CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022572Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	See electronic stamp date
From	Renata Albrecht, MD Division of Transplant and Ophthalmology Products[1]
Subject	Division Director Summary Review
NDA Number	NDA 22-572
Related IND	IND 75734
Applicant Name	Mobius Therapeutics, LLC
Date of Submission **Date of Receipt**	June 21, 2010 June 22, 2010
Complete Response Letter	December 22, 2010
Resubmission (class 2)	August 8, 2011
PDUFA Goal Date	February 8, 2012
Application Type	505(b)(2)
Proprietary Name / **Established (USAN) Name**	Mitosol mitomycin for solution
Formulation **Dosage form**	Topical solution, 0.2 mg/vial Powder for ophthalmic solution
Proposed Indication(s)	For use as an adjunct to ab externo glaucoma surgery
Action	*Approval*

[1] The Office of Antimicrobial Products was reorganized effective May 2011; specifically the Division of Special Pathogen and Transplant Products (DSPTP) and Division of Anti-Infective and Ophthalmology Products (DAIOP) were reorganized into the Division of Transplant and Ophthalmology Products (DTOP) and the Division of Anti-Infective Products (DAIP).

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Bill Boyd, Wiley Chambers 2/2/2012
CDTL Review	Bill Boyd, Wiley Chambers 2/2/2012
Deputy Director Review	Wiley Chambers 2/6/2012
Statistical Review	Mushfiqur Rashid, Yan Wang 12/6/2010
Pharmacology/Toxicology Review	Amy Nostrandt, Wendelyn Schmidt 10/28/2010
Clinical Pharmacology Review	Kimberly Bergman, Charles Bonapace 11/18/2010 Yongheng Zhang, Philip Colangelo 10/12/2011
ONDQA/DNDQAII/ Branch V Review	Mark Seggel, Rapti Madurawe 2/2/2012
OPS/NDMS/Product Quality Microbiology Review	Danise Miller, Bryan Riley 11/21/2011
OC/Facilities Inspection	Acceptable
CDRH consult	Nikhil Thakur, 11/19/2010
OSI/DGCPC	N/A
OSE/DMEPA Proprietary Name Letter (name acceptable)	Denise Baugh, Lubna Merchant, Carol Holquist, 12/6/2011 Carol Holquist, 12/13/2011
OSE/DMEPA Labeling Review	Denise Baugh, Lubna Merchant, Carol Holquist, 1/4/2012
OPDP/DPP (formerly DDMAC)	Christine Corser, 1/9/2012
Pediatric Review Committee	N/A
Advisors and Consultants Staff	N/A

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
ONDQA/DNDQAII=Office of New Drug Quality Assessment/ Division of New Drug Quality Assessment
OPS/NDMS=Office of Pharmaceutical Sciences/New Drug Microbiology Sterility
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance (formerly Division of Scientific Investigation (DSI)
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OPDP/DPP=Office of Prescription Drug Promotion/Division of Professional Promotion; formerly, DDMAC=Division of Drug Marketing, Advertising and Communication
PMHT=Pediatric and Maternal Health Staff

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1. Summary and Recommendations

Mitosol (mitomycin for solution) is to be approved. Mobius Therapeutics, LLC was issued a *Complete Response* letter on December 22, 2010, listed the following deficiencies, and submitted a Class 2 resubmission on August 8, 2011 with information to address these 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.

3. 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.

The Class 2 resubmission included CMC information and labeling which was reviewed and further discussed with Mobius. The final reviews by the Product Quality and Product Quality Microbiology staff recommend approval of the application, facilities inspections are acceptable, and the package insert, instructions for use, carton and container labeling and proprietary names are all acceptable. For details regarding the findings during the first review cycle, the primary, secondary and tertiary reviews should be consulted.

1.1 Deficiencies

None (addressed in resubmission)

1.2 Post-Marketing Studies

None

1.3 Other Issues

None

2. Background

Mobius developed Mitosol (mitomycin for solution) to provide an ophthalmic form of mitomycin to be used in glaucoma filter surgery. There are currently no approved products for the proposed indication of use as an adjunct to ab externo glaucoma surgery. Based on off label use of the marketed mitomycin (Mutamycin, ANDA 62336, BMS) it is considered that mitomycin can potentially reduce the amount of scar tissue formed after trabeculectomy in patients with glaucoma requiring trabeculectomy.[2] Systemic mitomycin for intravenous use was initially approved as Mutamycin, BMS NDA 50-450 on December 17, 1974; this NDA has since been withdrawn.

