

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022572rig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review of NDA 22-572 Review #2

|                                |   |
|--------------------------------|---|
| <b>Date</b>                    | February 2, 2012  |
| <b>From</b>                    | William M. Boyd, M.D.   |
| <b>Subject</b>                 | Cross-Discipline Team Leader Review   |
| <b>NDA #</b>                   | 22-572  |
| <b>Applicant</b>               | Mobius Therapeutics, LLC  |
| <b>Date of Submission</b>      | 8/8/2011  |
| <b>PDUFA Goal Date</b>         | 2/8/2012  |
| <b>Type of Application</b>     | 505(b)(2)   |
| <b>Name</b>                    | Mitosol (mitomycin for solution)  |
| <b>Dosage forms / Strength</b> | Topical solution  |
| <b>Proposed Indication(s)</b>  | Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery |
| <b>Recommended:</b>            | Recommended for Approval  |

### 1. Introduction

NDA 22-572 for Mitosol (mitomycin for solution) received a Complete Response Letter dated December 22, 2010, which cited the following deficiencies:

1. There is insufficient information about the drug product to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling. The labeling of the product as submitted is not adequate to ensure safe and reliable reconstitution, transportation, and application of the product for the intended indication. We will continue to work with you on your labeling and packaging plans for Mitosol (mitomycin for solution) and encourage you to discuss any future protocols for labeling comprehension studies with the Division.
2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug substance and drug product are inadequate to preserve its identity, strength, quality, purity, and stability. Specifically,
  - a. You have not demonstrated that the proposed drug product, Mitosol (mitomycin for solution), 0.2 mg/vial, is of comparable identity, strength, quality, purity and potency to the commercially available, currently approved drug product upon which the clinical studies are based (e.g., cross-referenced mitomycin for injection RLD ANDA 64-144).
  - b. There is insufficient justification of the drug product specification (e.g., acceptance criteria for impurities and pH).
  - c. There is insufficient justification of the expiration dating period.
  - d. The drug product as proposed does not comply with 21 CFR 200.50. The containers of ophthalmic preparations must be sterile at the time of filling and

closing, and the container or individual carton must be so sealed that the contents cannot be used without destroying the seal. Eye cups, eye droppers, and other dispensers intended for ophthalmic use should be sterile, and may be regarded as falling below their professed standard of purity or quality if they are not sterile. These articles, which are regulated as drugs, if packaged with the drugs with which they are to be used, should be packaged so as to maintain sterility until the package is opened.

- The methods used in and the facilities and controls used for, the manufacture, processing, packing, or holding of the drug product do not comply with the current good manufacturing practice (cGMP) regulations in parts 210 and 211. Specifically, during a recent preapproval inspection conducted at Synergetics, Inc. (FEI 1000119053), significant deviations from Current Good Manufacturing Practices (cGMP) were observed and disclosed to the firm's management. All facilities and controls will need to comply with the cGMP regulations. Please amend the application with facilities that are in compliance with current good manufacturing practice (cGMP) or notify us when all currently submitted facilities are in compliance with cGMPs.

Mobius Therapeutics, LLC submitted an amendment on August 8, 2011, which constituted a Complete Response.

## 2. CMC

Per the CMC review completed on 02/02/2012:

### Description and Composition of the Drug Product

#### Drug Product Components/Composition

| Ingredients         | Compendial Reference | Qty. (mg) / mL | Batch Quantity |
|---------------------|----------------------|----------------|----------------|
| Mitomycin           | USP/Ph. Eur.         | 0.2            | (b) (4)        |
| Mannitol            | USNF/Ph. Eur.        | 0.4            | (b) (4)        |
| Water for Injection | USP/Ph. Eur.         | 1 mL           | (b) (4)        |

### Specification(s)

The specification for Mitomycin for Ophthalmic Solution, 0.2 mg/Vial, as revised (*latest in eCTD 0027*), is presented in the table below. To facilitate comparison the reviewer has included the current specifications for Mitomycin for Injection USP, and for the Intas and Bedford/BVL Mitomycin for Injection products.

