

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022572Orig1s000**

**CHEMISTRY REVIEW(S)**

**NDA 22-572**

**Mitosol™ Kit for Ophthalmic Use**

**Mitosol™  
(mitomycin for solution)  
0.2 mg / Vial**

**Mobius Therapeutics LLC**

**Mark R. Seggel  
ONDQA  
Branch V  
Division of New Drug Quality Assessment II**

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-572
2. REVIEW #: 3
3. REVIEW DATE: 31-JAN-2012
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents (eCTD)  
Original Application 0000  
Amendments thru 0020

Document Date  
22-JUN-2010  
28-JUN-2010 thru 22-NOV-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)  
Response to CDRH comments (0023)  
NDA Resubmission (0024)  
Labeling (0025)  
Response to CMC information request (0027)  
Revised Labeling (0028)  
Final Draft Labeling (0029)

Document Date  
06-DEC-2010  
08-AUG-2011  
30-SEP-2011  
03-JAN-2012  
20-JAN-2012  
27-JAN-2012

7. NAME & ADDRESS OF APPLICANT:

Name:	Mobius Therapeutics LLC
Address:	4041 Forest Park Avenue St. Louis, MO 63108
Representative(s):	Ed Timm, President
Telephone:	314-615-6930

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: MitoSol™
- b) Non-Proprietary Name (USAN): Mitomycin
- c) Code Name/#: MMC

## Chemistry Review Data Sheet

- d) CAS Registry Number: 50-07-7  
e) Chem. Type/Submission Priority:  
i. Chem. Type: 3  
ii. Submission Priority: P

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

10. PHARMACOL. CATEGORY: Cytotoxic Agent/Antimetabolite  
Ophthalmic - Antibiotic (4041310)

11. DOSAGE FORM: Powder for Ophthalmic Solution

12. STRENGTH/POTENCY: 0.2 mg / Vial

13. ROUTE OF ADMINISTRATION: Topical, ocular

14. Rx/OTC DISPENSED:  Rx  OTC

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

SPOTS product – Form Completed

Not a SPOTS product

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

USAN, INN, BAN: Mitomycin

JAN: Mitomycin C

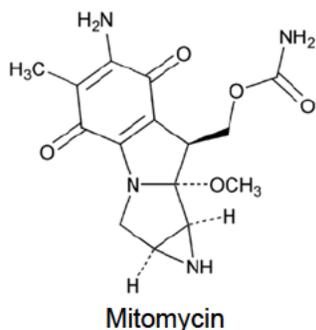
Chemical Names:

1) Azirino[2',3': 3,4]pyrrolo[1,2-a]indole-4,7-dione, 6-amino-8-[[aminocarbonyl]oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1aR-(1a $\alpha$ ,8 $\beta$ ,8a $\alpha$ ,8b $\alpha$ )]-

2) 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3': 3,4]-pyrrolo[1,2-a]indole-4,7-dione carbamate (ester).

3) (1aS,8S,8aR,8bS)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3': 3,4]pyrrolo[1,2-a]-indol-8-yl]methyl carbamate.

## Chemistry Review Data Sheet

Molecular Formula: C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>

Molecular Weight: 334.33

## 17. RELATED/SUPPORTING DOCUMENTS

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	DMF STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Mitomycin USP	1	Adequate	28-NOV-2010	Minor changes only Last review 3/10/2009
	III		(b) (4)	4	Adequate		
	III			3	Adequate	22-JUL-2009	Additional CMC information in NDA
	II			1	Adequate	Micro: 17-NOV-2010 CMC: 02-MAR-2010	Additional CMC information in NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

## B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
IND 75734	Trabomycin (Mitomycin); for use in trabeculectomy procedures to delay	21-SEP-2006 Mobius

Chemistry Review Data Sheet

	wound healing and improve the success of surgery.	
ANDA 64-144*	Mitomycin for Injection 5, 20 and 40 mg/vial	Approved: 30-APR-1998 Accord Healthcare Inc.^ Antitumor - Antibiotic (4010800)
ANDA 62-336	Mitomycin for Injection	Approved: 24-AUG-1981 BMS Reference Listed Drug#

For other Mitomycin ANDAs and NDAs, see Review Section Iv. Miscellaneous Attachments.

