information above) as (b) (4) however in the Communication to the Sponsor for IND (b) (4) (sent 7/11/08) in DARRTS, the Sponsor is indicated to be (b) (4).

Drug substance

The applicant uses Sodium Chloride USP as the active ingredient in the proposed drug product. Sodium Chloride USP is obtained from (b) (4), and it is produced at (b) (4) facility.

(b) (4)
performs testing and release of the Sodium Chloride USP according to the USP monograph for Sodium Chloride. It is stated that (b) (4) does not have a DMF for this drug substance. This NDA contains a document from (b) (4) with information about their cGMP practices for production of Sodium Chloride USP (see Attachment 3.2.S.2.2-1). This document was used for much of the information in the drug substance section of the NDA, according to the applicant.

Sodium chloride is naturally occurring and mined from the earth. (b) (4)

“Sodium chloride” is the name accepted by USP, INN, IUPAC, CAS and RTECS. Addresses of (b) (4) the manufacturer, are listed in section 3.2.S.2.1.

Comment: The reviewer should check to see that the applicant has a written agreement with (b) (4) to notify the applicant in advance of any changes in the manufacturing process or its controls.

The following information, in italics, is from the NDA:

“3.2.5.2.2.2

-

*Detailed Description of the Manufacturing Process and Process Controls
(Sodium Chloride, USP, (b) (4))*

Summary of Process: The manufacturing process that yields Sodium Chloride, USP is an
(b) (4)

(b) (4)

Reworking may be performed for failure of (b) (4) specifications, according to the applicant & (b) (4). (b) (4) used in production of Sodium Chloride, USP. (b) (4)

[REDACTED] (b) (4)

Control of critical steps and intermediates are discussed in Section 3.2.S.2.4, mainly focused on [REDACTED] (b) (4). There is also a visual inspection. [REDACTED] (b) (4)

Section 3.2.S.2.5 provides a brief summary of process validation and/or evaluation studies. These studies are focused on minimizing impurities in the sodium chloride, and [REDACTED] (b) (4).

Drug substance impurities are listed in Section 3.2.S.3.2, and these consist of a list of impurities and limits from the USP monograph.

Specifications: drug substance is tested for the attributes listed in the current USP monograph for sodium chloride, including the following attributes: assay, appearance (solution), identification, acidity or alkalinity, [REDACTED] (b) (4), bacterial endotoxins, [REDACTED] (b) (4)

Comment: it may be noted that the sodium chloride drug substance is not sterile, however, bacterial endotoxins are controlled.

Analytical methods are those of the USP monograph.

Stability testing uses sodium chloride in “containers that approximate the container used to ship Sodium Chloride USP.” Stability lots are tested (per the USP monograph) for the following attributes (per USP): assay, [REDACTED] (b) (4), [REDACTED] (b) (4), [REDACTED] (b) (4) and bacterial endotoxins. A batch of drug substance is defined as that manufactured during approximately a [REDACTED] (b) (4) production period assigned one lot number.

Comment for applicant: Specify which tests you perform on receipt for the drug substance, and confirm that you periodically perform all tests for which results are accepted on a Certificate of Analysis.

Comment: Batch analyses (4 batches) are provided in Section 3.2.S.4.4-1. Most of the test results are listed as “pass,” and this is reasonable given that most of the USP tests are limit tests. No failures are reported.

Reference standards are indicated to be those listed in the USP monograph.

The container closure system consists of [REDACTED] (b) (4)

A product data sheet which includes labeling is provided for sodium chloride. (b) (4)

Comment for applicant: Clarify whether the (b) (4) component of the container closure system of the drug substance conforms to USP physicochemical tests and specify its food additive status.

Stability: An expiration date is not assigned. This is indicated to be based on years of stability studies (using USP methods current at the time). Test attributes included the following: (b) (4), (b) (4), alkalinity, assay, (b) (4) and bacterial endotoxins. "All samples met expectations."

Comment for applicant: provide the most recent stability results for the drug substance and confirm that stability testing by (b) (4) is continuing. Provide assurance that the data will be provided to you, and that you will submit the data to this application.