The goal of providing an approved mitomycin for topical ophthalmic use is to provide (a) assurance of sterility, concentration, and delivered dosage, (b) a secure method of sterile product transfer from the circulating nurse to the surgical field and (c) stable, known amount of mitomycin in the sponge applied to the surgical site.

Mitomycin C is an antibiotic derived from *Streptomyces caespitosis* that has antimetabolytic properties, although the Chemistry Reviewer notes mitomycin is currently derived from *Streptomyces verticillatus Yingtannnensis.*[3]. Mitomycin has been shown to inhibit fibroblast proliferation by preventing DNA synthesis.

In the United States, patients with glaucoma are generally managed with intraocular pressure (IOP) lowering medications and patients who have inadequate control may undergo surgical procedures to facilitate escape of excess aqueous humor to lower the IOP. Various procedures have been employed including:[4]

- Trabeculoplasty to modify the trabecular meshwork, via a laser beam
- Iridotomy to make puncture-like openings through the iris

[2] Medical officer review,
[3] CMC review #3, page 64 of 75
[4] Glaucoma surgery http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af8020c788

- Iridectomy, to remove a portion of iris tissue
- Filtering procedures: penetrating vs. non-penetrating

  Filtering surgeries are done to control intraocular pressure; they can be penetrating or non-penetrating (depending upon whether there is intraoperative entry into the anterior chamber).

  Bleb forming procedures include ab externo trabeculectomy and deep sclerectomy. Ab externo trabeculectomy (AET) involves cutting from outside the eye inward to reach Schlemm's canal, the trabecular meshwork, and the anterior chamber.

The intent of using this Mitosol kit is to treat patients with glaucoma as an adjunt to ab externo glaucoma surgery by topically applying mitomycin soaked surgical sponges to the relevant site to prolong the closing of the surgically created fistula.

2.1 Regulatory History

A pre-NDA meeting request was sent September 21, 2006, to discuss the suitability of the literature to support submission of a 505(b)(2) New Drug Application. A Pre-Investigational New Drug Application (PIND 75,734) file for this drug product was opened on October 5, 2006, and a Pre-IND meeting was held on December 6, 2006. A second Pre-IND meeting was held on July 20, 2009.

An orphan designation for mitomycin for solution for the treatment of treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery was granted on January 8, 2008.

The applicant submitted a 505(b)(2) application for the Mitosol product in December 2010, which contained published clinical and nonclinical studies to support approval. Mobius identified BMS ANDA 62336 as the RLD, however this product has been withdrawn by BMS and the Orange Book currently lists ANDA 64144 from Accord Healthcare, a wholly owned subsidiary of Intas. [5]

3. CMC/Product Quality Microbiology

3.1 Product Quality

Per the Chemistry (Product Quality) Reviewer, the proposed packaging for Mobius product includes a carton which contains three kits. Each kit includes a vial of mitomycin for solution (containing a sterile, lyophilized mixture of 0.2 mg mitomycin and 0.4 mg mannitol) and associated components for the reconstitution of mitomycin and for the delivery of drug to the eye. Essential components of the packaging/kit include a prefilled syringe containing 1 mL of sterile water for injection for reconstitution of mitomycin and pre-cut surgical sponges for administration of the resulting solution to the eye. The sponges are held in a plastic tray which also serves as a container for the saturation with the drug solution. Other components are provided for handling and disposal of the cytotoxic agent. Components are packaged in (b) (4) trays with (b) (4) lidding.

[5] CMC review #3.

The kit is opened in the operating room and the contents are sterile. An expiry of 24 months is established.

The application could not be approved during the first cycle because of manufacturing deficiencies as itemized in Section 1, above. These apparently consisted of "an apparent misunderstanding of the degradation pathways of mitomycin and misinterpretation of the results form analytical testing for impurities (degradants) in the drug product." (ONDQA, page 12 of 75). Details about the product composition, testing, results, and limits are included in the CMC review. The Product Quality Reviewer further notes that mitomycin is a potent cytotoxic agent whose safety and activity are unlikely to be adversely affected by the impurity profile.