\*Ownership transferred from SuperGen to Accord Healthcare effective April 29, 2007. Manufacturing facility changed to Intas Pharmaceuticals per CBE-30 supplement submitted Sept. 15, 2008 (S-003; approved 04/01/2009; see Product Quality Microbiology Review dated 03/24/2009).

^Accord Healthcare is a wholly owned subsidiary and the marketing arm of Intas.

# The applicant has identified the BMS product as the RLD. The current Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations indicates that the ANDA 64-144 products are now the RLD. The BMS application has been withdrawn.

18. CONSULT STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	Follow-up to initial review not required		
Biometrics	N/A		
EES	Acceptable	19-SEP-2011	A. Inyard, Office of Compliance
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA (Label and Labeling Review)	Revisions recommended	04-JAN-2012	D. Baugh
DDAMC	Revisions recommended	09-JAN-2012	C. Corser
Proprietary Name	Acceptable	06-DEC-2011 13-DEC-2011	D. Baugh K. Townsend
EA	Acceptable	28-NOV-2010	M. Seggel
Product Quality	Revisions recommended	23-NOV-2010	D. Miller
Microbiology	Acceptable	21-NOV-2011	D. Miller

## Executive Summary Section

# The Chemistry Review for NDA 22-572

## The Executive Summary

### I. Recommendations

#### A. 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. 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.

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

Not Applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Mitomycin C (mitomycin, MMC) is a potent cytotoxic antimetabolite isolated from (b) (4) *Streptomyces* species including strains of *S. caespitosus* and *S. verticillatus*. A strain or variant of the latter is currently used in the production of mitomycin. Mitomycin has been well characterized in the literature and has been the subject of total syntheses. It is isolated as a blue-violet crystalline powder. Mitomycin is slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. It is freely soluble in dimethylacetamide. Mitomycin is light-sensitive, and degrades in aqueous solutions by well established pathways depending on pH.

Mitomycin used in the manufacture of 'Mitomycin for Solution' will be supplied by (b) (4). The manufacture and control of mitomycin API by (b) (4) is documented in Type II DMF (b) (4). The DMF was previously found adequate (for use in the manufacture of Mitomycin for Injection USP). Only minor changes are reported in recent updates to the DMF.

The Mitosol Kit for Ophthalmic Use was developed with the intention of providing a safe, effective, and convenient means of delivering a controlled amount of mitomycin to the eye. The Kit will also greatly reduce waste mitomycin. Mitomycin for Injection

## Executive Summary Section

has been used off-label as an adjunct to trabeculectomy surgery for many years. There are currently no approved products for this use.

Mitomycin has been available since 1974 when Bristol-Myers' Mutamycin (mitomycin for injection) was approved for use in cancer treatment. The innovator's product (and, with one exception, subsequent generic versions including the Accord (Intas) versions described below) consist of a lyophilized mixture of mitomycin and mannitol in a 1 to 2 ratio. Vials of 'Mitomycin for Injection' contain 5, 20, and 40 mg mitomycin.

'Mitosol Kit for Ophthalmic Use' consists of 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. Mitomycin for Solution is manufactured (b) (4) by Intas Pharmaceuticals Limited, India. Intas also currently manufactures Mitomycin for Injection under ANDA 64-144.

The product 'quality strategy' includes established manufacturing procedures and controls for the drug substance (b) (4) (drug substance meets USP, (w) (4) and Intas (b) (4) quality standards).

This, along with the drug product specification (test attributes, analytical procedures, and acceptance criteria) provides assurance that Mitosol (mitomycin for solution) 0.2 mg/vial has the requisite identity, strength, quality, purity and potency.

