

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022572Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 22572	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Mitosol Established/Proper Name: mitomycin for solution Dosage Form: sterile lyophilized powder for reconstitution with sterile water for injection Strengths: 0.2 mg per vial		
Applicant: Mobius Therapeutics, LLC		
Date of Receipt: June 22, 2010		
PDUFA Goal Date: February 8, 2012		Action Goal Date (if different):
Proposed Indication(s): treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery		

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)
Published literature	Clinical and nonclinical data
Mutamycin Injection	Specific sections of label: Specific Populations, Description, Clinical Pharmacology, Non-Clinical Toxicology

*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)

mutamycin for injection is the reference listed drug. The product has been repackaged for ophthalmic use for a new indication. The published literature describes use of the reference listed product used off-label in glaucoma surgery. The reconstituted solutions have the same concentrations.

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 X 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 X

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)
Mutamycin	62-336	Yes

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 X 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: Mutamycin

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").

This application provides for a change in dosage form, from injection to topical.

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 X

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

N/A

(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 X 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 X

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

YES X 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): There are other generic pharmaceutical alternatives listed in the Orange Book.

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 X *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.

N/A

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.

X 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

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

/s/

JUNE GERMAIN
02/01/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

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

Memorandum

Date: January 9, 2012

To: June Germain, MS, M.T. (ASCP), Regulatory Project Manager
Division of Transplant and Ophthalmology Products

From: Christine Corser, Pharm.D., Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA #22572
Mitosol™ (mitomycin for solution)

As requested in your consult dated August 24, 2011, the Office of Prescription Drug Promotion (OPDP) has reviewed the proposed draft labeling for Mitosol™ (mitomycin for solution). The materials reviewed include a package insert (PI) and Instructions for Use (IFU).

OPDP's comments on the PI are based on the substantially complete version of the PI titled, "NDA 22572 Dec 6 2011.doc," which was sent via email from June Germain on January 3, 2012. OPDP's comments on the proposed IFU are based on the substantially complete version of the IFU titled, "NDA 22572 Kit Dec 6 2011.doc," which was also sent via email from June Germain on January 3, 2012.

OPDP's comments are attached in the substantially complete version of the labeling.

Please note that the substantially complete PI titled, "NDA 22572 Dec 6 2011.doc," sent via email on January 3, 2012 did not include a clinical studies section. In an email dated January 5, 2012, Dr. William Boyd stated that the following should be included in Section 14 Clinical Studies section of the proposed PI:

"14 CLINICAL STUDIES

In placebo-controlled studies reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 3 mm Hg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery.

In studies with a historical control reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 5 mm Hg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery.”

OPDP has cut and paste the above Clinical Studies information in the PI for review.

If you have any questions about OPDP's comments, please contact Christine Corser at 6-2653 or at christine.corser@fda.hhs.gov.

Thank you for the opportunity to provide comments on this proposed labeling.

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

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

/s/

CHRISTINE G CORSER
01/09/2012

**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 January 4, 2012

Reviewer Denise V. Baugh, PharmD, BCPS
Division of Medication Error Prevention and Analysis

Team Leader Lubna Merchant, PharmD, M.S.
Division of Medication Error Prevention and Analysis

Division Director Carol Holquist, R.Ph.
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Mitosol (Mitomycin for Solution)
0.2 mg/vial

Application Type/Number NDA 022572

Applicant Mobius Therapeutics, LLC

OSE RCM 2011-3206

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

1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling, instructions for use, and the usability study for Mitosol (Mitomycin) for Ophthalmic Solution for areas of vulnerability that could lead to medication errors.

1.1 REGULATORY HISTORY

On December 22, 2010, the Agency issued a complete response to the NDA 22-572 submitted on June 21, 2010. The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the usability study and the IFU during the first cycle. We identified concerns with the Instructions for Use and communicated our findings and recommendations to the Applicant. The Applicant incorporated our recommendations and retested the IFU. In the current submission, the Applicant submitted a complete, class 2 response to the December 22, 2010, action letter.

The Reference Listed Drug (RLD) for Mitosol is Mitomycin for Injection (ANDA 064144).