Specification for Mitomycin for Ophthalmic Solution (MIM3325-1 and MIM3325-S1)

| Attribute   | Analytical Procedure                | Acceptance Criteria  | ANDA 64144 Intas Mitomycin for Injection* | ANDA 64117 BenVenue Mitomycin for Injection                  | Mitomycin for Injection USP  |
|---|-------------------------------------|--|---|--|--|
| Appearance  | In house                            | Blue-violet cake or powder, free from visible evidence of contamination in amber vial.   | Same                                      | Grey cake or powder free from visible signs of contamination | -  |
| Constituted Solution                              | USP<1>                              | a) Sample powder should dissolve completely leaving no visible residue.<br><br>b) Sample solution is not significantly less clear than an equal volume of diluent (water for injection) in a similar vessel and examined similarly.<br><br>c) Sample solution should be essentially free from particles of foreign matter than could be observed on visual inspection. | Same                                      | Same   | Meets requirements for Constituted Solutions under Injections <1>. |
| Identification                                    | USP                                 | The Rf value of the principal spot obtained from the sample solution should correspond to that of the Mitomycin standard solution similarly prepared.  | By TLC                                    | By TLC   | By TLC   |
| Reconstitution Time                               | In house                            | (b) (4)  |   |  |  |
| pH  | USP<791>                            |  |   |  |  |
| Particulate Matter                                | USP<789> Method 1 Light Obscuration |  |   |  |  |
| Bacterial Endotoxin                               | USP<85>                             |  |   |  |  |
| Sterility   | USP<71>                             |  |   |  |  |
| Water   | USP<921>                            |  |   |  |  |
| Uniformity of dosage unit (By content uniformity) | USP<905>                            |  |   |  |  |
| Related substances                                | In house (based on                  |  |   |  |  |

|                   |          |         |
|-------------------|----------|---------|
|                   | Ph.Eur.) | (b) (4) |
| Assay             | USP<621> |         |
| Residual Solvents |          |         |

The range of tests performed for release of the drug product is adequate. While the acceptance criteria for several attributes (assay, related substances, pH) (b) (4) somewhat based on the available batch release data and stability data, the allowed ranges do not materially add to the risks associated with the use of mitomycin, a potent cytotoxic agent.

The specification provides assurance of the identity, strength, quality, purity and potency of the drug product.

Given that the FDA-approved products currently available for off-label use in the proposed indication have Assay limits of (b) (4) the proposed acceptance criterion represents no increased risk to safety or efficacy.

While the acceptance criteria for pH and Related Substances (b) (4) this is not to suggest that 'Mitomycin for Solution' will perform any differently than those 'Mitomycin for Injection' products used off-label and that form the basis for the clinical evidence of efficacy and safety.

The acceptance criteria are acceptable as revised.

### **Stability/Expiry**

Three registration batches were placed on stability:

- accelerated 40°C/75% RH 1, 2, 3, and 6 months
- long term 25°C/60% RH 3, 6, 9, and 12 months, updated with 18 and 24 months in the 08-AUG-2011 resubmission (ongoing to 36 months)

Mobius has proposed an expiration dating period of 24 months for product stored at room temperature.

The approved expiration dating period for Intas (ANDA 64-144) 5, 10 and 20 mg vials of mitomycin for injection is (b) (4). The proposed 24-month expiration dating period for Mitosol (mitomycin for solution), 02. mg/ vial is supported by the available stability data.

### **Sterility**

Based on the 22-DEC-2010 Complete Response, and on 03-JAN-2011 and 08-FEB-2011 teleconferences to discuss Kit sterility requirements and (b) (4) Mobius undertook an evaluation of the effect of (b) (4) on the drug product vial. As noted in the Product Quality Microbiology review dated 21-NOV-2011, and not unexpectedly, (b) (4) does not penetrate the drug vial. This determination allowed the simplification of the Kit design and (b) (4).

### **Recommendation and Conclusion on Approvability**

The applicant has adequately addressed deficiencies in chemistry, manufacturing and controls identified in the 22-DEC-2010 Complete Response and in related correspondence to the applicant. All facilities involved in the manufacture of the product now have acceptable cGMP status; the Office of Compliance has issued an overall recommendation of Acceptable for this application.

Product labeling is acceptable as recently revised. It is therefore recommended, from the Chemistry Review perspective, that this New Drug Application be approved.