3.2 Product Quality Microbiology Sterility

The original kit proposed by the sponsor (b) (4) Following the review of the original NDA, the Product Quality Microbiology Sterility Reviewer recommended that the entire kit be sterile. (b) (4)

3.3 Manufacturing facilities

The Synergetics facility was not in compliance with current Good Manufacturing Practices (cGMP) noted on the form FDA 483 (issued and signed 12/10/2010) . These deficiencies were corrected and the Office of Compliance issues an "acceptable" recommendation in their EES report.

Comment: All manufacturing deficiencies have been addressed and the CMC/Microbiology Sterility reviewers conclude the product can be approved. Concerns regarding comparability of identify, strength, quality, purity and potency of the proposed Mitosol product to the marketed RLD ANDA 64144 product are adequately addressed.

4. Nonclinical Pharmacology/Toxicology

As summarized by the Pharmacology/Toxicology Reviewer, the applicant submitted published non-clinical studies demonstrating toxicity of mitomycin on the ciliary body, trabecular meshwork, fibroblasts and corneal endothelial cells, and these studies appeared to have been done to evaluate effect observed in humans. Toxicity was seen after a single mitomycin application. Mitomycin is an antimetabolite that inhibits DNA replication and suppresses cell proliferation in fibroblasts and vascular endothelial cells. Potential risks of mitomycin in the eye include inadequate control of aqueous humor, hypotony, damage to the cornea, and endophthalmitis. Although no specific genetic toxicity, carcinogenicity, or reproductive studies have been submitted, the proposed labeling will include information on the toxicity associated with the systemic form, which includes a Pregnancy category X. Mobius cross-referenced ANDA 62336 for nonclinical toxicology information; IV mitomycin is approved as an anticancer agent.

Comment: The application is recommended for approval from a Pharmacology/Toxicology perspective.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Reviewer notes that this 505(b)(2) application describes the pharmacokinetic characteristics of the IV formulation of mitomycin, which has the same active and inactive ingredients, and that the applicant requested a waiver of required in vivo bioavailability testing. This request was considered acceptable and granted because the bioavailability to the RLD is considered self-evident by the Reviewer because the Mobius 505(b)(2) NDA is based on the BMS product, NDA 062336.

The labeling will note that Mitosol® inhibits the synthesis of deoxyribonucleic acid (DNA), the guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking, and cellular RNA and protein synthesis may also be suppressed.

Absorption
The systemic exposure of mitomycin following ocular administration of Mitosol® in humans is unknown. Based on a comparison of the proposed dose of up to 0.2 mg to intravenous (IV) doses of mitomycin used clinically for treatment of oncologic indications (up to 20 mg/m^2), systemic concentrations in humans upon ocular administration are expected to be multiple orders of magnitude lower than those achieved by IV administration.

Metabolism
In humans, mitomycin is cleared from ophthalmic tissue after intraoperative topical application and irrigation, as metabolism occurs in other affected tissues. Systemic clearance is affected primarily by metabolism in the liver. The rate of clearance is inversely proportional to the maximal serum concentration because of saturation of the degradative pathways.

Excretion
Approximately 10% of an injectable dose of mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases.

Comment: The application is considered acceptable from a Clinical Pharmacology perspective.

6. Clinical Microbiology/Immunology

N/A

7. Clinical/Statistical-Efficacy

This 505(b)(2) application relies on published clinical studies to support efficacy of mitomycin. The Medical Officer Review provides a summary of the MEDLINE search strategy used to identify clinical studies, and the search results are considered acceptable. There were 22 prospective studies identified which are included in the Clinical and Statistical

Reviews. There were nine prospective, randomized, controlled, masked studies which were considered to meet the criteria of adequate and well controlled trials as defined under 21 CFR 314.126, which reported on the results of mitomycin as adjuvant therapy to glaucoma filtration surgery, primarily trabeculectomy, and are considered by the reviewers to demonstrate efficacy of mitomycin for the intended use. The nine studies are summarized below:

Tables 1 through 4 provide information on the populations, doses and duration of follow up in these studies, and the text that follows each Table includes a brief summary of efficacy:

Table 1: Summary of Mitomycin versus Placebo Studies (4 Studies)

