

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**202832Orig1s000**

**OTHER REVIEW(S)**

505(b)(2) ASSESSMENT

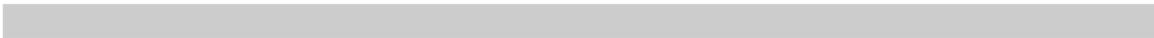
Application Information		
NDA # 202832	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: (b) (4)		
Established/Proper Name: sodium chloride injection in plastic syringes (1mL, 2mL, 2.5mL, 3mL, 5mL, 10mL)		
Dosage Form: injection		
Strengths: 0.9%		
Applicant: Medefil		
Date of Receipt: Received February 1, 2011; User Fee Received/Small Business Waiver Accepted: March 7, 2011 (Division Receipt Date)		
PDUFA Goal Date: January 7, 2011		Action Goal Date (if different): January 6, 2012
Proposed Indication(s): To dilute or dissolve drugs for intravenous, intramuscular, or SQ injection.		

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product OR is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?

YES  NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE  
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

Source of information* (e.g., published literature, name of referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
0.9 Sodium chloride injection, USP- Package Insert, Hospira, Inc., Lake Forest IL, 60045 USA	1.1 Dilution or Dissolution 2.1 Recommended Dose; 2.3 Preparation and Handling Precautions; 5.3 Pregnancy (Teratogenic Effects); 6 Adverse Reactions; 8.4 Pediatric Use; 11 Description; 12 Clinical Pharmacology

\*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

N/A. The sponsor has requested a waiver of in vivo bioavailability requirements

**RELIANCE ON PUBLISHED LITERATURE**

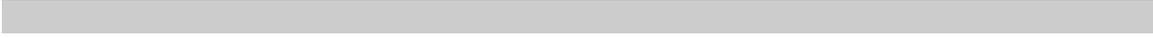
- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES  NO   
*If “NO,” proceed to question #5.*

- (b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES  NO   
*If “NO,” proceed to question #5.  
If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?  
YES  NO



**RELIANCE ON LISTED DRUG(S)**

*Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.*

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES  NO

*If "NO," proceed to question #10.*

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Sodium Chloride 0.9% injection in plastic container	NDA 18803 (Hospira)	Y

*Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A  YES  NO

*If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".*

*If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.*

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES  NO

*If "YES", please list which drug(s).*

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES  NO   
If “YES”, please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES  NO   
If “YES”, please list which drug(s) and answer question d) i. below.  
If “NO”, proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES  NO

*(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)*

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsule to solution”).

Sodium chloride is considered a drug when used for diluting or dissolving drugs for IV, IM or SQ injection. This is a combination product where the sponsor would like to change from a plastic container to a 510k approved plastic syringe (prefilled). Thus, a new drug application was filed. The change is the change from their plastic container (vial) to a plastic syringe.

*The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.*

*The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered **YES to question #1**, proceed to question #12; if you answered **NO to question #1**, proceed to question #10 below.*

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including*

potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES  NO

If "**NO**" to (a) proceed to question #11.  
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?

YES  NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

**Note** that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES  NO

If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?

YES  NO

If **“YES”** and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If **“NO”** or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Sodium Chloride 0.9% in plastic container 9mg/mL (NDA 20178-Baxter, NDA16677-Baxter, NDA17464-Braun, NDA 19635-Braun)

Sodium chloride 0.45% injection in plastic container (NDA 18016- Baxter)

3% sodium chloride (NDA19022-Baxter)

5% sodium chloride (NDA 19022-Baxter)

ANDA products also exist

### PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed  proceed to question #14

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES  NO

If **“NO”**, list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

Method(s) of Use/Code(s):

- 15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

(a) Patent number(s):

- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?

YES  NO

*If "NO", please contact the applicant and request the signed certification.*

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.

YES  NO

*If "NO", please contact the applicant and request the documentation.*

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES  NO  Patent owner(s) consent(s) to an immediate effective date of approval

Drafted by: EChung-Davies  
Initialed by: SBarnes  
505b2 team  
Finalized by: EChung-Davies

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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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EUNICE H CHUNG-DAVIES  
01/05/2012

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF PULMONARY, ALLERGY, AND  
RHEUMATOLOGY PRODUCTS

**DATE:** December 16, 2011

**FROM:** Carol F. Hill, M.S., Senior Regulatory Health Project Manager

**APPLICATION/DRUG:** NDA 202832/NaCl Injection

**SUBJECT:** Labeling Negotiations

**BACKGROUND**

On November 23, 2011, the FDA sent labeling edits and comments to Medefil regarding the package insert and carton and container labels for NDA 202832 submitted on July 5, 3011. Medefil responded via email on December 12, 2011. Medefil requested clarification regarding the FDA comment listed below.

**FDA Comment**

We have investigated the regulatory precedent for combining drug and device labels for your product. The separation of the drug and device indications has been deemed necessary.

**Medefil's Question for Clarification**

Could you please provide the basis for deeming the separation of the drug and device indications to be necessary? (b) (4)

(b) (4)

Please clarify FDA's position on this matter.

**SUMMARY OF TELEPHONE CONVERSATION**

The FDA spoke with (b) (4) and Pradeep Aggrawal of Medefil, LLC on December 14, 2011 and discussed the issue of inclusion of a device indication in a PLR drug label. The FDA explained that the regulation of sodium chloride (NaCl) products for dilution and administration of drugs injection as well as for flushing intravenous access devices has evolved over the years. Currently, when NaCl solutions are to be used as diluents for other drugs they are regulated by CDER as a drug product. Conversely, when the intended use is that of a device to flush intravenous access devices, the product is regulated as a device under the auspices of CDRH. Because labeling/intended use instructions are handled and regulated

differently by the separate drug and device Centers, a combined drug/device package insert is unacceptable.