1.2 PRODUCT INFORMATION

The following product information is provided in the September 30, 2011 proprietary name submission:

- Established Name: Mitomycin for Solution,
- Indication of Use: treatment of refractory glaucoma by topical application
- Route of administration: topical, ophthalmic
- Dosage form: vial of Mitosol which contains 0.2 mg of lyophilized Mitomycin
- Dose: Add 1 mL of sterile water for injection to one vial of Mitosol which contains 0.2 mg of mitomycin. (b) (4)

- How Supplied: Three Mitosol Kits for Ophthalmic Use are in one carton. Each kit contains (b) (4)

- Storage: store kits at (b) (4) 15°C to 30°C (59°F – 86°F)
- Container and Closure systems: Items for use during surgery are packaged in (b) (4) trays with (b) (4) lidding

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis¹ and postmarketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following which were all submitted August 8, 2011 except where indicated:

- Carton Labeling (See Appendix A)
- Outer Tray Labeling (see Appendix B)
- Inner Tray Labeling (see Appendix C)
- Container Label (See Appendix D)
- Container Label for Pre-filled Syringe (See Appendix E)
- Insert Labeling (no image)
- Instructions for Use (Appendix F)
- Comprehension/Usability Test Findings (no image)

Additionally, the Applicant submitted a prototype of the product December 8, 2011 per our request via correspondence December 7, 2011.

3 RESULTS AND DISCUSSION

The following sections describes our risk assessment of the Mitosol product design as well as the associated label and labeling.

3.1 PRODUCT DESIGN

This kit was developed with the intention of providing a safe, effective, and convenient means of delivering mitomycin to the eye. While the pharmacist traditionally compounded the approved injectable product for topical administration by the ophthalmologist, this product will be dispensed as a kit to the operating room where it will be compounded by the operating room staff just prior to its topical application to the patient's eye. Presentation of this proposed product is in a vial and is misleading because it resembles the packaging configuration for injectable products which are administered systemically (e.g., intravenous, intramuscular, intravitreally, or subcutaneous).

Therefore, there is a risk that the user will misinterpret the route of administration for Mitomycin for Solution in its proposed form. In discussion with the Division September 29, 2011, the accidental administration of this product into the eye may cause adverse outcomes such as permanent blindness. However, since it is unlikely that this packaging configuration can be altered at this time in the drug development process, we will monitor for any errors with this packaging design in our routine post-marketing surveillance activities.

(b) (4)



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

(b) (4)

Although the list of kit contents on the carton labeling and the outer tray labeling includes six half moon sponges and one instrument wedge sponge, these items were not found in the prototype for our review. However, in the list of items for the sterile inner tray in the revised IFU, reference is made to (b) (4)

(b) (4)

Consistency in the use of terminology and clear identification of items in the kit will minimize confusion for the user. .

3.2 CARTON LABELING - INNER AND OUTER TRAY (SEE APPENDICES A, B AND C)

Although the comprehension testing did not identify specific problems with the “Graphic Instructions for Use”, the proposed inner tray labeling is not comprehensive and may lead the reader to believe that this information is sufficient to properly and safely use this drug product. Specifically, information (b) (4) is missing. Additionally, as proposed, it does not reinforce the proper disposal method after use. However, we recognize that the options to convey clear and thorough instructions is limited given the sterile requirements for preparing this product and the limited space on the lidding. Therefore, our recommendations for the inner tray labeling were limited to adding disposal instructions. Recommendations for the carton and outer tray labeling were made to improve the readability of the labeling, improve the prominence of important information and decrease clutter. See the Recommendations in Section 4.

3.3 CONTAINER LABEL FOR DRUG VIAL (SEE APPENDIX D)

The container label is cluttered with information that is not useful or misleading. Additionally, we discourage negative statements (b) (4)

(b) (4)

3.4 CONTAINER LABEL FOR PREFILLED SYRINGE (SEE APPENDIX E)

Although the prefilled syringe contains 1 mL of sterile water for diluting this drug product, we note that the markings on the syringe are “0.2”, “0.4”, and “0.5”. These numbers have no relationship to the amount of fluid in the syringe and are not mentioned in the dosage and administration section of the insert labeling or in the IFU. As such, they are viewed as extraneous markings. Although we would normally request removal of these extraneous markings, our concern with this issue is minimized because this

syringe is prefilled and does not require manipulation by the user nor is there a requirement for a partial dose. Thus, these markings may be (appropriately) overlooked during the preparation phase of this drug product. Additionally, the comprehension/usability testing did not reveal a problem with this discrepancy.