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Carlson, 1995	Randomized Placebo-controlled Double-masked	Combined phacoemulsification and trabeculectomy in adults	14/14 15/15	Mitomycin 0.5mg/mL/3.5 min Placebo	6 to 30 months
Cohen, 1996	Randomized Placebo-controlled Double-masked	Combined glaucoma/ cataract surgery in Adults	36/36 35/35	0.5mg/mL/ 2.5 min Salt solution	12 months
Costa, 1996	Randomized Placebo-controlled Double-masked	Adults with Advanced glaucoma	14/14 14/14	0.2mg/mL/3 min Saline	Up to 24 months
Robin 1997	Long-term Dose-response Prospective Placebo-controlled Double-masked	Patients undergoing trabeculectomy	75/71 75/78 75/77 75/74	Placebo 0.2mg/mL/2 min Mitomycin0.2mg/ mL/4 min Mitomycin 0.4mg/mL/2 min	12 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.

1. Four placebo-controlled studies (Carlson, Cohen, Costa, and Robin) show the mean IOP in the mitomycin-treated groups was ~3 mmHg lower compared to placebo-treated groups from 6 to 24 months.
    a. In Carlson et al, 1995, the difference in mean IOP at Month 12 was not statistically significant, although mitomycin-treated subjects had numerically lower IOPs (roughly 13 mm Hg versus 16 mmHg).
    b. In Cohen et al, 1996, mitomycin-treated subjects had lower mean IOPs (roughly 15 mm Hg versus 17 mmHg, $p = 0.058$).
    c. In Costa et al, 1996, the mean IOP was significantly lower in the mitomycin treated group at the following time points: first postoperative day ($p=0.021$), 6-month interval ($p=0.001$), and at the final visit ($p=0.002$) (without correction for multiplicity). Mean IOP at Month 6 was roughly 12 mmHg for mitomycin-treated subjects and 17 mmHg for placebo. Mean IOP at last follow-up (ranging from Month 7-24) was roughly 13 mmHg for mitomycin-treated subjects and 18 mmHg for placebo.
    d. In Robin et al, 1997, all three mitomycin-treated groups showed a statistically significant difference in IOP compared with placebo at Month 12 ($p \leq 0.001$). Mean IOP data for the four groups were not provided. The estimated between group difference in IOP between placebo and Group 2 was 2.0 mmHg. The estimated between group difference in IOP between placebo and Group 3 and Group 4 was 3.0 mmHg. (Group1: placebo; Group 2: mitomycin 0.2mg/mL/2min; Group 3: mitomycin 0.2mg/mL/4min, and Group 4: mitomycin 0.4mg/mL/2 min) No statistically significant difference in IOP was seen among Group 2, Group 3 and Group 4.

Table 2: Summary of Mitomycin versus No Treatment (3 Studies)

Study	Design	Population	No. Patients/No. Eyes	Doses	Duration of Follow-up
Andreanos, 1997	Long-term Dose-response Prospective Placebo-controlled Double-masked	Adults with uncontrolled POAG after previous filtering surgery failure	24 patients 22 patients	2nd trab w/Mitomycin 0.4mg/mL 2nd trab without Mitomycin	18 months
Martini, 1997	Prospective Randomized Controlled Evaluator-masked	Adults	24/30 Mitomycin 24/30 Untreated	0.1mg/mL/3 min	12 months
Rasheed, 1999	Prospective Randomized Single-masked POAG/CACG	Adults	25/25 25/25	0.3-0.4mg/mL/ 4min Trab alone	18 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: POAG = Primary open-angle glaucoma; Trab = Trabeculectomy.

2. Three studies compared surgery plus mitomycin versus surgery-alone (Andreanos, Martini, and Rasheed) showed that mean IOP was lower by ~ 5 mmHg.
    a. In Andreanos et al, 1997, the mean (±SD) postoperative IOP was 12.5 (±3.2) mmHg in the mitomycin group and 19.6 (±6.1) mmHg in the control group at Month 18; this between group difference was statistically significant: $p < 0.001$
    b. In Martini et al, 1997, the difference in mean IOP at Month 12 was statistically significant; mitomycin-treated subjects had lower IOPs (roughly 11 mm Hg versus 16 mmHg).
    c. In Rasheed et al, 1999, the mean postoperative IOP at Month 18 (average IOP recorded during last six months of follow-up) is lower for mitomycin treated subjects (roughly 10 mmHg) versus non-mitomycin treated subjects (roughly 16 mmHg). It is not clear that this difference is statistically significant.