**FDA CDER EES  
 ESTABLISHMENT EVALUATION REQUEST  
 SUMMARY REPORT**

|                       |               |   |                                  |
|-----------------------|---------------|---|----------------------------------|
| <b>Application:</b>   | NDA 22572/000 | <b>Sponsor:</b>   | MOBIUS THERAPEUTICS              |
| <b>Org. Code:</b>     | 590           |   |                                  |
| <b>Priority:</b>      | 3             |   |                                  |
| <b>Stamp Date:</b>    | 22-JUN-2010   | <b>Brand Name:</b>  | Optomycin Kit for Ophthalmic Use |
| <b>PDUFA Date:</b>    | 08-FEB-2012   | <b>Estab. Name:</b>                                       |                                  |
| <b>Action Goal:</b>   |               | <b>Generic Name:</b>                                      | MITOMYCIN                        |
| <b>District Goal:</b> | 09-AUG-2011   | <b>Product Number; Dosage Form; Ingredient; Strengths</b> | 001; KIT; MITOMYCIN; .2MG/1VIL   |
| <b>FDA Contacts:</b>  | A. CUFF       | <b>Project Manager</b>                                    | (HF-01) 301-796-4061             |
|                       | M. SEGCEL     | <b>Review Chemist</b>                                     | 301-796-1455                     |
|                       | L. NG         | <b>Team Leader</b>  | 301-796-1426                     |

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|                                |            |                |              |     |
|--------------------------------|------------|----------------|--------------|-----|
| <b>Overall Recommendation:</b> | ACCEPTABLE | on 19-SEP-2011 | by A. INYARD | ( ) |
|                                | PENDING    | on 12-SEP-2011 | by EES_PROD  |     |
|                                | WITHHOLD   | on 12-SEP-2011 | by EES_PROD  |     |
|                                | PENDING    | on 22-AUG-2011 | by EES_PROD  |     |
|                                | ACCEPTABLE | on 25-JUL-2011 | by EES_PROD  |     |
|                                | PENDING    | on 27-JUN-2011 | by EES_PROD  |     |
|                                | WITHHOLD   | on 15-DEC-2010 | by EES_PROD  |     |

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|                          |                                      |                        |      |
|--------------------------|--------------------------------------|------------------------|------|
| <b>Establishment:</b>    | <b>CFN:</b>                          | <b>FEI:</b> 3003157498 |      |
|                          | INTAS PHARMACEUTICALS LIMITED        |                        |      |
|                          | (b) (4)                              |                        |      |
|                          | (u) (4) AHMEDABAD, GUJARAT, , INDIA  |                        |      |
| <b>DMF No:</b>           |                                      | <b>AADA:</b>           |      |
| <b>Responsibilities:</b> | FINISHED DOSAGE MANUFACTURER         |                        |      |
| <b>Profile:</b>          | SMALL VOLUME PARENTERAL, LYOPHILIZED | <b>OAI Status:</b>     | NONE |
| <b>Last Milestone:</b>   | OC RECOMMENDATION                    |                        |      |
| <b>Milestone Date:</b>   | 25-AUG-2011                          |                        |      |
| <b>Decision:</b>         | ACCEPTABLE                           |                        |      |
| <b>Reason:</b>           | DISTRICT RECOMMENDATION              |                        |      |

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Establishment: CFN: FEI: 1000119053  
SYNERGETICS INC  
3845 CORPORATE CENTRE DR  
O FALLON, MO 633688678  
DMF No: AADA:  
Responsibilities: FINISHED DOSAGE PACKAGER  
Profile: SMALL VOLUME PARENTERAL, LYOPHILIZED OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 22-AUG-2011  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

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Establishment: CFN: FEI: (b) (4)  
(b) (4)  
DMF No: AADA:  
Responsibilities: (b) (4)  
Profile: (b) (4) OAI Status: NONE  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 25-AUG-2011  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION

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### 3. Sterility Assurance

Per the Product Quality Microbiology review completed on 11/21/11:

(b) (4)  
it was recommended that the entire kit be sterile.

In the Complete Response letter of 22 December 2010, it was proposed that the drug product vial be included in the sterile inner procedure tray (b) (4)

In the resubmission the kit was redesigned and the inner tray now contains the drug product vial. (b) (4)

Recommend to approve [New Drug Application] from a quality microbiology standpoint.

#### **4. Other Relevant Regulatory Issues**

##### **DSI**

This is a 505(b)(2) application primarily based on literature. The studies were conducted 10-15 years ago and demonstrate consistency in replication. After discussion with the Division of Scientific Investigations (DSI), a DSI audit was not considered a good use of resources.

##### **FINANCIAL DISCLOSURE**

This is a 505(b)(2) application primarily based on literature.