Drug product

The applicant states that the proposed drug product meets the USP requirements for Sodium Chloride, Injection. There are multiple presentations of the product in terms of fill volume (see below), and the applicant states that there are two syringe barrel sizes, namely, 6 mL and 12 mL. The materials of construction of the two barrels are said to be identical, and the diameters are said to be the same but the lengths differ. "The 6 mL syringe can be pre-filled with 1 mL, 2 mL, 2.5 mL, 3 mL and 5 mL volumes. The 12 mL syringe can be pre-filled with 3 mL, 5 mL and 10 mL fill volumes." See below for the list of the various drug product presentations which are proposed.

The applicant has provided the following description of the drug product (in the draft drug product labeling/package insert):

(b) (4)

(b) (4)

Dosage form presentations:

- 1 ml fill in 6 ml syringe (b) (4)
- 2 ml fill in 6 ml syringe (b) (4)
- 2.5 ml fill in 6 ml syringe (b) (4)
- 3 ml fill in 6 ml syringe (b) (4)
- 3 ml fill in 12 ml syringe (b) (4)
- 5 ml fill in 6 ml syringe (b) (4)
- 5 ml fill in 12 ml syringe (b) (4)
- 10 ml fill in 12 ml syringe (b) (4)

This NDA claims that the proposed product, sterile, nonpyrogenic, single-use, injectable normal saline (syringe), is identical to that marketed as Class II devices except that they are terminally sterilized. [Note, the applicant has also provided documents indicating that they now have a 510(k) for terminally sterilized drug product. See above.] The "normal saline i.v. flush syringes" are said to have been approved under a 510(k) application for use in maintaining patency of in-dwelling intravenous access devices. The product proposed under NDA 202832 is proposed "to dilute or dissolve drugs for intravenous, intramuscular, or subcutaneous injection and to maintain patency of IVADs."

Drug Product Composition:

The following Table is from the NDA:

Composition of the Dosage Form: The unit dose composition of the drug product is provided in the following table.

Labeled Fill Volume	Syringe Size	Ingredient Concentration (mL)	
		Sodium Chloride, USP	Water for Injection, USP (b) (4)
1 mL	6 mL	9 mg/mL	
2 mL	6 mL	9 mg/mL	
2.5 mL	6 mL	9 mg/mL	
3 mL	6 mL and 12 mL	9 mg/mL	
5 mL	6 mL and 12 mL	9 mg/mL	
10 mL	12 mL	9 mg/mL	

3.2.P.2 Pharmaceutical Development. This is a brief section. The concentration of sodium chloride in the drug product solution (9 mg/mL) is substantially (b) (4)

The only excipient is Water for Injection, USP. Desired characteristics of the drug product are listed in section

3.2.P.2.2.1 and in Section 3.2.P.2.2.3. (b) (4)

The applicant's experience with sterile, non-pyrogenic, single-use injectable products is discussed. Characteristics of the container closure system components are discussed (including, for example, compatibility with (b) (4)) and references to DMFs for container closure materials are given. USP <87> and <88> testing of materials used in the device construction is discussed. Syringe performance tests per ISO 7886-1 are discussed. Microbiological attributes are discussed and compatibility to support the proposed use of the drug product (diluting or dissolving drugs for i.v., i.m. or s.c. injection, and for flushing of i.v. catheters. Results of product characterization testing are provided in multiple amendments to section 3.2.P.2.

Comment: it may be noted that extractables and leachables from container closure components are not discussed. Later in this IQA, it is also noted that the stability study does not include leachables testing. Such information and testing should be requested from the applicant.