Medefil stated that while understanding the FDA's stance, they were not comfortable with a requirement for placing their product on the market with two separate labels for essentially the identical product because of the obvious issues surrounding possibly having the label the same product for 2 different uses and with 2 different sets labels/instructions. The FDA stated that they will confer with CDRH regarding the combined labeling issue and look into whether other saline ANDAs or NDAs contained combined device/drug labeling. and hoped to settle any issues by January 7, 2011. Medefil noted that they will provide carton and container labeling and submit a proposal on how to appropriately label and package the product.

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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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EUNICE H CHUNG-DAVIES  
01/04/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label and Labeling Review**

Date: December 06, 2011

To: Badrul Chowdhury, MD, Director  
Division of Pulmonary and Allergy Products

Reviewer(s): Walter Fava, RPh, MSED, Safety Evaluator  
Division of Medication Error Prevention and Analysis

Team Leader Zachary Oleszczuk, PharmD, Team Leader  
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, RPh, Director  
Division of Medication Error Prevention and Analysis

Product Name(s): Sodium Chloride Injection, USP, 0.9%

Application Type/Number: NDA 202832

Applicant: Medefil, Inc.

OSE RCM #: 2011-1117

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

## 1 INTRODUCTION

This review evaluates the proposed container labels, carton and insert labeling for Sodium Chloride Injection, USP, 0.9% for NDA 202832. This review responds to a request from the Division of Pulmonary and Allergy Products (DPARP) to review the container labels and carton and insert labeling for this Application.

### 1.1 PRODUCT INFORMATION

Sodium Chloride Injection, USP, 0.9% is indicated for diluting or dissolving drugs for intravenous, intramuscular, or subcutaneous injection, according to instructions of the manufacturer of the drug to be administered, or (b) (4) for flushing (b) (4) indwelling access devices only. The volume of preparation is dependent on the vehicle concentration, dose, and route of administration, as recommended by the manufacturer. It will be available in single-use, plastic luer lock pre-filled syringes in the following fill volumes: 1 mL, 2 mL, 2.5 mL, 3 mL, and 5 mL in 6 mL syringes; and 2 mL, 5 mL, and 10 mL in 12 mL syringes and packaged in 30, 60, or 120 count boxes. The pre-filled syringes are stored at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F).

## 2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis<sup>1</sup>, the principles of human factors, and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Syringe Labels submitted on April 20, 2011 (Appendix A)
- Carton Labeling submitted on April 20, 2011 (Appendix A)
- Insert Labeling submitted on April 20, 2011
- Heparin 10 units/mL pre-filled syringe labels and carton labeling submitted on August 19, 2011 (Appendix B)
- Heparin 100 units/mL pre-filled syringe labels and carton labeling submitted on August 19, 2011 (Appendix B).

Additionally, since Sodium Chloride Injection, USP, 0.9% is currently marketed, DMEPA searched the FDA Adverse Event Reporting System (AERS) database to identify medication errors involving Sodium Chloride Injection, USP, 0.9%. The August 9, 2011 AERS search used the following search terms: active ingredient “sodium chloride injection%”, and verbatim terms “0.9% sodium chloride injection%”. The reaction terms used were the MedDRA High Level Group Terms (HLGT) “Medication Errors” and “Product Quality Issues”. No time limitation was set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the label or labeling of the product, the case was considered pertinent to this review. Reports excluded from the case series include those that did not describe a medication error involving pre-filled syringes.

### **3 RESULTS**

#### **3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) CASES**

Following the exclusions in Section 2, our search of the AERS database retrieved eight relevant cases described below (See Appendix C for ISR numbers).

##### **3.1.1 Wrong Drug (n=4)**

Of the four wrong drug medication errors identified, two involved confusion between prefilled syringes of sodium chloride and heparin due to similar cap colors, labels and labeling. One of these reports involved syringes manufactured by Abbott but did not provide any outcome information, while the other report cited the potential for error due to similar carton labeling for prefilled syringes of heparin and sodium chloride manufactured by Kendall.

The remaining two reports from 2006 cited confusion between sodium chloride prefilled syringes and morphine prefilled syringes and involved patients receiving morphine instead of sodium chloride. Neither case included any manufacturer information. In one of these cases, a nurse flushed a patient's intravenous tubing with morphine instead of sodium chloride but the patient was receiving morphine anyway and did not experience any adverse events. In the other case, a child in cardiac arrest received morphine accidentally during resuscitation efforts instead of sodium chloride. The child expired due to sepsis.

##### **3.1.2 Other (Labeling n=4)**

One case involved confusion as to whether or not the prefilled syringes of sodium chloride USP contained preservative because the prefilled syringes lacked any statement about the presence of a preservative on the principal display panel. The name of the manufacturer was not included in the report.

Two cases involved prefilled sodium chloride syringes packaged individually in plastic overwraps. The reports stated that once the overwraps were removed, important identifying information was missing as it was only on the overwrap and not on the syringe. One of these cases stated the overwrapped prefilled sodium chloride syringes were manufactured by (b) (4) and Rocap. The other case did not provide any manufacturer information.

The fourth case cited the wrong NDC number printed on 10 mL and 12 mL prefilled syringes of sodium chloride manufactured by Excelsior Medical, resulting in the wrong size syringes being distributed.