3.5 INSERT LABELING (NO IMAGE)

As stated in Section 3.3, the use of negative statements may have unintended consequences. (b) (4)

3.6 REVISED INSTRUCTIONS-FOR-USE (IFU) – SEE APPENDIX F

Although the Applicant revised the IFU based upon participant feedback, it appears that this revised document has not been validated with re-testing. As such, we cannot state that the revised document is an acceptable improvement over the previous one and we do not know if the revision has introduced other problems. Our comments are therefore limited to the review of the recommendations made by the participants and whether these concerns were addressed in the revised IFU. Additionally, when evaluating the revised IFU in association with the prototype kit, there were items referred to in the IFU which were not available in the kit. These items include (b) (4)

This discrepancy further hinders our ability to provide a thorough evaluation of this packaging configuration and the ability of the IFU to assist the user in safely and efficiently using the drug product.

3.7 PROPRIETARY AND ESTABLISHED NAMES – CONSISTENCY IN LABEL AND LABELING

The proprietary name and established name are referred to inconsistently throughout the documents submitted to DMEPA for review. For example, (b) (4)

All of the labels and labeling should refer to the proprietary name and established name as “Mitosol (Mitomycin for Solution) 0.2 mg/vial”. Additionally, in correspondence dated December 13, 2011, the Division will consider our recommendation to add the route of administration (“For Topical Administration to the Eye”) to the carton labeling to minimize confusion between this ophthalmic product and the approved injectable product.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed label and labeling introduce vulnerability that can lead to medication errors because (1) the instructions for use have not been re-tested to validate that the revised document is improved without introducing new problems; (2) the IFU refers to items which were not found in the prototype kit; and (3) there is inconsistent use of terminology in the IFU. In view of the hazardous nature of this drug product and the multiple steps required for its preparation, the directions must be clear to facilitate safe and efficient use of Mitosol. We recommend the following:

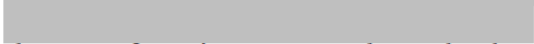
A. Product Design

1. We recommend the kit include chemotherapeutic gloves for the safe and efficient handling of hazardous waste materials such as Mitosol. Although gloves are typically available in an operating room setting, they are likely to be inadequate for handling chemotherapeutic drugs and waste.
2. All listed items on the carton labeling and the outer tray labeling should be found in the kit. For example, although the list of items refers to sponges, we could not find any sponges in the prototype kits provided to DMEPA for our review. Additionally, the descriptors for each item should be consistent throughout the label and labeling.

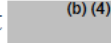
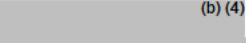
B. Revised IFU (See Appendix G)

1. Items referred to in the IFU should be included in the kit to avoid confusion. (b) (4)
Additionally, the descriptors for each item should be consistent with the label and labeling.
2. Include the statement, (b) (4) on the first page of the IFU along with references to the sterile and non-sterile nature of the items within the kit since the comprehension/usability study identified confusion in how to handle these components of the kit.
3. Delete abbreviations in the list of items, (b) (4)
Use of abbreviations are discouraged as they may transfer into the medication use system (e.g., prescribing, drop down menus) and are vulnerable to misinterpretation.
4. (b) (4)

C. Carton Labeling (See Appendix A)

1.  (b) (4)
 Revise these letters to have the same font size, typography and color as the remaining letters in their names to improve readability.
2. Revise the proposed proprietary name from lower case letters to title case to improve readability of the name.
3. Delete the large grey graphic in the background to improve the readability of the information.
4. Decrease the prominence of your company name/logo, “Mobius” so that it is less prominent than the proprietary and established names and the strength statement.
5. Revise the established name from  (b) (4) to read, “Mitomycin for Solution” and the statement “Kit for Ophthalmic Use” to read “For Topical Administration to the Eye”. Following the established name, add the statement of strength “0.2 mg/vial”. These recommendations may be presented in the following manner:

Mitosol
(Mitomycin for Solution)
0.2 mg/vial
For Topical Administration to the Eye

6. Delete the statement,  (b) (4) as this information is redundant and clutters the label.
7. Delete the statement, “Contents STERILE in unopened undamaged package” as this statement is confusing and clutters the label.
8. Relocate the NDC# from the bottom of the principal display panel to the top.
9. Revise the statement,  (b) (4) to read “Each Kit Contains Sterile and Non-Sterile Items. Separate the list of items accordingly to reinforce this difference among the users.
10. Under the statement,  (b) (4) revise the statement  (b) (4) to read “one vial Mitosol (Mitomycin for Solution) 0.2 mg”.
11. Under the statement,  (b) (4) delete the statement,  (b) (4) in the line listings and replace  (b) (4) with the word descriptor. For example,  (b) (4) should be revised to read  (b) (4)

9. Delete the following statements from the side panel: “Mfg.Lic.No.: G/1026” and “10 9750 (b) (4)” as this information is not useful, clutters the label, and can be included in the insert labeling.
10. Revise the statement “Single Use Vial” to read “Single Dose Vial” to reflect the correct USP terminology for this packaging configuration.

G. Container Label for Prefilled Syringe (Appendix E)

Revise the statement (b) (4) to read “Sterile Water for Injection 1 mL” to avoid confusion.

H. Insert Labeling (no image)

1. Delete the statement, (b) (4)

2. Add the statement, “For Topical Administration to the Eye” to reflect the proper route of administration for this drug product.
3. In the Dosage and Administration subsection under the Highlights of Prescribing Information and the Full Prescribing Information Sections, revise the statement which ends “for defined disposal” to read “for disposal consistent with procedures for proper handling and disposal of anti-cancer drugs” to reinforce proper disposal for this drug product.

If you have further questions or need clarifications, please contact Karen Townsend, OSE Project Manager, at 301-796-5413.

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

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

/s/

DENISE V BAUGH
01/04/2012

LUBNA A MERCHANT
01/04/2012

CAROL A HOLQUIST
01/04/2012

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

Memorandum

*****Pre-Decisional Agency Information*****

MEMO TO FILE – INTERNAL

Date: March 7, 2011

From: Christine Corser, Pharm.D.
Division of Drug Marketing, Advertising and Communications

Subject: Mitosol (mitomycin for solution), NDA 22572

We acknowledge receipt of your July 15, 2010, consult request for the proposed product labeling (Package Insert, (PI)) for NDA 22572. DDMAC notes the email correspondence with DAIOP on November 16, 2010, which conveyed that final labeling negotiations would not be initiated during the current review cycle. We also note that a Complete Response letter was issued December 22, 2010. Therefore, DDMAC will provide comments regarding labeling for this application during a subsequent review cycle. DDMAC requests that DAIOP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on these proposed materials. If you have any questions, please contact Christine Corser at 301-796-2653.

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

/s/

CHRISTINE G CORSER
03/07/2011



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

onsDate: November 19, 2010

From: Nikhil Thakur, Combination Products Team Leader WO66, RM2562
CDRH/ODE/DAGID/ General Hospital Devices Branch

To: Althea Cuff, Regulatory Health Project Manager, WO21, RM 2627
CDER/OPS/ONDQA

Subject: NDA 22572 (Optomycin™ Kit for Ophthalmic Use)

Center for Drug Evaluation and Research has requested a consult from the Center for Devices and Radiological Health, regarding Mobius Therapeutics, LLC's drug product, Optomycin™. In this submission, the Sponsor has stated that they are providing the Optomycin™ in a Kit for ophthalmic use. The Kit contains several device constituents such as (b) (4). A complete list of device constituents that are part of this combination product is provided in the Device Description section of this memorandum.