3.2.P.1 Drug product is manufactured, tested, labeled and released by Medefil, Inc. in Glendale Heights, Illinois. Plunger stoppers (b) (4)

(b) (4). Stability testing is conducted by (b) (4).
Written cGMP certification is provided for Medefil, Inc., (b) (4)

3.2.P.3.2 Batch formula: The batch formula includes (b) (4)

(b) (4). The batch formula table below is provided by the applicant:

Table 3.2.P.3.2-1: Maximum Batch Sizes (Dosage Units, Fill Volumes, Formula Requirements)

Unit Dose Volume	1 mL Syringe	2 mL Syringe	2.5 mL Syringe
Maximum Batch Size (dosage units)	(b) (4)	(b) (4)	(b) (4)
Syringe Fill Volume			
Sodium Chloride, USP			
Water for Injection, USP			
Unit Dose Volume	3 mL Syringe	5 mL Syringe	10 mL Syringe
Maximum Batch Size (dosage units)	(b) (4)	(b) (4)	(b) (4)
Syringe Fill Volume			
Sodium Chloride, USP			
Water for Injection, USP			

3.2.P.3.3 Manufacturing process and process controls are described in a flow chart. The drug product is terminally sterilized (b) (4)

A written description of the manufacturing process is also provided.

Comment for applicant: Identify the approved vendors who manufacture the individual components of the syringe device, and indicate compositions of the components if any additives are used by the manufacturers of the components.

3.2.P.3.4 Control of critical steps. The table below was provided in the NDA:

Active Ingredient: Sodium Chloride, USP, using the tests and specifications listed in **Table 3.2.S.4.1-1**, is released by (b) (4) Medefil purchases Sodium Chloride, USP from (b) (4) and conducts the tests summarized in **Table 3.2.P.3.4 - 1**.

Table 3.2.P.3.4 - 1: Testing of Sodium Chloride, USP Prior to Manufacture

Test	Test Method	Method Number	Specification
Certificate of Analysis Review	Not applicable	Not applicable	Meets USP monograph
Assay	Titration	USP monograph	(b) (4)
Bacterial Endotoxins	LAL	USP <85>	NMT (b) (4) EU/mL

A test result table is provided for a lot of drug substance used in the manufacture of the drug product.

Bulk sodium chloride solution is tested (b) (4) for the following attributes: concentration, pH, bacterial endotoxins, microbial limit. In process test results are provided for three bulk lots of drug product. Results are within the acceptance criteria.

(b) (4)

A receiving and history record is provided for a single lot of drug product which provides test results.

3.2.P.3.5 Process validation – this consists of sterilization and bacterial endotoxin validation protocols and reports and related information to be evaluated by the microbiology reviewer. It is in volumes 1.4, 1.5 and 1.6.

3.2.P.4.1 Specifications for Water for Injection, USP
 The following Table is from the NDA:

Table 3.2.P.4.1-1: Specifications for Water for Injection, USP

Test Procedure	Acceptance Criteria	Test Methodology
pH	(b) (4)	Medefil SOP 315
Total Organic Carbon		USP <643>
Conductivity		USP <645>
Bacterial Endotoxin		USP <85> / Medefil SOP 319
Bio Burden		USP <61> / Medefil SOP 350

Data are provided indicating compliance of (b) (4) Water for Injection USP.

Comment: the specifications match those of the USP monograph for Water for Injection, and they include two other attributes: pH and BioBurden. Medefil’s SOP 319 is provided for Bacterial Endotoxin testing, and SOP 350 for Bioburden. These methods and their validation reports should be reviewed by the microbiology reviewer (consult was sent by Ms. Swati Patwardhan, Project Manager, ONDQA).

3.2.P.5.1 Drug Product Specifications

The following Table is from the NDA. Information is also provided on methods validation, justification of specifications and batch analyses of 6 terminally sterilized lots:

Table 3.2.P.5.1-1: Release Specifications for Sodium Chloride Injection, USP Syringes (b) (4)	
Test	Specification
Concentration	(b) (4)
pH	(b) (4)
Bacterial Endotoxin	Not more than (b) (4) USP EU/ml
Sterility	Sterile
Particulate Matter / container	Not more than (b) (4) particles of size (b) (4) and not more than (b) (4) particles of size (b) (4)
Appearance	Clear, Colorless
Weight	Not less than the claim
Volume	Not less than label claim
(b) (4)	Less than (b) (4)
(b) (4)	Less than (b) (4)

Comment: Specifications for each fill volume of Medefil’s Normal Saline I.V. Flush Syringe are provided and it appears that these may also be the specifications for the proposed Sodium Chloride Injection USP product. This should be clarified. Specifications are justified by being those of the USP monograph for the drug product (however, see comments below):

Comment for applicant: Clarify the attachments to section 3.2.P.5.1 (Material Specifications for each presentation of drug product) which are titled “Normal Saline I.V. Flush Syringes...” do these apply completely to the proposed Sodium Chloride Injection product? This also applies to all other documents in the NDA which are identified as being for the Normal Saline I.V. Flush Syringe.