## 4 DISCUSSION

Prefilled syringes have overlapping product characteristics which may contribute to product selection errors, such as syringe sizes, fill volumes, similar use of colors, and limited space for prominently presenting the product name and other important identifying information. This is compounded by manufacturers who market different products in prefilled syringes using similar labels and labeling across product lines. The similar appearance of the labels and labeling of different products from the same manufacturer, is likely to have contributed to the postmarketing errors evaluated in this review. Based on the postmarketing cases of medication errors involving prefilled sodium chloride syringes and prefilled Heparin and prefilled Morphine Sulfate syringes, DMEPA verified that the Applicant also manufactures prefilled syringes of Heparin. We requested a copy of their Heparin prefilled syringe labels and labeling to ensure that they are well differentiated from the proposed labels and labeling for their prefilled syringes of Sodium Chloride Injection, USP.

We also considered other packaging and labeling issues identified in the AERS reports which could be relevant to the proposed packaging and labeling of the Applicant's prefilled sodium chloride, USP syringes. However, since no labeled plastic overwrap is proposed for this product, and the label is affixed directly to the syringe, those errors involving syringes that have no information on them after removing the overwrap would not be relevant to this product. One case involved confusion as to whether the prefilled syringe of sodium chloride, USP contained preservative. The proposed labels and labeling includes a statement that the product is preservative free, so we do not anticipate confusion concerning the preservative. Additionally, Sodium Chloride Injection, USP, as defined by the USP monograph does not contain preservative, thus including preservative free statements on the labels and labeling of prefilled sodium chloride, USP products may not be necessary. However, most health care providers are unfamiliar with USP and do not reference this book for product information at the point of care and because we have a report of confusion due to the lack of this statement on the label, it may be useful to keep this statement on the syringe.

## 5 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed syringe labels and carton labeling introduce vulnerability that can lead to medication errors because the presentation of important information is not optimal. DMEPA notes there is no color overlap with the proposed syringe labels and carton labeling of the Sodium Chloride Injection, USP, 0.9% pre-filled syringes and the currently marketed Heparin 10 unit/mL and 100 unit/mL pre-filled syringe labels and carton labeling from the same manufacturer, which will help minimize the potential for confusion between these products. We also acknowledge that the Applicant has withdrawn the proposed proprietary name, (b) (4) and will market the product under the established name, 'Sodium Chloride Injection, USP, 0.9%', and (b) (4) will be removed from the labels and labeling. We do however have the following recommendations:

- A. Syringe Label (1 mL fill in 6 mL; 2 mL fill in 6 mL; 2.5 mL in 6 mL; 3 mL fill in 6 mL; 5 mL fill in 6 mL; 3 mL fill in 12 mL; 5 mL fill in 12 mL; 10 mL fill in 12 mL)
1. Delete the proposed proprietary name, (b) (4)
  2. Revise the presentation of the established name to read, 'Sodium Chloride Injection, USP, 0.9%'.
  3. Increase the font size and prominence of the Sodium Chloride Injection, USP, 0.9%' statement, to help minimize the risk of wrong product selection.
  4. Revise the statement, (b) (4) to read, 'Not made with natural rubber latex'.
  5. To decrease clutter and improve readability, please make the following revisions:
    - a. Delete the statement, (b) (4)
    - b. Delete the (b) (4) appearing after, 'Syringe'.
    - c. Relocate the statement, '0.308 mOSM/mL', to appear following the statement, 'Each mL contains 9 mL Sodium Chloride, USP' and before the statement, '...in Water for Injection'.
    - d. Delete the (b) (4) on the principal display panel.
- B. Carton Labeling (60 count cartons of: 1 mL fill in 6 mL; 2 mL fill in 6 mL; 2.5 mL in 6 mL; 3 mL fill in 6 mL; 5 mL fill in 6 mL; 3 mL fill in 12 mL; 5 mL fill in 12 mL; 10 mL fill in 12 mL)
1. See comments A.1 through A.5(a-d) above and apply accordingly.
  2. Revise the statement, (b) (4), to read, 'Usual Dose'.
  3. Include the concentration statement, '0.308 mOSM/mL', as presented on the syringe label.
  4. Delete the statement, (b) (4), which appears at the top of the principal display panel.
- C. Insert Labeling
1. Revise the package insert to omit (b) (4) as the proprietary name.
  2. Revise the presentation of the 'How Supplied' section to remove (b) (4) statement following each syringe size.

If you have further questions or need clarifications, please contact Nichelle Rashid, Project Manager, at 301-796-3904.

18 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

**Appendix C: Summary of AERS cases identified**

ISR #	Case #	Type	Date Received	Narrative	Outcome
4096511	6518405	Potential	04/22/2003	Look-alike packaging for Kendall's heparin lock flush syringe 10 units/mL 2.5mL syringes-NDC 17474-0123-2- and Kendall's 0.9% NaCl flush 2.5mL syringes -NDC 17474-3002-2- Both products are packaged in the same box labeled "Flush syringes", preprinted on three sides of the box. The only distinguishing feature is the label affixed to the top. The label runs down the front of the box, but if the tops are removed and both boxes were turned sideways on a shelf they look exactly the same. Medication error	NA
4705024	5832449	Other: Labeling	06/03/2005	Abstracted by onsite FDA rep 0.9% Sodium Chloride injection prefilled 10 ml syringe has clear plastic wrapper with lot number and expiration date stamped on wrapper. Once wrapper is removed expiration, lot number and NDC are not visible because They are not stamped on the syringe.. Medication Error	NA