### **DMEPA**

The Division of Medication Error Prevention and Analysis (DMEPA) initially reviewed the name Optomycin, (b) (4) alternative names provided by the applicant ((u) (4) and (u) (4)). DMEPA notified Mobius that they considered the proposed name Optomycin unacceptable, and Mobius withdrew the name.

Mobius submitted a new proprietary name, (b) (4) DMEPA found this name unacceptable (b) (4)

Mobius withdrew the name, (b) (4) and submitted a new proprietary name, Mitosol.

In a review dated 12/6/10 there were no concerns identified by DMEPA, and the name was found acceptable. DMEPA conditionally approved the name, Mitosol, in a letter dated 12/9/2010.

In a submission dated and received on 9/30/11, Mobius again requested review of the proposed proprietary name, Mitosol. DMEPA conditionally approved the name, Mitosol, in a letter dated 12/13/2011.

In a labeling review dated 1/4/12, DMEPA reviewed the substantially complete labeling for Mitosol (mitomycin for solution) and provided labeling comments. DMEPA was present at the NDA wrap-up meeting held 1/9/12 and at the labeling meeting held 1/12/12. DMEPA provided informal feedback on the Applicant's submitted draft labeling from 1/20/12.

### **DPP (DDMAC)**

In a labeling review dated 1/9/12, the Division of Professional Promotion (DPP) reviewed the substantially complete labeling for Mitosol (mitomycin for solution) and provided labeling comments. DMPA was present at the labeling meeting held 1/12/12.

### **CDRH**

A consult from the Center for Devices and Radiological Health (CDRH), regarding Mobius Therapeutics, LLC drug product, was completed on November 19, 2010. CDRH had concerns about potential performance issues related to elements of the mitomycin kit components and labeling. Their problem list/information request was transmitted to Mobius. A teleconference was held between the review division, CDRH, and Mobius on 12/8/10.

CDRH recommended additional labeling comprehension work for the mitomycin product. In the August 8, 2011, Complete Response, the kit was redesigned to include the drug product vial in the sterile inner procedure tray. See Section 3 of this review (Sterility Assurance). (b) (4)

A "naive" ophthalmologist Medical Officer assembled the revised kit on 7/25/11 with the draft labeling received in the August 8, 2011, submission. She was able to follow the instructions under observation and assemble the kit correctly.

## 5. Labeling

NDA 22-572 Mitosol (mitomycin for solution) is recommended for approval for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery with the labeling found in this review.

The revised package insert submitted on 01/27/2012 is acceptable.

The revised carton and container labeling submitted on 01/27/2012 are acceptable. The prefilled syringe label submitted on 1/20/2012 is acceptable.

The package insert, carton and container labeling, and prefilled syringe label are located in the Appendix at the end of this review.

## 6. Recommendations/Risk Benefit Assessment

### **RECOMMENDED REGULATORY ACTION:**

NDA 22-572 Mitosol (mitomycin for solution) is recommended for approval for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery with the labeling found in this review.

### **RISK BENEFIT ASSESSMENT:**

There is adequate support from the literature to support efficacy for Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery, if the drug product is adequately manufactured and stored. In the four placebo-controlled studies (Carlson, Cohen, Costa, and Robin), the mean IOP in the mitomycin-treated groups as compared with placebo-treated groups was lower. It was statistically significant in favor of the mitomycin groups from 6 to 24 months in the majority of these trials (Cohen, Costa, and Robin).

In placebo-controlled studies reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 3 mmHg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery by Month 12.

In studies with a historical control reported in the medical literature, mitomycin reduced intraocular pressure (IOP) by 5 mmHg in patients with open-angle glaucoma when used as an adjunct to ab externo glaucoma surgery by Month 12.

There is adequate support from the literature to support the safety for Mitosol (mitomycin for solution) in treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery provided the mitomycin can be adequately manufactured, stored and labeled for reconstitution and administration. The most frequent adverse reactions to Mitosol occur locally and are often related to an extension of the pharmacological activity of the drug and/or markedly reduced

intraocular pressure from trabeculectomy. These include hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression.

Pharmacology/Toxicology, Biostatistics, Clinical, CMC, Product Quality Microbiology, and Clinical Pharmacology have recommended approval for this application.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events.

There are no recommended Postmarketing Requirements.

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

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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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WILLIAM M BOYD  
02/02/2012

WILEY A CHAMBERS  
02/02/2012