Essential components of the Kit include a prefilled syringe containing 1 mL sterile water for injection (sWFI) 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. All components including the sponges are (b) (4) kit redesign has greatly simplified the instructions for use.

No clinical studies were conducted with the Mitosol Kit for Ophthalmic Use. Rather, the application is based on literature reports describing the use mitomycin solutions (typically 0.2 to 0.4 mg/mL in either sWFI or sterile saline, and presumably prepared from approved Mitomycin for Injection products) applied with commercially available surgical sponges).

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

'Mitomycin for Solution' (and associated Kit) is indicated for the treatment of refractory glaucoma as an adjunct to *ab externo* glaucoma surgery by topical

## Executive Summary Section

application to the exposed site of a filtering bleb created 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.

The Kit is opened in the operating room and a sterile inner tray removed. (b) (4)

The entire Kit and used materials are then disposed of in a chemotherapy waste bag.

The Kit and included 0.2 mg mitomycin vial are to be stored at 20-25°C, and protected from light. The reconstituted solution can be stored for 1 hour at 25°C. An expiration dating period of 24 months has been established for the 0.2 mg mitomycin vial and for the Kit.

### C. Basis for Approvability or Not-Approval Recommendation

The primary CMC-related deficiency identified during review of the original submission can be summarized as an apparent misunderstanding of the degradation pathways of mitomycin and misinterpretation of the results from analytical testing for impurities (degradants) in the drug product.

As a consequence of uncertainty in the characterization of the drug product impurity/degradation profile, setting of useful acceptance criteria and establishing an expiration dating period was complicated. Furthermore, comparison of 'Mitomycin for Solution' with the 'Mitomycin for Injection' products that have been used off-label in the proposed indication and that were, presumably, used in the "clinical studies" that form the basis for approval of this application.

The manufacturer of 'Mitomycin for Solution' has now provided additional data that now allows a more complete interpretation of the Related Substances data, and allows establishment of a reasonable specification.

The range of tests performed for release of the drug product is adequate. While the acceptance criteria for several attributes (assay, related substances, pH) probably could be (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 in and of itself. The (b) (4) in 'Mitomycin for Solution' should not be interpreted as being directly applicable to 'Mitomycin for Injection' products.

## Executive Summary Section

Based on the totality of information submitted in the NDA (original, resubmission and amendments), concerns regarding the comparability of the identity, strength, quality, purity and potency of the proposed drug product, Mitosol (mitomycin for solution), 0.2 mg/vial, 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) have been adequately addressed.

Originally there were a number of challenges to successfully using the Kit, including complicated directions for use as identified in a labeling comprehension study and by the observations of the review team. The Product Quality Microbiology reviewer, Dr. D. Miller, OPS NDMS, concluded that “this submission [i.e., the original application] is approvable pending resolution of microbiological deficiencies.” Specifically, (b) (4)

 (b) (4)

The CDRH reviewer has identified several concerns with Kit components and has recommended that a Human Factors Validation Study be conducted. These comments were conveyed to the applicant during the first review cycle. The responses were not received in time to be reviewed before the original Complete Response letter was issued on 22-DEC-2010. While the responses, including additional information provided in the 08-AUG-2011 resubmission, were not reviewed by CDRH, they have been taken into consideration in our final evaluation of kit components and the review team’s assessment of the adequacy of the instructions for use (IFU). Some of the issues identified, become less critical (b) (4)



At the time of the 22-DEC-2010 CR, the Synergetics facility (Kit assembly) had an unacceptable inspection. Those cGMP issues have been resolved; all facilities involved in the manufacture, packaging and testing of mitomycin API, mitomycin for solution, and the finished kit now have acceptable cGMP status. The Office of Compliance has made a final overall recommendation of ACCEPTABLE for this application (see attached EES summary report).