Table 3: Summary of Mitomycin versus 5-Fluorouracil Study

Study	Design	Population	Total # of Patients (103)/ No. of Eyes	Doses	Duration of Follow-up
WuDunn 2002	Prospective Double-masked Randomized	Patients with uncontrolled IOP despite maximally tolerated medical therapy or laser	-/57 -/58	5-FU 50mg/mL/5 min Mitomycin 0.2mg/mL/2 min	12 months

Data source: Table 1 (Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: 5-FU = 5-Fluorouracil

3. One double-masked study used an active-control (WuDunn 2002), and the success rate of the mitomycin-treated group was similar to that of the 5-FU-treated group (F-5U is not approved for this indication).

Table 4: Summary of Mitomycin Dose Comparison Study

Study	Design	Population	No. Patients/ No. Eyes	Doses	Duration of Follow-up
Sanders 1998	Prospective Randomized POAG/previous surgery	Patients who are at higher risk from previous conjunctival incisional surgery	25/25 25/25	0.2mg/mL/2 min 0.4mg/mL/2 min	12 months

Data source: Table 1(Page 14) in Module 2.7 Clinical Summary of the NDA submission.
Note: POAG = Primary open-angle glaucoma

4. One study used a dose-comparison control (Sanders 1998)

A total of 480 eyes were treated with mitomycin, with doses ranging from 0.1 to 0.5 mg/mL and exposure times from 2 to 4 minutes (with duration of follow-up after surgery from 12 to 24 months).

There were thirteen additional prospective studies, but not necessarily randomized or controlled. The findings from the remaining 13 prospective studies are summarized in the Statistical review, Appendix 3, and the Medical Officer review. These studies provided supporting evidence of the efficacy of mitomycin in glaucoma filtration surgery. The Statistical reviewer concludes that based on the review of the submitted studies, despite variations of designs and doses, the results were convincing because all the studies showed the advantage of using mitomycin in glaucoma filtration surgery.

In addition, 14 retrospective studies and 2 review articles were submitted but not reviewed in detail.

Comment:
The Clinical and Statistical Reviewers conclude there is adequate evidence of efficacy in the published studies to support approval of the application.

8. Safety

As noted in the Clinical Review, the adverse reaction evaluation of mitomycin was obtained from the review of the literature and search of the Adverse Events Reporting System (AERS). The applicant provided tabulated results by study design to facilitate review for the literature safety report: information from 23 controlled trials, 32 observational studies, 9 case series, and 65 case reports, was summarized separately. The 23 controlled trials were conducted in 1,588 eyes, 1,085 of which were treated with mitomycin. All 23 controlled trials included at least 1 arm where mitomycin was topically applied to the exposed site of a filtering bleb, as adjunct therapy during trabeculectomy. Five were conducted in the United States, 10 in Europe (Croatia, Greece, Italy, the Netherlands, and Poland), 6 in Asia (India and Japan), and 2 in Africa (Congo and Ghana). Sixteen trials used randomized controlled designs, 1 used a randomized controlled trial with case control, 4 used randomized crossover designs, 1 used a sequential crossover design, and 1 used a prospective non-comparative, nonrandomized, unmasked design. Among the controlled trials, doses of mitomycin ranged from 0.04 mg/mL

to 0.5 mg/mL, and application times ranged from 0.5–5 minutes. A summary of 33 AERS reports was also provided.

The most frequent adverse reactions to Mitosol occurred locally and were often related to an extension of the pharmacological activity of the drug and/or markedly reduced intraocular pressure from trabeculectomy. Hypotony, choroidal detachment, shallow anterior chamber, hyphema, corneal endothelial defects, and cataract progression were seen with a lower frequency range of 0-3% and an upper frequency range of approximately 30-50%. It should also be noted that all of these are known adverse events seen with the trabeculectomy procedure alone. Given the great variation in the adverse reaction rates reported for these more serious adverse events; it is possible these rates are presumably dependant on the skill of the surgeon and the specific surgical population.

The Clinical review concludes the literature is adequate to support the safety of Mitosol (mitomycin for solution) in the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery, given that the Mitosol kit configuration, labeling and instructions for use have been addressed.