Documents Reviewed:

NDA 22572 eCTD Submission
DMF (b) (4)

Device Description:

The Optomycin™ Kit for ophthalmic use (Rx only), contain an outer tray (non sterile) and inner tray (sterile) that further house the device and drug constituents of this combination product. The outer tray, shown in Figure 1, contains:



7 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

(b) (4)

Human Factors:

5. *Your submission contains an “Instruction for Use Testing” report dated September 2010 (eCTD Sequence 15, Section 1.14.1.4.3). However, this test does not satisfy CDRH’s requirement regarding Human Factors / Usability testing for devices. The intent of a human factors validation study is to demonstrate that the device can be used by representative users under simulated conditions without patterns of failures that could result in clinical impact to patients or, in some cases, to users themselves. To the extent that failures with use do occur, the study should collect sufficient and appropriate data such that these failures can be described in terms of their cause from the perspective of the representative users. The test report should present a summary of these results within a discussion with respect to failures and whether they may be related to device design, labeling, or the content or proximity of training. The test report should also state if modifications are indicated. The Agency may agree or disagree with your analyses. If a design flaw could result in a risk to health, we do not agree that deferred modifications are acceptable.*

If you have not conducted human factors validation testing, FDA recommends that you first develop a study protocol and then submit a preIDE to receive Agency feedback prior to initiating a study. Guidance on preIDEs can be found at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm>.

Please provide a summative validation study, which addresses the following items:

- a. *Relative priority of tasks: The Agency needs to understand the relative priority of the tasks selected for testing in terms of the potential results of inadequate performance on these tasks. The rationale applied to their priority should be clearly provided.*
- b. *Comprehensiveness of task set: The Agency needs to understand that the tasks you chose to test represent the extent of the tasks that could lead to use-related problems (as defined). Please provide a rationale for the group of tasks you include in your Summative testing.*
- c. *Number of study participants: The Agency’s expectations for the number of study participants to be used in Human Factors/Usability Validation (or “Summative Test”) include a minimum of 15 or more. The user groups should represent the United States population.*
- d. *Realism of simulated use: The testing environment and realism of the simulated use should be described in sufficient detail to determine if it is reasonable for a validation study of the subject device. Please describe the conditions under which the testing was undertaken.*
- e. *Performance criteria: Please describe the performance criteria and clearly state what the results mean in terms of failures that could correspond to*

potential harm to patients. Please provide study results that contain comprehensive assessment of test results particularly for high-priority use problems and failures.

- f. Objective and Subjective data: Please describe the objective and subjective data that will be collected during the study and discuss how variability in the data will be analyzed. Please provide study results that clarify use difficulties and failures.*
- g. Training: The training you provide users should equate to your best assessment of the extent of training actual users will receive. Please clarify your description of the training provided to the participants in this test with respect to the extent to which it corresponds to realistic training levels.*
- h. Unexpected failures: Your test plan should address how unexpected failures will be identified, recorded and reported.*

For additional guidance on Medical Device Use-Safety and Human Factors, please go to the Center's guidance at:

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094461.pdf>.

Please contact Nikhil Thakur at (301) 796 – 5536, if you have any questions.

Sincerely,

Nikhil Thakur
Combination Products Team Leader
General Hospital Devices Branch
Division of Anesthesiology, General Hospital,
Infection Control and Dental Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

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

/s/

ALISON K RODGERS
12/20/2010

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: CDRH

Division:

Mail Code: HF_-

Consulting Reviewer Name: Nikhil Thakur

Building/Room #:

Phone #:

Fax #:

Email Address:

RPM/CSO Name and Mail Code:

From (Originating Center):

Center: CDER

Division: Division of Anti-Infective and Ophthalmology Products

Mail Code: HFD-

Requesting Reviewer Name: William Boyd

Building/Room #: WO 22, 6110

Phone#: 301-796-0686

Fax #:

Email Address: william.boyd@fda.hhs.gov

RPM/CSO Name and Mail Code: Alison Rodgers

Requesting Reviewer's Concurring Supervisor's Name:

Wiley Chambers

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: 12-7-10

Submission/Application Number: NDA 22572

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

Submission Receipt Date: 12-7-10

Name of Product: mitomycin for solution

Requested Completion Date: **1-15-10**

Submission Type: NDA

Official Submission Due Date: 12-22-10

Name of Firm: Mobius Therapeutics, LLC

Intended Use: Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
Electronic submission dated 12-7-10 – Response to Nikhil Thakur's comments sent to sponsor on 11-22-10.