## Executive Summary Section

We previously noted that we thought that the established name should be 'mitomycin for ophthalmic solution' rather than (b) (4) or (b) (4)

(b) (4)

Based on Agency recommendations, extensive revisions have been made to the labels and labeling, including instructions for use. The revised labeling is factually accurate; it is acceptable from the CMC perspective. Ideally, the pre-filled syringe label should be revised to eliminate any potential confusion that the graduations may cause. However, because the instructions for use of the Kit specify using the entire contents of the syringe, the review team has agreed, that revision of the syringe label is not required.

### III. Administrative

#### A. Reviewer's Signature

Mark. R. Seggel

*{see electronic signature page}*

#### B. Endorsement Block

Rapti Madurawe, PhD, Branch Chief

*{see electronic signature page}*

#### C. CC Block

W. Boyd, J. Germain, A. Cuff, B. Shanmugam, D. Miller

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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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MARK R SEGCEL

02/02/2012

I recommend approval of NDA 22-572.

RAPTI D MADURawe

02/02/2012

# **NDA 22-572**

## **Mitosol™ Kit for Ophthalmic Use**

**Mitosol™  
(mitomycin for ophthalmic solution)  
0.2 mg / Vial**

**Mobius Therapeutics LLC**

**Mark R. Seggel  
ONDQA  
Branch V  
Division of New Drug Quality Assessment II**

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S.2    Manufacture .....	11
S.2.1    Manufacturers .....	11
<b>P    DRUG PRODUCT [0.2 mg Mitomcyin / Vial].....</b>	<b>12</b>
P.3    Manufacture .....	12
P.3.1    Manufacturers .....	12
<b>P    DRUG PRODUCT [Kit] .....</b>	<b>13</b>
P.3    Manufacture .....	13



P.3.1 Manufacturers ..... 13

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-572
2. REVIEW #: 2
3. REVIEW DATE: 15-DEC-2010
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)

Original Application 0000

Amendments thru 0020

Document Date

22-JUN-2010

28-JUN-2010 thru 22-NOV-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Mobius Therapeutics LLC
Address:	4041 Forest Park Avenue St. Louis, MO 63108
Representative(s):	Ed Timm, President
Telephone:	314-615-6930

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mitosol™
- b) Non-Proprietary Name (USAN): Mitomycin
- c) Code Name/#: MMC
- d) CAS Registry Number: 50-07-7
- e) Chem. Type/Submission Priority:
  - i. Chem. Type: 3
  - ii. Submission Priority: P

## Chemistry Review Data Sheet

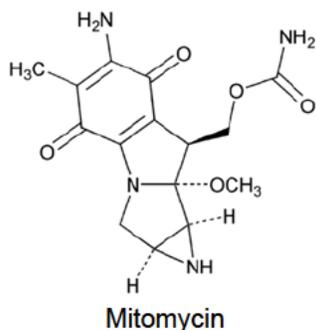
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Cytotoxic Agent/Antimetabolite  
Ophthalmic - Antibiotic (4041310)
11. DOSAGE FORM: Powder for Ophthalmic Solution
12. STRENGTH/POTENCY: 0.2 mg / Vial
13. ROUTE OF ADMINISTRATION: Topical, ocular
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

USAN, INN, BAN: Mitomycin  
JAN: Mitomycin C

## Chemical Names:

- 1) Azirino[2',3': 3,4]pyrrolo[1,2-a]indole-4,7-dione, 6-amino-8-[[aminocarbonyl]oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1aR-(1a $\alpha$ ,8 $\beta$ ,8a $\alpha$ ,8b $\alpha$ )]-
- 2) 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3': 3,4]-pyrrolo[1,2-a]indole-4,7-dione carbamate (ester).
- 3) (1aS,8S,8aR,8bS)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3': 3,4]pyrrolo[1,2-a]-indol-8-yl]methyl carbamate.