3461907	3438401	Other: Labeling	02/24/2000	A prefilled sodium chloride syringe (5 mL in a 12 mL syringe) which has all labeling printed on the plastic overwrap and nothing printed on the syringe, so when the syringe is removed from the plastic overwrap, the syringe has no identifying information on it. The report referenced two manufacturers, (b) (4) and 'Rocap' but did not cite any specific errors which occurred as a result of this labeling convention.	NA
4923309	5996109	Wrong drug	02/22/2006	confusion resulting from similar green caps on pre-filled syringes of morphine and sodium chloride which resulted in a nurse flushing a patient's intravenous tubing with morphine instead of sodium chloride. The patient was receiving morphine and did not experience any harm. The report did not include any manufacturer information	No harm
5097012	6131177	Wrong drug	(b) (6)	A child in cardiac arrest who received morphine accidentally during resuscitation efforts instead of sodium chloride. The patient expired due to sepsis.	Cardiac arrest/death

5606138	6541957	Other: Labeling	01/25/2008	The wrong NDC number on 10 mL and 12 mL prefilled syringes of sodium chloride manufactured by Excelsior Medical. The NDC number for the 12 mL syringe is labeled on the 10 mL syringe resulting in the wrong size syringe being distributed. The larger syringe is necessary for maintaining pressure in central intravenous lines.	NA
3439323	3411911	Wrong drug	01/07/2000	Involved 'errors' occurring due to similar purple syringe caps causing confusion between heparin and sodium chloride flushes manufactured by Abbott Laboratories. No additional details were provided.	NA
3715351	3648452	Other: Labeling	05/02/2001	Confusion whether or not prefilled syringes of sodium chloride USP contains a preservative because it lacks any statement about the presence of a preservative on the principal display panel of the syringe label. The specific manufacturer was not included in the report.	NA

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/s/  
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WALTER L FAVA  
12/06/2011

ZACHARY A OLESZCZUK  
12/06/2011

CAROL A HOLQUIST  
12/06/2011

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** October 19, 2011

**To:** Eunice Chung-Davies, Regulatory Project Manager  
Division of Pulmonary, Allergy, and Rheumatology Products  
(DPARP)

**From:** Roberta Szydlo, Regulatory Review Officer  
Division of Professional Promotion (DPP), Office of Prescription  
Drug Promotion (OPDP)

**CC:** Lisa Hubbard, Group Leader, DPP  
Matthew Falter, Regulatory Review Officer, Division of Direct-to-  
Consumer Promotion (DDTCP), OPDP  
Robyn Tyler, Group Leader, DDTCP

**Subject:** NDA 202832  
DDMAC labeling comments for Sodium Chloride Injection USP,  
0.9% Syringe

---

OPDP has reviewed the proposed product labeling (PI) and carton and container labeling for Sodium Chloride Injection USP, 0.9% Syringe submitted for consult on March 23, 2011. OPDP's comments on the PI are based on the proposed draft marked-up labeling titled "NaCl label Highlights.doc" and "NDA 202832 sodium chloride SCPI\_OCT2011.doc" that were sent via email from DPARP to OPDP on October 12, 2011. OPDP's comments on the PI are provided directly in the marked-up document attached (see below).

OPDP has also reviewed the proposed carton and container labeling titled "nda202832 carton and container labels\_color.pdf" which was last modified in the DPARP eRoom on August 31, 2011 at 10:17am. We have no comments at this time on the proposed carton and container labeling.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or [roberta.szydlo@fda.hhs.gov](mailto:roberta.szydlo@fda.hhs.gov).

7 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/  
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ROBERTA T SZYDLO  
10/19/2011

## **Memo-To-File**

NDA No.: 202,832  
Submission Date: January 18, 2011  
Reviewer Name: Luqi Pei, Ph.D.  
Completion Date: August 31, 2011  
Subject: Labeling review - nonclinical

This memo documents a decision of the review team regarding the nonclinical sections of the label of the 0.9% sodium chloride injectables (NDA 202,832). The clinical and nonclinical disciplines of the team discussed the format and content of the product label on August 31, 2011. It was agreed that the product label should be kept as succinct as possible. It was felt that the draft text for Sections 8.1 and 13 as recommended in the nonclinical review completed by Dr. Luqi Pei on May 23, 2011 do not convey any clinically meaningful data. These sections, therefore, should be eliminated.

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/s/  
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LUQI PEI  
08/31/2011

**MANDATORY:** Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

**For additional information:** Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: \_\_\_\_\_

Reviewer Initials: \_\_\_\_\_

Supervisory Concurrence: \_\_\_\_\_

## Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center:

Division: DAGID

Mail Code: HF

Consulting Reviewer Name: Nikhil Thakur

Building/Room #: WO 66 Room 2562

Phone #: 301-795-5536

Fax #:

Email Address: Nikhil.Thakur@fda.hhs.gov

RPM/CSO Name and Mail Code:

**From (Originating Center):**

Center: CDER

Division: Division of Pulmonary, Allergy, and Rheumatology Products

Mail Code: HF-570

Requesting Reviewer Name: Eunice Chung-Davies

Building/Room #: WO BLDG 22; Room 3343

Phone#: 301-796-4006

Fax #: 301-796-9728

Email Address: Eunice.Chung-Davies@fda.hhs.gov

RPM/CSO Name and Mail Code: Eunice Chung-Davies

Requesting Reviewer's Concurring

Supervisor's Name: Sandy Barnes

**Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.**

Date of Request: May 6, 2011

**Requested Completion Date:** August 10, 2011 (Mid Cycle Meeting)

Submission/Application Number: NDA 202832  
(Not Barcode Number)

Submission Type: NDA (original)  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: March 7, 2011

Official Submission Due Date: January 7, 2011

Name of Product:

Name of Firm:

Intended Use:

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

We are requesting participation in the NDA review of this product. This new drug application is for a combination product consisting of saline (sodium chloride 0.9%) and a syringe. Saline is considered a drug when used for the purpose of dissolving drugs. The syringe is an approved 510k device. We are requesting participation at the midcycle review meeting scheduled on August 10, 2011 at 1:30 to 3 P.M. in White Oak Campus Bldg 22 Room 3270. Once a reviewer is assigned, certain volumes of paper copy will be delivered as we only have limited copies available. Please evaluate the performance, robustness and manufacturability of the device as appropriate. Please perform a human factors evaluation as appropriate. Please contact me if you have any questions. Thank you.