Drug product analytical procedures are indicated to include those in the USP monograph, and they are provided. It is noted that sodium chloride is assayed using a silver nitrate titration for the chloride ion. SOPs are provided for the methods, and microbiological quality related SOPs will be evaluated by the microbiology reviewer.

Batch analyses are provided (Section 3.2.P.5.4) for the 6 NDA stability batches (see below).

Comment: The release specifications for the drug product are same as the USP monograph for Sodium Chloride Injection, except for the addition of tests for appearance, weight and volume, and the deletion of the specification for identification. It is not clear whether terminal sterilization (b) (4) The reviewer should consider asking for one-time characterization information on (b) (4) of the sterilized product.

Comment: It may be noted that only two of the multiple proposed product presentations are represented in the NDA stability batches, namely, syringes with 1 mL in a 6 mL syringe, and syringes with 10 mL in a 12 mL syringe. The applicant claims that these

batches were terminally sterilized. (The reviewer should determine whether these presentations adequately cover all presentations of the product for the stability studies. See comments later in this review.) Release data are provided for these batches. It is noted that the “certificates of analysis and sterility” provided in this section with the same drug product lot numbers are listed as being for the “Normal Saline I.V. Flush Syringe.” The applicant needs to clarify whether these batches are indeed those of the proposed product Sodium Chloride Injection manufactured with terminal sterilization or whether they are for the “Normal Saline I.V. Flush Syringe.”

Comment for applicant: modify your drug product specifications to include USP monograph tests for identification of sodium and of chloride.

3.2.P.5.5 Characterization of Impurities – no quantitative information is available for the level of drug product impurities, since the USP tests for drug substance and drug product are limit tests.

3.2.P.6 Reference Standards or Materials: these are defined by the USP monograph for Sodium Chloride Injection.

3.2.P.7 Container Closure System

The following two tables are from the NDA. Engineering drawings of the components are also provided by the applicant:

Table 3.2.P.7 -1: Summary of Primary Container/Closure Components		
Component	Specifications	Suppliers
Syringe Barrels	(b) (4)	(b) (4)
Tip Caps	(b) (4)	(b) (4)
Plunger Stoppers	(b) (4)	(b) (4)
Plunger Rods	(b) (4)	(b) (4)

Secondary Packaging Information: Each finished syringe is enclosed in a (b) (4) plastic overwrap that functions primarily to protect the finished syringe from dust. Information on the overwrap is provided in **Table 3.2.P.7-2**.

Table 3.2.P.7-2: Summary of Secondary Container/Closure Components

Component	Specifications	Suppliers
Over Pouch	(b) (4)	

Technical Drawings: Attachment 3.2.P.7-1 contains technical drawings for the packaging components.

Syringe Barrels, Tip Caps and Plunger Rods are received (b) (4).
Plunger Stoppers (b) (4) Barrels are available in 6 mL and 12 mL sizes, and the other container closure components do not differ from one drug product presentation to another.

Container closure components: “Each unit dose syringe is packaged as a disposable, single-use plastic syringe, consisting of a syringe barrel with luer lock, plunger stopper, plunger rod, and tip cap.” As indicated above, there are two syringe barrel sizes: 6 mL and 12 mL.

Comment: as indicated earlier in this review, we will ask for the identities of the other approved vendors of the container closure components. (b) (4)

(b) (4) Referenced DMFs for raw materials for the device components are listed later in this review. The reviewer needs to ascertain that the other device components (other than the plunger stoppers) (b) (4)

Comment for applicant: provide a certificate of analysis for the (b) (4) used on the plunger stoppers and syringe barrel, and provide information on the impurity profile of the (b) (4). Provide specifications for the amounts of (b) (4) (maximum and minimum) used on the plunger stoppers and syringe barrels. Clarify with data whether any constituents of the secondary container/closure components may migrate into the drug product formulation through the primary packaging.