## Chemistry Review Data Sheet

Molecular Formula: C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>

Molecular Weight: 334.33

## 17. RELATED/SUPPORTING DOCUMENTS

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	DMF STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Mitomycin USP	1	Adequate	28-NOV-2010	Minor changes only Last review 3/10/2009
	III	(b) (4)		4	Adequate		
	III	(b) (4)		3	Adequate	22-JUL-2009	Additional CMC information in NDA
	II	(b) (4)		1	Adequate	Micro: 17-NOV-2010 CMC: 02-MAR-2010	Additional CMC information in NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

## B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
IND 75734	Trabomycin (Mitomycin); for use in trabeculectomy procedures to delay wound healing and improve the success of surgery.	21-SEP-2006 Mobius

Chemistry Review Data Sheet

ANDA 64-144*	Mitomycin for Injection 5, 20 and 40 mg/vial	Approved: 30-APR-1998 Accord Healthcare Inc.^ Antitumor - Antibiotic (4010800)
ANDA 62-336	Mitomycin for Injection	Approved: 24-AUG-1981 BMS Reference Listed Drug#

For other Mitomycin ANDAs and NDAs, see Review Section Iv. Miscellaneous Attachments.

\*Ownership transferred from SuperGen to Accord Healthcare effective April 29, 2007. Manufacturing facility changed to Intas Pharmaceuticals per CBE-30 supplement submitted Sept. 15, 2008 (S-003; approved 04/01/2009; see Product Quality Microbiology Review dated 03/24/2009).

^Accord Healthcare is a wholly owned subsidiary and the marketing arm of Intas.

# The applicant has identified the BMS product as the RLD. The current [October, 2010] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations indicates that the ANDA 64-144 products are now the RLD. The BMS application has been withdrawn.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	Numerous concerns identified; conveyed to applicant 22-NOV-2010	19-NOV-2010	N. Thakur, CDRH, ODE
Biometrics	N/A		
EES	Overall recommendation: Withhold (see attached Report)	15-DEC-2010	C. Cruz, Office of Compliance, HFD-323
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	Proprietary Name granted	09-DEC-2010	D. Toyer
EA	Acceptable	28-NOV-2010	M. Seggel
Product Quality Microbiology	Approvable pending resolution of microbiological deficiencies (b) (4)	23-NOV-2010	D. Miller

# The Chemistry Review for NDA 22-572

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

As noted in Chemistry Review #1, 09-DEC-2010, deficiencies in the chemistry, manufacturing and controls have been identified. It was, and continues to be recommended that a Complete Response be issued for this new drug application.

Since completion of Chemistry Review #1, inspections of all manufacturing and testing facilities have been completed. GMP issues were identified at the Kit manufacturing facility, Synergetics. The Office of Compliance has therefore issued an overall recommendation of Withhold for this application.

As noted in the previous review, the suitability of several Kit components remains to be demonstrated (as recommended in a CDRH consult). Product quality microbiology deficiencies have been identified. Labeling issues have not been resolved. Critical issues related to the directions for use (DFU) have been identified by the review team and remain to be resolved.

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

Not Applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

See Chemistry Review #1

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

See Chemistry Review #1

#### C. Basis for Approvability or Not-Approval Recommendation

See Chemistry Review #1.

During the recently completed inspection of Synergetics, the Kit manufacturing site, cGMP deficiencies were noted. Of particular concern are the lack of appropriate

### Executive Summary Section

acceptance criteria for incoming materials and the lack of complete manufacturing and control instructions.

All other facilities now have acceptable cGMP status. The Office of Compliance has issued an overall recommendation of Withhold for this application.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

Mark. R. Seggel

*{see electronic signature page}*

**B. Endorsement Block**

Stephen P. Miller, PhD, Acting Branch Chief

*{see electronic signature page}*

**C. CC Block**

L. Ng, W. Boyd, S. Miller, A. Rodgers

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/s/  
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MARK R SEGCEL  
12/15/2010

STEPHEN P MILLER  
12/16/2010

I concur - this NDA cannot be recommended for approval from the CMC perspective at this time