Reference ID: 2943238

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/s/

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EUNICE H CHUNG-DAVIES  
05/06/2011

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--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page <http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>.

**For Consulting Center Use Only:**

Date Received: \_\_\_\_\_

Assigned to: \_\_\_\_\_

Date Assigned: \_\_\_\_\_

Assigned by: \_\_\_\_\_

Completed date: 8/5/11

Reviewer Initials: COM

Supervisory Concurrence: NT For Jackie Ryan

8/5/2011

### Intercenter Request for Consultative or Collaborative Review Form

**To (Consulting Center):**

Center: CDRH

Division: DAGID

Mail Code: HF

Consulting Reviewer Name: Nikhil Thakur

Building/Room #: WO 66 Room 2562

Phone #: 301-795-5536

Fax #: \_\_\_\_\_

Email Address: Nikhil.Thakur@fda.hhs.gov

RPM/CSO Name and Mail Code: \_\_\_\_\_

**From (Originating Center):**

Center: CDER

Division: Division of Pulmonary, Allergy, and Rheumatology Products

Mail Code: HF-570

Requesting Reviewer Name: Eunice Chung-Davies

Building/Room #: WO BLDG 22; Room 3343

Phone#: 301-796-4006

Fax #: 301-796-9728

Email Address: Eunice.Chung-Davies@fda.hhs.gov

RPM/CSO Name and Mail Code: Eunice Chung-Davies

Requesting Reviewer's Concurring Supervisor's Name: Sandy Barnes

**Receiving Division:** If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: May 6, 2011

Requested Completion Date: August 10, 2011 (Mid Cycle Meeting)

Submission/Application Number: NDA 202832  
(Not Barcode Number)

Submission Type: NDA (original)  
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product:  Drug-device combination  Drug-biologic combination  Device-biologic combination  
 Drug-device-biologic combination  Not a combination product

Submission Receipt Date: March 7, 2011

Official Submission Due Date: January 7, 2011

Name of Product: (b) (4) (sodium chloride 0.9% injection) in plastic syringes

Name of Firm: Medefil

Intended Use: To dilute or dissolve drugs for intravenous, intramuscular, or SQ injection and to maintain patency of IVADS

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

Labeling  
Quality Information

Documents to be returned to Requesting Reviewer?  Yes  No

**Complete description of the request.** Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request:  Consultative Review  Collaborative Review

We are requesting participation in the NDA review of this product. This new drug application is for a combination product consisting of saline (sodium chloride 0.9%) and a syringe. Saline is considered a drug when used for the purpose of dissolving drugs. The syringe is an approved 510k device. We are requesting participation at the midcycle review meeting scheduled on August 10, 2011 at 1:30 to 3 P.M. in White Oak Campus Bldg 22 Room 3270. Once a reviewer is assigned, certain volumes of paper copy will be delivered as we only have limited copies available. Please evaluate the performance, robustness and manufacturability of the device as appropriate. Please perform a human factors evaluation as appropriate. Please contact me if you have any questions. Thank you.

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/s/  
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EUNICE H CHUNG-DAVIES  
05/06/2011



Food and Drug Administration  
Center for Devices and  
Radiological Health  
Office of Device Evaluation  
White Oak Building 66  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

**Date:** August 5, 2011  
**From:** Keith G Marin, Nurse Reviewer, WO66, RM 2567  
General Hospital Devices Branch, DAGID, ODE, CDRH  
**To:** Eunice Chung-Davies, Senior Regulatory Health Project Manager, WO22 RM3343  
HF-570  
OND/ODEII/DPARP  
**Subject:** CDRH Consult, NDA 202832 Medefil Industry Meeting  
(b) (4) (sodium chloride 0.9% injection) in plastic syringes

**1. Issue**

The Center for Drug Evaluation and Research has requested a consult from the Center for Devices and Radiological Health (CDRH), regarding NDA 202832. The device constituent of this combination product references the Medefil Normal Saline IV Flush Syringe (K020999 and K091583), and the Medefil Heparin I.V. Flush Syringe (K020996 and K092491).

**2. Device Description**

The device constituent of this combination product appears to be the Medefil Normal Saline Flush Syringe. The Normal Saline Flush Syringe is a single dose, disposable, sterile, plastic pre-filled syringe. The device consists of a hypodermic syringe with a hypodermic barrel, stopper plunger, plunger rod, tip cap and prefilled with 0.9% Sodium Chloride Injection, USP. The proposed product will be supplied in 1mL, 2mL, 2.5mL, 3mL, 5mL, and 10mL fill volume in plastic syringes.

**3. Documents Reviewed**

PIND (b) (4)  
K020999, K091583, K020996, K092491  
DMF (b) (4)

**4. CDRH Review and Comments**

CDRH's Review of the device constituent for this Combination Product consisted of an assessment of Device Performance and Human Factors.

Human Factors for the pre-filled syringe was evaluated (b) (4)

This device does not contain Electrical and/or Software Components.

The Sponsor provided letters of authorization from (b) (4) to access their Drug Master Files (DMF (b) (4) and DMF (b) (4) for the (b) (4), and

(b) (4). CDRH has reviewed this DMF, and has posed questions to the DMF holder, if required.