Documents to be returned to Requesting Reviewer? π Yes π 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 π Collaborative Review

Please evaluate the sponsor's responses to your comments regarding the non-drug components of the Mitosol Kit. The submission is electronic, dated 12-7-10, and posted in the EDR.

A Complete Response letter will be issued for this NDA. The sponsor expects to resubmit the application in January 2011.

Thank you.

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

/s/

ALISON K RODGERS
12/08/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Anti-Infective and Ophthalmology Products

Application Number: 22572

Name of Drug: Optomycin (mitomycin) Kit for Ophthalmic Use

Applicant: Mobius Therapeutics, LLC

Material Reviewed:

Submission Date(s): June 21, 2010

Receipt Date(s): June 22, 2010

Submission Date of Structure Product Labeling (SPL): June 21, 2010

Type of Labeling Reviewed: WORD

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in the proposed labeling and will be forwarded to the sponsor:

HIGHLIGHTS OF PRESCRIBING INFORMATION:

- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: “(Drug Product) is a (name of class) indicated for (indication(s)).”
- Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
- 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)]

- A revision (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

Contents (Table of Contents)

- Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.

FULL PRESCRIBING INFORMATION: DETAILS

- Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
- Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.
- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [*see Use in Specific Populations (8.4)*] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
- Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.456(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively [See 21 CFR 201.57 (c)(18)].
- If the “Rx only” statement appears anywhere in labeling, delete it. This statement is not required for the prescribing information, only container and carton labels. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to Patient Package Inserts and Medication Guides.

Recommendations

Please address the identified deficiencies/issues and incorporate the changes into revised labeling. This updated version of labeling will be used for further labeling discussions.

Alison Rodgers
Regulatory Health Project Manager

Supervisory Comment/Concurrence:

Maureen P. Dillon-Parker
Chief, Project Management Staff

Drafted: AR/7-15-10

Revised/Initialed:

Finalized:

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

ALISON K RODGERS
12/06/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 22572 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Optomycin Kit for Ophthalmic Use (Rx Only) Established/Proper Name: Mitomycin Dosage Form: Sterile lyophilized powder for reconstitution with sterile water for injection Strengths: mitomycin: 0.2 mg per vial		
Applicant: Mobius Therapeutics, LLC Agent for Applicant (if applicable):		
Date of Application: June 21, 2010 Date of Receipt: June 22, 2010 Date clock started after UN:		
PDUFA Goal Date: December 22, 2010		Action Goal Date (if different): December 15, 2010
Filing Date: August 21, 2010		Date of Filing Meeting: July 14, 2010
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3		
Proposed indication(s)/Proposed change(s): For treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application to the exposed site of a filtering bleb during trabeculectomy surgery to prolong the closing of the surgically created fistula, thereby allowing maintenance of sub-hypertensive intraocular pressure in patients refractory to maximal medical therapy in whom trabeculectomy surgery is indicated.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☐ 505(b)(1) ☒ 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device	
☐ Fast Track ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)]	

☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Other:				
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s):				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, 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 not, 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			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <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 UN letter and contact user fee staff.</i>	Payment for this application: ☐ Paid X Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ 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>	Payment of other user fees: X Not in arrears ☐ In arrears			

Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).

505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment																
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		X																		
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 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))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>		X																		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm If yes, please list below:		X																		
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
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>																				
Exclusivity	YES	NO	NA	Comment																
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X																		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>																				
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) 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		
If yes , 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>	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) If no , explain.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>			X	
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #			X	

Forms and Certifications				
<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>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?		X		Not required because no “covered clinical studies” in application.
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<i>Note: Debarment Certification should use wording in FD&C Act 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>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <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> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>			X	Electronic submission

Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)</i> <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 & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Request for Waiver due to Orphan Designation
If studies or full waiver not included, 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>			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>		X		
Prescription Labeling	☐ Not applicable			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	NO	NA	Comment
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?	X			Formatting off – will convey to sponsor.
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>		X		
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		DMEPA will review at time of proprietary name review.
OTC Labeling	X Not Applicable			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	NO	NA	Comment
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?				
Consults	YES	NO	NA	Comment
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>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>		X		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7-20-09 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 14, 2010