Comment:
The Clinical Reviewers consider that the safety of the product is adequately addressed with the new Mitosol kit configuration, instructions for use, and professional labeling.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

10. Pediatrics

The Pediatric Research Equity Act of 2003 (PREA), and 21 CFR 3 14.55 (a) require that sponsors submitting a new application or supplement under section 505 of the Federal Food Drug and Cosmetic Act that involves a new ingredient, new indication, new dosage form, new dosing regimen or new route of administration, submit an assessment of the safety and efficacy of the drug or biological product for the claimed indication in all relevant pediatric subpopulations.

Mobius' Mitosol (mitomycin for solution) has received Orphan Designation; a pediatric assessment is therefore not required and has not been provided in this application.

Safety and effectiveness of Mitosol (mitomycin for injection) in pediatric patients has not been established.

11. Other Relevant Regulatory Issues

11.1 Compliance Inspection –

The Chemistry Reviewer notes that facility inspections in EES are acceptable. This information was provided on September 19, 2011 by April Inyard, Office of Compliance.

11.2 Office of Scientific Investigation (OSI) Audits

As summarized by the Medical Officer, 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.

Comment:
The nine controlled, randomized masked trials were published between 1996 and 2002; the thirteen additional prospective studies were published between 1993 and 2005. There are multiple studies providing adequate detail on study design, conduct and analysis; these provide consistent evidence of efficacy and describe the adverse reaction profile of mitomycin. Basing approval on these published studies is consistent with the Guidance to Industry - Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.[6]

11.3 Debarment Certification

This 505(b)(2) application relies on clinical studies from the published literature.

11.4 Financial Disclosure

This 505(b)(2) application relies on clinical studies from the published literature.

11.5 Orphan Designation

Orphan Designation was granted January 8, 2008 for the treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery.

11.6 Center for Devices and Radiologic Health Consult

CDRH/ODE/DAGID provide a consult to ONDQA regarding the Mitosol kit on November 19, 2010 and expressed concerns about the assembly of the kit and clarify of instructions, including recommendations for Human Factor Testing. These recommendations were provided to Mobius along with the Division's comments on issues to address in redesigning the configuration and instructions for use for the Mitosol kit.

12. Labeling

The package insert and carton and container labeling were reviewed as applicable by the Division, DMEPA and OPDP/DPP. On note, given the complexity of the kit and instruction for use labeling, a meeting of DTOP, ONDQA, DMEPA and OPDP reviewers was held January 12, 2012 during which outstanding concerns regarding the labeling were discussed and recommendation to the applicant finalized. The labeling submitted January 27, 2012 included all the revisions requested by these groups.

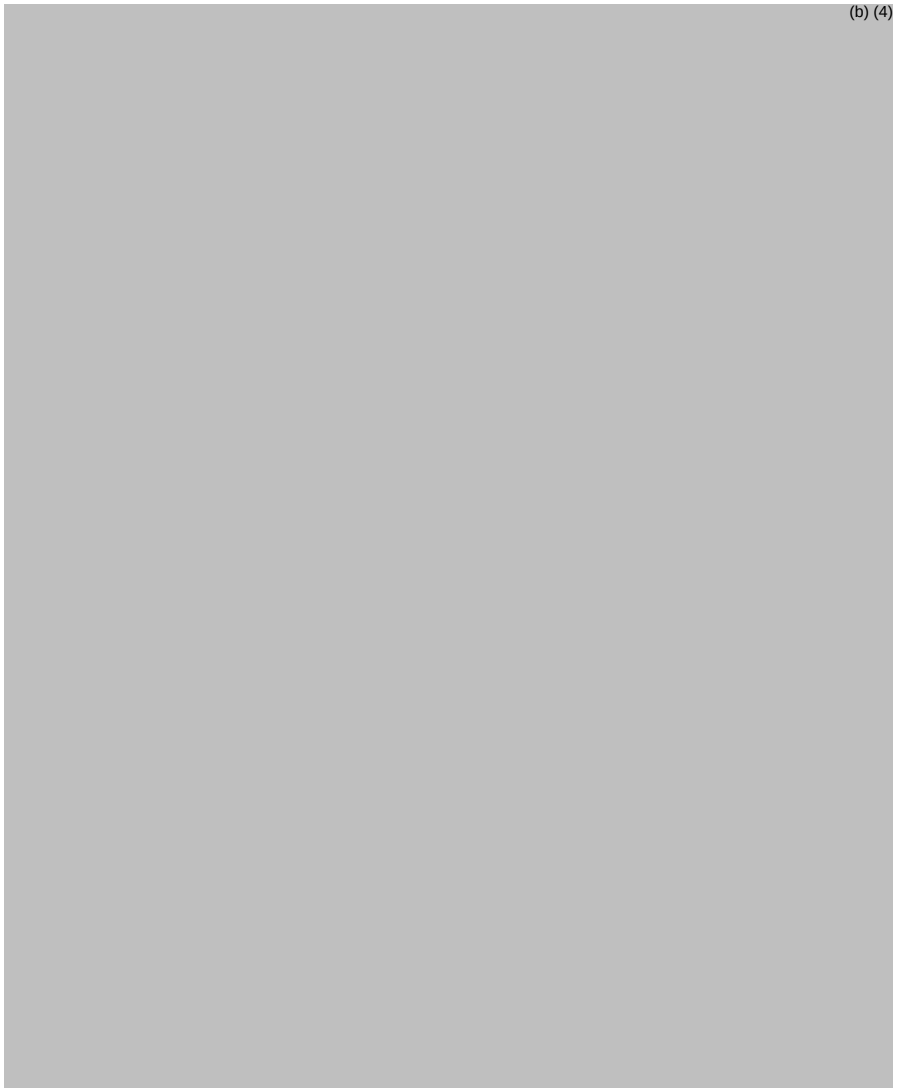
- **Proprietary Name**: DMEPA considered the originally-proposed names Optomycin and (b) (4) unacceptable but agreed with the new proprietary name, Mitosol, and issued a letter to Mobius December 13, 2011 accepting the name.