**NDA 22-572****Mitosol<sup>™</sup> Kit for Ophthalmic Use**

**Mitosol<sup>™</sup>**  
**(mitomycin for ophthalmic solution)**  
**0.2 mg / Vial**

**Mobius Therapeutics LLC**

**Mark R. Seggel**  
**ONDQA**  
**Branch V**  
**Division of New Drug Quality Assessment II**

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## Chemistry Review Data Sheet

# Chemistry Review Data Sheet

1. NDA 22-572
2. REVIEW #: 1
3. REVIEW DATE: 02-DEC-2010; revised 09-DEC-2010
4. REVIEWER: Mark R. Seggel
5. PREVIOUS DOCUMENTS:

Previous Documents

N/A

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed (eCTD)

Original Application 0000

Amendments thru 0020

Document Date

22-JUN-2010

28-JUN-2010 thru 22-NOV-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	Mobius Therapeutics LLC
Address:	4041 Forest Park Avenue St. Louis, MO 63108
Representative(s):	Ed Timm, President
Telephone:	314-615-6930

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Mitosol™
- b) Non-Proprietary Name (USAN): Mitomycin
- c) Code Name/#: MMC
- d) CAS Registry Number: 50-07-7
- e) Chem. Type/Submission Priority:
  - i. Chem. Type: 3
  - ii. Submission Priority: P

## Chemistry Review Data Sheet

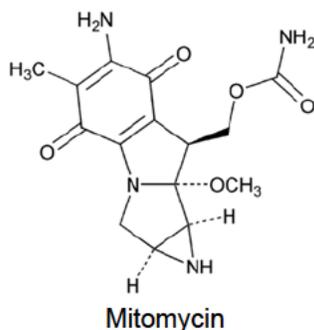
9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)
10. PHARMACOL. CATEGORY: Cytotoxic Agent/Antimetabolite  
Ophthalmic - Antibiotic (4041310)
11. DOSAGE FORM: Powder for Ophthalmic Solution
12. STRENGTH/POTENCY: 0.2 mg / Vial
13. ROUTE OF ADMINISTRATION: Topical, ocular
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

USAN, INN, BAN: Mitomycin  
JAN: Mitomycin C

## Chemical Names:

- 1) Azirino[2',3': 3,4]pyrrolo[1,2-a]indole-4,7-dione, 6-amino-8-[[aminocarbonyl]oxy]methyl]-1,1a,2,8,8a,8b-hexahydro-8a-methoxy-5-methyl-, [1aR-(1a $\alpha$ ,8 $\beta$ ,8a $\alpha$ ,8b $\alpha$ )]-
- 2) 6-Amino-1,1a,2,8,8a,8b-hexahydro-8-(hydroxymethyl)-8a-methoxy-5-methylazirino[2',3': 3,4]-pyrrolo[1,2-a]indole-4,7-dione carbamate (ester).
- 3) (1aS,8S,8aR,8bS)-6-Amino-8a-methoxy-5-methyl-4,7-dioxo-1,1a,2,4,7,8,8a,8b-octahydroazirino[2',3': 3,4]pyrrolo[1,2-a]-indol-8-yl]methyl carbamate.

## Chemistry Review Data Sheet

Molecular Formula: C<sub>15</sub>H<sub>18</sub>N<sub>4</sub>O<sub>5</sub>

Molecular Weight: 334.33

## 17. RELATED/SUPPORTING DOCUMENTS

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	DMF STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	Mitomycin USP	1	Adequate	28-NOV-2010	Minor changes only Last review 3/10/2009
	III	(b) (4)		4	Adequate		
	III	(b) (4)		3	Adequate	22-JUL-2009	Additional CMC information in NDA
	II	(b) (4)		1	Adequate	Micro: 17-NOV-2010 CMC: 02-MAR-2010	Additional CMC information in NDA

<sup>1</sup> Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

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

## B. Other Documents:

APPLICATION NUMBER	DESCRIPTION	NOTES
IND 75734	Trabomycin (Mitomycin); for use in trabeculectomy procedures to delay wound healing and improve the success of surgery.	21-SEP-2006 Mobius

Chemistry Review Data Sheet

ANDA 64-144*	Mitomycin for Injection 5, 20 and 40 mg/vial	Approved: 30-APR-1998 Accord Healthcare Inc.^ Antitumor - Antibiotic (4010800)
ANDA 62-336	Mitomycin for Injection	Approved: 24-AUG-1981 BMS Reference Listed Drug#

For other Mitomycin ANDAs and NDAs, see Review Section Iv. Miscellaneous Attachments.