The sponsor has provided a letter of authorization from (b) (4) to access their Drug Master Files (DMF (b) (4)) for their (b) (4). CDRH has reviewed this DMF, and has posed questions to the DMF holder, if required.

The sponsor provided a letter of authorization from (b) (4) to access their Drug Master Files (DMF (b) (4)) for their (b) (4). CDRH has reviewed this DMF, and has posed questions to the DMF holder, if required.

To maintain confidentiality of the information within these DMF's in accordance with 21 CFR 314.430 and 21 CFR 20.61, we have specifically addressed our questions to the various DMF Holders or to the Sponsor (where appropriate). For convenience, we have provided the points of contact where the questions concerning the various DMFs should be sent.

#### Device Performance

NDA 202832 references the various 510(k)'s (listed above) that will be pre-filled with 0.9% Normal Saline. Specific concerns regarding the prefilled syringe constituent will be addressed below. However, you reference 510(k)s for pre-filled heparin syringes but do not mention using pre-filled heparin syringes in your NDA application. Clarification has been repeatedly requested by CDER but not acknowledged.

NDA 202832 did not provide any information regarding the performance of the device (dimensional and functional testing). However, the syringes that you intend to prefill are all cleared syringes. As a result, there are no additional performance concerns.

#### Human Factors

NDA 202832 pre-filled 0.9% Normal Saline syringes are intended to be used (b) (4). You have provided the patient insert that will be included with the device. However, you have not indicated how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a justification for why an HF/usability validation study is not necessary for the proposed product.

#### Biocompatibility

Biocompatibility in NDA 202832 was not addressed by CDRH. Discussions with CDER indicated that as the syringe to be used is 510(k) cleared, it is their belief that biocompatibility would be acceptable and not need to be evaluated again.

#### Drug / Device Interaction

With regard to Drug / Device interaction, CDRH defers to CDER to determine whether the stability of the drug can be maintained over its shelf life, accelerated aging and expiration date testing.

#### Sterilization

With regard to sterilization, CDRH defers to CDER to determine whether the pre-filled syringe will be able to maintain sterility over the shelf life of the product.

### **5. CDRH Recommendation:**

### Performance

1. You have indicated that your syringe is intended to be pre-filled with saline. However, you have referenced two pre-filled heparin syringes in this submission. It is not clear to the Agency why you have referenced these syringes as there is no mention of heparin within your submission. Please provide clarification on why you have included the pre-filled heparin syringe as one of your listed predicate devices.

### Human Factors

The submission does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a justification for why an HF/usability validation study is not necessary for the proposed product. If you choose to submit an HF/usability validation protocol, please note the following comments:

2. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable. The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

a. Devices and Labeling Used and Training

For design validation, the devices used in your testing should represent the final design, which includes instructions for use, or any other labeling materials.

The training you provide to your test participants should approximate the training that your actual end users will receive. Please describe the training you plan to provide in your validation study and how it corresponds to realistic training levels.

Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

b. User Tasks and Use-Related Risks Analysis

(b) (4) (sodium chloride 0.9% injection in plastic syringes)

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

c. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

Identification of potentially challenging use conditions should be derived through analyses of use hazards prior to conducting validation testing and aspects of use that can be reasonably anticipated, such as use with gloves or wet fingers, dim lighting, noisy situations, etc., should be included in your testing. Please evaluate use of your device under whatever conditions you identify as potentially occurring and hazardous.

Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

d. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

e. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

Empirical Data – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

(b) (4) (sodium chloride 0.9% injection in plastic syringes)

Qualitative Data – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Please describe and provide a rationale for including each type of data you collect.

3. Please review the Center Guidance on Human Factors and Risk Management available at:  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>

Questions to (b) (4) (DMF (b) (4) and DMF (b) (4).

CDRH does not have any questions regarding the information provided in NDA 202832.

Questions to (b) (4) (DMF (b) (4).

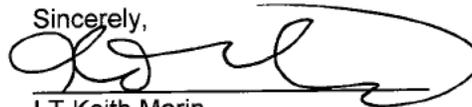
CDRH does not have any questions regarding the information provided in NDA 202832.

Questions to (b) (4) (DMF (b) (4).

CDRH does not have any questions regarding the information provided in NDA 202832.

If you have any questions, please contact LT Keith Marin at 301-796-2462.

Sincerely,



LT Keith Marin  
Regulatory Research Officer

Concurred By:

 8/5/2011  
Richard Chapman  
General Hospital Device Branch Chief

(b) (4) (sodium chloride 0.9% injection in plastic syringes)

**Human Factor Consult: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID, Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID, Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID**

DATE: **August 4, 2011**  
FROM: QuynhNhu Nguyen, Biomedical Engineer/Human Factors Reviewer, CDRH/ODE/DAGID  
THROUGH: Ron Kaye, MA, Human Factors and Device Use-Safety Team Leader, CDRH/ODE/DAGID  
Molly Story, PhD, Human Factors and Accessible Medical Technology Specialist, DAGID  
TO: Keith Marin, Regulatory Research Officer, CDRH/ODE/DAGID/GHDB  
SUBJECT: NDA 202832, Medefil prefilled plastic syringes  
Project Manager: Eunice Chung-Davies  
CTS Consult: (b) (4) - Human Factors/Usability Review

---

**Per your request, I have reviewed the package insert information provided for a pre-filled saline syringe (b) (4) Please see my request for additional information below:**

The submission does not indicate how you have systematically evaluated use-related risk and how you would validate user-performance based on performance of the highest priority task pertinent to their device. To complete our review, we will need this information to assess the safety and effectiveness of your device in the hands of representative users. Please provide a comprehensive use-related risks and a justification for why an HF/usability validation study is not necessary for the proposed product. If you choose to submit an HF/usability validation protocol, please note the following comments:

3. We recommend that you submit a draft of the test protocol before you implement it for our review and feedback to ensure that your methods will be acceptable.  
The purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users. Tasks included in the study should be those identified through completion of a risk assessment of hazards that may be associated with use-related problems and represent greater than minimal risk to users. The study should collect sufficient and appropriate data to facilitate identification and understanding of the root causes of any use failures or problems that do occur. The causes may be related to the design of the device, the device labeling (including instructions for use), and/or the training of test participants. The test report should present a summary of your test results, data analysis, and conclusions regarding safe and effective use and including whether any modifications are indicated; if they are, these modifications should be described and if significant, the modifications should also be validated.