3.2.P.8 Stability

The following tables are from the NDA:

Drug Product Lot Number	Sodium Chloride, USP Lot Number	Date of Manufacture	Fill Volume	Date on Stability (b)(4)
(b)(4) 001	DEC077BC01			
002	DEC077BC01			
005	DEC077BC01			
006	DEC077BC01			
503	DEC077BC01			
504	DEC077BC01			

Test	Time Point (Months)							
	0	3	6	9	12	18	24	36
Appearance	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X
Sodium Chloride	X	--	--	--	X	--	X	X
(b)(4)	X	--	--	--	X	--	X	X
	X	--	--	--	X	--	X	X
Sterility	X	--	--	--	X	--	X	X
Bacterial Endotoxins	X	--	--	--	X	--	X	X
Particle Counts	X	X	X	X	X	X	X	X
Weight Loss Check	X	--	--	--	X	--	X	X
Adhesive Migration Study	X	--	--	--	X	--	X	X
Extraction Volume	X	--	--	--	X	--	X	X
Degree of Coloration	X	--	--	--	X	--	X	X
Clarity of Opalescence	X	--	--	--	X	--	X	X
Identification of Sodium (A and B)	X	--	--	--	X	--	X	X
Identification of Chloride (A and B)	X	--	--	--	X	--	X	X

Stability data are provided for accelerated conditions (40° C and either 75% RH or 25% RH), intermediate conditions (30°C and 65% and 75% RH) and Controlled Room Temperature (25°C/40% RH).

Specifications for the stability study are summarized in **Table 3.2.P.8.1.1.1-3**.

Table 3.2.P.8.1.1.1-3: Specifications		
Procedure	Test Method	Acceptance Criteria
pH	USP <791>	(b) (4)
Concentration	USP Sodium Chloride Injection	(b) (4)
Appearance	Visual (b) (4)	Clear, Colorless Liquid
		Not more than (b) (4)
		Not more than (b) (4)
Sterility	USP <71> / EP 2.6.1	No growth
Bacterial Endotoxins	USP <85> EP 2.6.14	(b) (4) USP EU/mL
Particle Counts	USP <788> Test 1.B EP 2.9.19 Method 1	μm (b) (4) μm (b) (4)
Weight Check	Gravimetric	(b) (4)
Extraction Volume	EP 2.9.17	Volume measured is NLT the nominal volume
Degree of Coloration	EP 2.2.2 Method II	Colorless
Clarity of Opalescence	EP 2.2.1	Clear
Identification of Sodium (A and B)	EP 2.3.1 A and B	Complies with Sodium Tests A and B
Identification of Chloride (A and B)	USP <191> EP 2.3.1 A and B	Positive Reaction for Chloride Tests A and B
Adhesive Migration Study	Celsis D10590	No migration of ink or adhesive into syringe

The methods used to test the stability samples are compendial methods with the exception of Celsis method D10590 (adhesive migration).

Comment: It may be noted that the primary stability protocol for the NDA involves both bracketing and matrixing approaches combined. All presentations are not represented, but only the 1 mL fill in the 6 ml barrel, and the 10 ml fill in the 12 ml barrel. In addition, many tests are only performed at annual intervals in the long term stability protocol. The acceptability of this approach should be determined after looking at the stability data provided. Stability specifications incorporate the drug product release specifications as well as others. The applicant states that under accelerated and long term stability storage conditions, all lots have meet specifications after 6 months of storage at the accelerated storage conditions and after 18 months at the long term storage conditions, with the exception of some 6 month pH failures for 3 batches stored under accelerated stability conditions. No summary data are provided, one must review batch to batch tables.

There are a significant number (35) of supportive stability batches for the 510(k) device “Normal Saline I.V. Flush Syringes” (which differ from the proposed product mainly in that the device wasn’t terminally sterilized). These include at least some of the other presentations as well as those used for the primary stability batches. Some of the primary stability tests were not performed on the supportive stability batches. Matrixing was also performed in this study; a number of the tests (including “concentration”) were only performed annually. The supportive stability data are indicated to include points through

24 months and the applicant claims that “There were no indications that the identity, strength, quality or purity of the lots was adversely affected.”