\*Ownership transferred from SuperGen to Accord Healthcare effective April 29, 2007. Manufacturing facility changed to Intas Pharmaceuticals per CBE-30 supplement submitted Sept. 15, 2008 (S-003; approved 04/01/2009; see Product Quality Microbiology Review dated 03/24/2009).

^Accord Healthcare is a wholly owned subsidiary and the marketing arm of Intas.

# The applicant has identified the BMS product as the RLD. The current [October, 2010] Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations indicates that the ANDA 64-144 products are now the RLD. The BMS application has been withdrawn.

18. STATUS

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	Numerous concerns identified; conveyed to applicant 22-NOV-2010	19-NOV-2010	N. Thakur, CDRH, ODE
Biometrics	N/A		
EES	<i>Pending</i>		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	<i>Pending</i>		
EA	Acceptable	28-NOV-2010	M. Seggel
Product Quality Microbiology	Approvable pending resolution of microbiological deficiencies (b) (4)	23-NOV-2010	D. Miller

# The Chemistry Review for NDA 22-572

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

Deficiencies in the chemistry, manufacturing and controls have been identified. It is therefore recommended that a Complete Response be issued for this new drug application. Additionally, because several facilities involved in the manufacture of the product remain to be inspected, the Office of Compliance has not issued an overall recommendation for this application. Per CDRH consult, the suitability of several Kit components remains to be demonstrated. Product quality microbiology deficiencies have been identified. Labeling issues have not been resolved. Critical issues related to the directions for use (DFU) have been identified by the review team and remain to be resolved.

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

Not Applicable.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

Mitomycin C (mitomycin, MMC) is a potent cytotoxic antimetabolite isolated from (b) (4) *Streptomyces* species including strains of *S. caespitosus* and *S. verticillatus*. Mitomycin has been well characterized in the literature and has been the subject of total syntheses. It is isolated as a blue-violet crystalline powder. Mitomycin is slightly soluble in water; soluble in acetone, in butyl acetate, in cyclohexanone, and in methyl alcohol. It is freely soluble in dimethylacetamide. Mitomycin is photosensitive, and degrades in aqueous solutions by well established pathways depending on pH.

Mitomycin used in the manufacture of 'Mitomycin for Ophthalmic Solution' will be supplied by (b) (4). The manufacture and control of mitomycin API by (b) (4) is documented in Type II DMF (b) (4). The DMF was previously found adequate. Only minor changes are reported in recent updates to the DMF.

The acceptance specification for the drug substance is adequate, although improvements can be made to the way related substances are reported.

## Executive Summary Section

Mitomycin has been available since 1974 when Bristol-Myers' Mutamycin (mitomycin for injection) was approved for use in cancer treatment. The innovator's product (and subsequent generic versions) consist of a lyophilized mixture of mitomycin and mannitol in a 1 to 2 ratio. Vials contain 5, 20, and 40 mg mitomycin.

Mitomycin for Injection has been used off-label as an adjunct to trabeculectomy surgery for many years. There is currently no approved product for this use. This Kit was developed with the intention of providing a safe, effective, and convenient means of delivering a controlled amount of mitomycin to the eye.

'Mitosol Kit for Ophthalmic Use' consists of vial of 'Mitomycin for Ophthalmic 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. Mitomycin for Ophthalmic Solution is manufactured (b) (4) by Intas Pharmaceuticals Limited, India. Intas also currently manufactures Mitomycin for Injection under ANDA 64-144.