Your validation study protocol should include the items listed below.

**b. Devices and Labeling Used and Training**

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Your participants should assess the clarity of the instructions for use and you should assess the extent to which the instructions support safe and effective use of your device. If any of the other labeling (e.g., packaging, inserts) is critical to use, include them in your validation testing as well. You may include these assessments in your validation testing or conduct them in a separate study.

If you decide to include the assessment of clarity of instructions for use and training as part of the validation study, the Agency expects that the results demonstrating effectiveness of your training and instructions for use are analyzed separately from the results of use performance.

c. User Tasks and Use-Related Risks Analysis

FDA expects to see a clear description of how you determined which user tasks would be included in the testing and how many trials each participant would complete. In order to adequately assess user performance and safety, the tasks selected for testing should be derived from the results of a comprehensive assessment of use-related hazards and risks that consider all functions of the device. The tasks should be prioritized to reflect the relative magnitude and severity of the potential impact of inadequate task performance on the safety of the device and the user.

Please provide use-related risks analysis, describe and provide a rationale for the tasks you include in your testing and their relative priority. Please also describe all activities in which your test participants will engage during the test.

d. Use Environment and Conditions

You should conduct your validation testing in an environment that includes or simulates all key aspects of the real-world environments in which you anticipate your device would be used.

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Please describe the testing environment and realism of the simulated use in sufficient detail for us and justify how they were appropriate for validation testing.

e. Study Participants

FDA expects you to test a minimum of 15 participants from each major user group for validation of device use. Your test participants should be representative of your intended end-user populations, as described in your indications for use statement. If users with distinctly different characteristics (e.g., age ranges, skill sets, or experience levels, level of disabilities/impairments) will use your device, you should include 15 from each distinct group.

(b) (4) (sodium chloride 0.9% injection in plastic syringes)

Regardless of the number of groups you test, please provide a rationale that these groups are representative the overall population of users for your device. Note that study participants should not be your own employees, or those that have been exposed to the products prior to the testing.

f. Data Collection

Any data collected and analyzed in a validation study should be described in terms of how it supports the safety case claim that your device can be used safely and effectively by the indicated users. FDA expects you to collect both empirical and qualitative data in a design validation study.

**Empirical Data** – Your test participants should be given an opportunity to use the device independently and in as realistic a manner as possible, without guidance, coaching, praise or critique from the test facilitator/moderator. Some data, such as successful or failed performance of key tasks or time taken to perform tasks – if time is a safety-critical criterion – should be measured directly rather than soliciting participant opinions. Observing participant behavior during the test is also important, in order to assess participants' adherence to protocol and proper technique and especially to assess and understand the nature of any errors or problems that occur.

**Qualitative Data** – The Agency expects you to ask open-ended questions of participants at the end of a usability validation, such as, "Did you have any difficulty using this device? [If so] can you tell me about that?" The questions should explore performance of each critical task involved in the use of the device and any problems encountered. Note that since the labeling and instructions for use are considered part of the user interface for your device, the questions should cover those components as well.

Your analysis of performance and subjective data should be directed toward understanding user performance and particularly task failures. The analysis should determine the nature of failures, the causes of failures, and the clinical impact. Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Please describe and provide a rationale for including each type of data you collect.

4. *Please review the Center Guidance on Human Factors and Risk Management available at:*  
<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>

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/s/  
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EUNICE H CHUNG-DAVIES  
12/07/2011

# REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

**To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements**

**Application:** NDA 202-832

**Name of Drug:** (b) (4) (sodium chloride 0.9% injection in plastic syringes)

**Applicant:** Medefil

## Labeling Reviewed

**Submission Date:** January 31, 2011

**Receipt Date:** February 1, 2011

**Accepted Date:** March 7, 2011

## Background and Summary Description

This application is an original NDA submitted under section 505 (b) (2) of the Federal Food, Drug, and Cosmetic Act for sodium chloride injection in plastic syringes. This product is considered a new drug because it is a combination product of sodium chloride and a syringe. Sodium chloride when used for the purpose, to dilute or dissolve a drug, is considered a drug and the syringe is a device approved through the 510 k process. The sponsor has submitted their proposed labeling in PLR format.

## Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. The PLR label review tool was used to review the labeling. The following should be addressed by the sponsor:

### Highlights

1. The Contraindications section must be included in this section and cannot be omitted. If there are no known contraindications, state “none.”
2. A Warnings and Precautions section is required in this section.
3. The Patient Counseling Information Statement is missing. The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR

201.57(a)(14)]

4. The highlights limitation statement appears twice. It needs to be stated only once.
5. The revision date at the end of the highlights replaces the “revision” or “issued” date at the end of the full prescribing information and should not appear in both places.

### **Recommendations**

All labeling issues identified in the review will be conveyed to the applicant in and information request. The applicant will be asked to resubmit labeling that addresses all the identified labeling issues by May 2, 2011. The resubmitted labeling will be used for further labeling discussions.