[6] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf

- **Package insert (PI):** The PI is written in PLR format and has been reviewed by multiple disciplines, and includes the recommendations made by these groups.

- **Carton and Container Label, including components of the Mitosol Kit**: The labels have been reviewed by DTOP, ONDQA, and DMEPA, the content of the kit and instructions diagram are provided below.

- **Instructions: How this product should be used (diagram)**
  The complete written instructions as well as pictures of the kit, tray, and diagrams have been reviewed by DTOP, ONDQA and DMEPA and found to be acceptable. The following diagram provides a summary of the steps involved in preparing the mitomycin for use during surgery.



Comment:
The final agreed-upon labeling for the product is included in the Medical Officer review dated February 2, 2012.

13. Decision/Action/Risk Benefit Assessment

13.1 Regulatory Action

The Mitosol NDA will be approved, given that all deficiencies have been addressed and final labeling, including package insert, carton and container labeling for the kit and its components, as well as instructions for use have been finalized and are acceptable.

There are no post marketing studies or requirements. The applicant has orphan designation and is exempt from PREA requirements.

An *Approval* letter will be issued to Mobius.

13.2 Risk Benefit Assessment

The efficacy of topical mitomycin was demonstrated in nine prospective clinical trials showing an approximately 3 to 5 mmHg reduction in IOP by month 12 with the use of mitomycin in glaucoma filtration surgery, and this information is included in the Clinical Studies section of labeling. Other prospective studies supported this conclusion. The product is intended for use in the operating room during the performance of glaucoma filtration surgery, thus all labeling is directly at the health professional staff that will be involved in the handling of this product, including circulating nurse, sterile scrub technician and surgeon.

The adverse reactions associated with use of topical mitomycin includes hypersensitivity, direct corneal and scleral damage, hypotony, cataract formation, blebitis, endophthalmitis, wound dehiscence, and other ocular events, These are described in the Contraindications, Warnings and Precautions, and Adverse Reactions section of the labeling.

The labeling also includes information on teratogenicity (Pregnancy category X) and carcinogenicity seen with the IV mitomycin product in animal studies; exposure after topical use is orders of magnitude lower than after IV treatment for cancer.

The Mitosol kit has now been redesigned; the contents of the kit include all components needed to use the mitomycin and to dispose of the mitomycin and other components after use. The instructions for use are now clear and acceptable as well. The directions for use also specify that the product should be used within 1 hour of reconstitution, should only be applied for up to 2 minutes, and the labeling includes a warning that higher doses and longer duration may be association with corneal and/or scleral damage, thinning or perforation.

In summary, the benefit of reducing the IOP, the risks of topical mitomycin, and instructions on the use of the Mitosol kit are adequately covered in the product labeling.

13.3 Recommendation for other Postmarketing Requirements and Commitments

N/A

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

/s/

RENATA ALBRECHT
02/06/2012