BLA/NDA/Supp #: 22572

PROPRIETARY NAME: Optomycin Kit for Ophthalmic Use (Rx Only)

ESTABLISHED/PROPER NAME: mitomycin

DOSAGE FORM/STRENGTH: Sterile lyophilized powder for reconstitution with sterile water for injection, 0.2 mg per vial

APPLICANT: Mobius Therapeutics, LLC

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application to the exposed site of a filtering bleb during trabeculectomy surgery to prolong the closing of the surgically created fistula, thereby allowing maintenance of sub-hypertensive intraocular pressure in patients refractory to maximal medical therapy in whom trabeculectomy surgery is indicated.

BACKGROUND: Mobius Therapeutics, LLC, submitted a pre-IND application for the product in December 2006. A Pre-NDA Meeting was held in July 2009. This is a 505b2 application. No clinical trials have been conducted. The product has been granted orphan designation.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Alison Rodgers	Y
	CPMS/TL:	Maureen Dillon-Parker	N
Cross-Discipline Team Leader (CDTL)	William Boyd		Y
Clinical	Reviewer:	William Boyd	Y
	TL:	William Boyd	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC</i>)	Reviewer:		

<i>products)</i>			
	TL:		
Clinical Microbiology (<i>for antimicrobial products)</i>	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Kim Bergman	Y
	TL:	Chuck Bonapace	N
Biostatistics	Reviewer:	Mushfiger Rashid	Y
	TL:	Yan Wang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Amy Nostrandt	Y
	TL:	Wendy Schmidt	Y
Statistics (carcinogenicity)	Reviewer:		NA
	TL:		NA
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		NA
	TL:		N A
Product Quality (CMC)	Reviewer:	Mark Seggel	Y
	TL:	Stephen Miller	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Denise Miller	Y
	TL:	David Hussong	N
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		NA
	TL:		NA
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	TBD	N
	TL:	TBD	N
OSE/DRISK (REMS)	Reviewer:	N/A	NA
	TL:		NA
Bioresearch Monitoring (DSI)	Reviewer:	Kassa Ayalew	Y
	TL:	Jean Mulinde	N

Other reviewers	DDMAC - Beth Carr	N
Other attendees	Wiley Chambers, Martin Nevitt, Jennifer Harris, Lucious Lim, Rhea Lloyd, Sonal Wadhwa, Victor Ng, Althea Cuff, Linda Ng, Brantley Dorch	

FILING MEETING DISCUSSION:

GENERAL 505(b)(2) filing issues? If yes, list issues:	☐ Not Applicable ☐ YES ☒ NO
Per reviewers, are all parts in English or English translation? If no, explain:	☒ YES ☐ NO
Electronic Submission comments List comments: No comments	☐ Not Applicable
CLINICAL Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
Clinical study site(s) inspections(s) needed? If no, explain: No clinical trials conducted.	☐ YES ☒ NO
- Advisory Committee Meeting needed? Comments: <i>If no, for an original NME or BLA application, include the reason. For example:</i> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure,</i>	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

<i>mitigation, treatment or prevention of a disease</i>	

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? Comments:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter

Comments:	

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	☐ Not Applicable X YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
<u>Quality Microbiology (for sterile products)</u> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	☐ Not Applicable X YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? Comments:	☐ Not Applicable X YES ☐ NO X YES ☐ NO
<u>Facility/Microbiology Review (BLAs only)</u> Comments:	X Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
<u>CMC Labeling Review (BLAs/BLA supplements only)</u> Comments:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Wiley Chambers, M.D.	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
X	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> ☐ No review issues have been identified for the 74-day letter. X Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> ☐ Standard Review X Priority Review
ACTIONS ITEMS	
X	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • 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) • notify DMPQ (so facility inspections can be scheduled earlier)
☐	Send review issues/no review issues by day 74
☐	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.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22572	ORIG-1	MOBIUS THERAPEUTICS	Optomycin Kit for Ophthalmic Use

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

/s/

ALISON K RODGERS
07/15/2010