Eunice Chung-Davies	April 20, 2011
<hr/>	
Regulatory Project Manager	Date
Sandy Barnes	April 22, 2011
<hr/>	
Chief, Project Management Staff	Date

# Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

## Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• <b>Highlights Limitation Statement</b> (required statement)
• <b>Drug names, dosage form, route of administration, and controlled substance symbol, if applicable</b> (required information)
• <b>Initial U.S. Approval</b> (required information)
• <b>Boxed Warning</b> (if applicable)
• <b>Recent Major Changes</b> (for a supplement)
• <b>Indications and Usage</b> (required information)
• <b>Dosage and Administration</b> (required information)
• <b>Dosage Forms and Strengths</b> (required information)
• <b>Contraindications</b> (required heading – if no contraindications are known, it must state “None”)
• <b>Warnings and Precautions</b> (required information)
• <b>Adverse Reactions</b> (required AR contact reporting statement)
• <b>Drug Interactions</b> (optional heading)
• <b>Use in Specific Populations</b> (optional heading)
• <b>Patient Counseling Information Statement</b> (required statement)
• <b>Revision Date</b> (required information)

- **Highlights Limitation Statement**
  - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
  
- **Product Title**
  - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
  
- **Initial U.S. Approval**
  - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
  
- **Boxed Warning**
  - All text in the boxed warning is **bolded**.
  - Summary of the warning must not exceed a length of 20 lines.
  - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
  - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
  
- **Recent Major Changes (RMC)**
  - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
  - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
  - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

## Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
  - 8.1 Pregnancy
  - 8.3 Nursing Mothers (not 8.2)
  - 8.4 Pediatric Use (not 8.3)
  - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the Full Prescribing Information are not listed.”

## Full Prescribing Information (FPI)

- **General Format**

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/  
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EUNICE H CHUNG-DAVIES  
04/22/2011

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 202832 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4)		
Established/Proper Name: sodium chloride 0.9% injection in plastic syringes		
Dosage Form: injection		
Strengths: 9mg/mL (0.9%)		
Applicant: Medefil		
Agent for Applicant (if applicable):		
Date of Application: 1/31/2011		
Date of Receipt: 2/1/2011		
Date clock started after UN: 3/7/2011		
PDUFA Goal Date: 1/7/2012	Action Goal Date (if different):	
Filing Date: 5/6/2011	Date of Filing Meeting: April 15, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3s		
Proposed indication(s)/Proposed change(s): To dilute or dissolve drugs for intravenous, intramuscular, or SQ injection and to maintain patency of IVADS		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1)	<input checked="" type="checkbox"/> 505(b)(2)
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(1)	<input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>	<input type="checkbox"/> Priority	
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input checked="" type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): (b) (4)				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Updated to 3S as per CMC reviewer, added 505 (b)(2), and standard classification
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>				
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?		X		Requested a copy of this user fee cover sheet on 4/6/ 2011. They have obtained a waiver for a fee due to the small business

					status.	
<b>User Fee Status</b>  <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>			<b>Payment for this application:</b>  <input type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input checked="" type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>			<b>Payment of other user fees:</b>  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<b>505(b)(2)</b>			<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>(NDAs/NDA Efficacy Supplements only)</b>						
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				X		This is a combination product and the sponsor would like to use an approved plastic syringe (510k)
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].				X		
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?				X		
<i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i>						
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?				X		
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a> <b>If yes, please list below:</b>						
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration			
<i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>						
<b>Exclusivity</b>			<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan						

exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</a></i>		X		
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<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ( <i>NDAs/NDA efficacy supplements only</i> )  If yes, # years requested:  <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X		
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use ( <i>NDAs only</i> )?		X		
<b>If yes</b> , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input checked="" type="checkbox"/> All paper (except for COL) <input type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission</b> , which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).			X	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50				

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>	<b>X</b>			
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>			<b>X</b>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?		X		Sponsor has submitted a patent certification
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>		X		There are no BE studies or any other clinical studies
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?				
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>				
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>				
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>		X		
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
<b>OTC Labeling</b>	<input type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)  <i>If yes, specify consult(s) and date(s) sent:</i>	X			CDRH consult pending
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>				

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> July 14, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 15, 2011

BLA/NDA/Supp #: NDA 202 832

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: sodium chloride 0.9% injection in plastic syringes

DOSAGE FORM/STRENGTH: 0.9%

APPLICANT: Medefil

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): To dilute or dissolve drugs for intravenous, intramuscular, or SQ injection and to maintain patency of IVADS

BACKGROUND: This application was transferred from DCRP after learning from OND IO that DPARP is responsible for this application. This product is a combination product consisting of saline and a syringe. Saline is considered a drug when used for diluting or dissolving drugs for IV, IM or SQ injection.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Eunice Chung-Davies	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Alan Schroeder		N
Clinical	Reviewer:	Xu Wang	Y
	TL:	Tony Durmowicz	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Lokesh Jain	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Feng Zhou	Y
	TL:	Joan Buenconsejo	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Luqi Pei	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Edwin Jao	N
	TL:	Alan Schroeder (PAL) Prasad Peri (Chief)	N Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Walter Fava	Y
	TL:	Carlos Mena-Grillasca	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers			
Other attendees			

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter

<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<b><u>CMC Labeling Review</u></b>	
Comments:	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<b>Signatory Authority:</b> Badrul A. Chowdhury  <b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):  Comments:	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing.  <u>Review Issues:</u>  <input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):  <u>Review Classification:</u>  <input checked="" type="checkbox"/> Standard Review  <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> </ul>

	<ul style="list-style-type: none"> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Initialed by: SBarnes/22APR2011

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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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EUNICE H CHUNG-DAVIES  
04/22/2011