Stability data are not reviewed here.

Supporting DMFs:

DMFs (b) (4)

DMF #	TYPE	HOLDER	ITEM REFERENCED
(b) (4)	III	(b) (4)	(b) (4)
	III		
	III		
	III		

Letters of authorization are provided in Module 1 for the above-listed DMFs.

IND for this drug product:

There appears to be no real IND for this drug product, however an IND number was assigned for a pIND meeting request. This IND is # (b) (4) (See comments at the beginning of this review.)

Filing Check List (reproduced from filing meeting slides):

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		Form 356h contains an attached Table listing facilities, and each facility is indicated to be ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	x		Categorical exclusion request in Module 1
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		
9	Have stability data and analysis been provided to support the requested expiration date?	x		stability data have been provided but no analysis
10	Has all information requested during the IND phase,	x		

	and at the pre-NDA meetings been included?			
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		minimal information; no other formulations are described
14	Is there a Methods Validation package?	x		

Certain review issues which were noted are listed below for consideration by the reviewer

The reviewer should check to see that the applicant has a written agreement with (b) (4) to notify the applicant in advance of any changes in the manufacturing process or its controls.

It may be noted that extractables and leachables from container closure components of the drug product are not discussed. It is also noted that the stability study does not include leachables testing. Such information and testing should be requested from the applicant (see comments for applicant, below).

The reviewer needs to ascertain that the other device components (other than the plunger stoppers) are (b) (4)

The reviewer should consider asking for one-time characterization information on (b) (4) of the sterilized product.

The primary stability protocol for the NDA involves both bracketing and matrixing approaches combined. All presentations are not represented, but only the 1 mL fill in the 6 ml barrel, and the 10 ml fill in the 12 ml barrel. In addition, many tests are only performed at annual intervals in the long term stability protocol. The acceptability of this approach should be determined after looking at the stability data provided.

Comments for the applicant (for filing letter):

Specify which tests you perform on receipt of the drug substance, and confirm that you periodically perform all tests for which results are accepted on a Certificate of Analysis.

Clarify whether the (b) (4) of the container closure system of the drug substance conforms to USP physicochemical tests and specify its food additive status.

Provide the most recent stability results for the drug substance and confirm that stability testing by (b) (4) is continuing. Provide assurance that the data will be provided to you, and that you will submit the data to this application.

Provide data pertaining to the extractables of the drug product container closure system, and the leachables that may appear in the drug product over its shelf life.

Identify the approved vendors who manufacture the individual components of the syringe device, and indicate compositions of the components if any additives are used by the manufacturers of the components.

Clarify the attachments to section 3.2.P.5.1 (Material Specifications for each presentation of drug product) which are titled "Normal Saline I.V. Flush Syringes..."; do these apply completely to the proposed Sodium Chloride Injection product? This also applies to all other documents in the NDA which are identified as being for the Normal Saline I.V. Flush Syringe.

Modify your drug product specifications to include USP monograph tests for identification of sodium and of chloride.

The following comments pertain to the drug product container closure system.

Provide a certificate of analysis for the (b) (4) used on the plunger stoppers and syringe barrel, and provide information on the impurity profile of the (b) (4)

Provide specifications for the amounts of (b) (4) (maximum and minimum) used on the plunger stoppers and syringe barrels.

Clarify with data whether any constituents of the secondary container/closure components may migrate into the drug product formulation through the primary packaging.

Recommendation: Acceptable for filing.

Attachment A: Nanotechnology product evaluating questions:

<p>1, This review contains new information added to the table below: ___x___ Yes; _____ No</p> <p>Review date: _____</p>
<p>2) Are any nanoscale materials included in this application? (If yes, please proceed to the next questions.) Yes _____; No ___x___; Maybe (please specify) _____</p>
<p>3 a) What nanomaterial is included in the product? (Examples of this are listed as search terms in Attachment B.) _____</p>
<p>3 b) What is the source of the nanomaterial? _____</p>
<p>4) Is the nanomaterial a reformulation of a previously approved product?</p> <p>Yes _____ No _____</p>
<p>5) What is the nanomaterial functionality?</p> <p>Carrier _____; Excipient _____; Packaging _____</p> <p>API _____; Other _____</p>
<p>6) Is the nanomaterial soluble (e.g., nanocrystal) or insoluble (e.g., gold nanoparticle) in an aqueous environment?</p> <p>Soluble _____; Insoluble _____</p>
<p>7) Was particle size or size range of the nanomaterial included in the application?</p> <p>Yes _____ (Complete 8); No _____ (go to 9).</p>
<p>8) What is the reported particle size?</p> <p>Mean particle size _____; Size range distribution _____; Other _____</p>
<p>9) Please indicate the reason(s) why the particle size or size range was not provided:</p> <p>_____</p> <p>_____</p>
<p>10, What other properties of the nanoparticle were reported in the application (See Attachment E)? _____</p>
<p>11) List all methods used to characterize the nanomaterial? _____</p> <p>_____</p>

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

/s/

ALAN C SCHROEDER
04/15/2011

PRASAD PERI
04/15/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

**CMC MICRO & STERILITY ASSURANCE
REVIEW REQUEST**

TO (Division/Office): **New Drug Microbiology Staff**

FROM: Swati Patwardhan 301-796-4085

E-mail to: CDER OPS IO MICRO

Paper mail to: WO Bldg 51, Room 4193

PROJECT MANAGER (if other than sender):

REQUEST DATE
3/18/2011

IND NO.

NDA NO.202-832

TYPE OF DOCUMENT-original

DATE OF DOCUMENT
1/31/2011 (accepted on
3/7/2011)

NAMES OF DRUG (b) (4)
(Sodium Chloride) Injection

PRIORITY CONSIDERATION

PDUFA DATE: 1/7/2012

DESIRED COMPLETION DATE:
11/7/2011

NAME OF APPLICANT OR SPONSOR: Medefil Inc.

GENERAL PROVISIONS IN APPLICATION

30-DAY SAFETY REVIEW NEEDED

NDA FILING REVIEW NEEDED BY: May 6, 2011

BUNDLED

DOCUMENT IN EDR

CBE-0 SUPPLEMENT

CBE-30 SUPPLEMENT

CHANGE IN DOSAGE, STRENGTH / POTENCY
 PA Supplement

COMMENTS / SPECIAL INSTRUCTIONS:

We request a review of the following sections of this NDA for all microbiology related aspects including the drug product sterilization process, its validation and release & stability sterility testing (the data are in multiple paper volumes which include various attachments).

Section 3.2.P.3. manufacture (multiple subsections, as appropriate in addition to that listed below))

Section 3.2.P.3.5 Process validation (sections as appropriate in addition to sections listed below)

Attachment 3.2.P.3.5-1: Sterilization Process Validation Package

Section 3.2.P.4.1 specifications for the excipient, Water for Injection, USP

Attachments 3.2.P.4.2-1, -2 and -3 Results for Water for Injection

Section 3.2.P.4.3 validation of analytical procedures (including attachment)

Section 3.2.P.5 control of drug product (subsections as appropriate in addition to those listed below)

Section 3.2.P.5.1 drug product specifications

Section 3.2.P.5.2 and subsections as appropriate - analytical procedures (drug product)

Section 3.2.P.5.3 validation of analytical procedures (with appropriate subsections)

Section 3.2.P.5.4 batch analyses

Section 3.2.P.7 container closure system (as appropriate, re: sterilization of container closure components)

Section 3.2.P.8 stability data (drug product) as appropriate

Section 3.2.R.1.P executed batch records, as appropriate

SIGNATURE OF REQUESTER: Swati Patwardhan

Reference ID: 2921374

REVIEW REQUEST DELIVERED BY (Check one):

DARRTS EDR E-MAIL MAIL HAND

DOCUMENTS FOR REVIEW DELIVERED BY (Check one):

EDR E-MAIL MAIL HAND

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

/s/

SWATI A PATWARDHAN
03/21/2011