Essential components of the Kit include a prefilled syringe containing (b) (4) sterile water for injection (sWFI) 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. (b) (4)

No clinical studies were conducted with the Mitosol Kit for Ophthalmic Use. Rather, the application is based on literature reports describing the use mitomycin solutions (typically 0.2 to 0.4 mg/mL in either sWFI or sterile saline, and presumably prepared from approved Mitomycin for Injection products) applied with commercially available surgical sponges).

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

Mitomycin for Ophthalmic Solution (and associated Kit) is indicated for the treatment of refractory glaucoma as an adjunct to *ab externo* glaucoma surgery by topical application to the exposed site of a filtering bleb created 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.

The Kit is open in the operating room and a sterile inner tray removed. (b) (4)

## Executive Summary Section

(b) (4)  
The entire Kit and used materials are then disposed of in a chemotherapy waste bag.

The applicant proposes that the 0.2 mg mitomycin vial should be stored (b) (4) protected from light. It is proposed that (b) (4) However, there is no apparent reason that, when the Kit is used as intended, the reconstituted solution will need to be stored at all.

A Shelf life of 24 months is proposed for the 0.2 mg mitomycin vial and for the Kit.

**C. Basis for Approvability or Not-Approval Recommendation**

From the chemistry perspective the applicant has not demonstrated that the proposed drug product will be of comparable quality, purity, and potency to the mitomycin products commercially available and used off-label for the proposed indication. This is particularly critical since the NDA is based solely on studies reported in the literature and which would have used commercially available sources of 'Mitomycin for Injection.'

In particular, the applicant is proposing (b) (4) This is unexpected (b) (4) Comments and questions in this regard were conveyed to the applicant on 19-OCT-2010; the applicant has not yet responded.

Furthermore, the applicant is proposing (b) (4)

Until additional information on the impurity and degradation profiles of Mitomycin for Ophthalmic Solution are provided, it is difficult to establish meaningful acceptance criteria and to interpret stability study results, and hence define an expiration dating period.

Several 'CMC' labeling issues have been identified, e.g. established name (should be 'Mitomycin for Ophthalmic Solution', not (b) (4) or (b) (4) stereochemistry of mitomycin structure in proposed package insert, among others.

## Executive Summary Section

There are currently a number of challenges to successfully using the Kit, including complicated directions for use as identified in a labeling comprehension study and by the observations of the review team.

The CDRH reviewer has identified several concerns with Kit components and has recommended that a Human Factors Validation Study be conducted. These comments were recently conveyed to the applicant.

The Product Quality Microbiology reviewer has concluded that “this submission is approvable pending resolution of microbiological deficiencies.” (b) (4)

Several facilities have acceptable cGMP status, however several others remain to be inspected. The Office of Compliance has, therefore, not made a final overall recommendation for this application.

**DRAFT COMMENTS FOR CR LETTER**

The applicant has not demonstrated that the proposed drug product, Mitomycin for Ophthalmic Solution, 0.2 mg/vial, is of comparable identity, strength, quality, purity and potency to the commercially available, approved drug products upon which this application is based (e.g., the Mitomycin for Injection RLD described in ANDA 64-144 which is cross-referenced in the application).

In addition, there is insufficient information to allow establishment of a suitable drug product specification (e.g., acceptance criteria for impurities) and determination of an appropriate expiration dating period.

Reference is made to our 19-OCT-2010 communication which outlines deficiencies regarding the drug product specification and the determination of impurities in the drug product.

Other comments to be conveyed are included in Section III of this review.

## Executive Summary Section

**III. Administrative****A. Reviewer's Signature**

Mark. R. Seggel

*{see electronic signature page}*

**B. Endorsement Block**

Stephen P. Miller, PhD, Acting Branch Chief

*{see electronic signature page}*

**C. CC Block**

L. Ng, W. Boyd, S. Miller, A. Rodgers

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/s/  
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MARK R SEGCEL  
12/09/2010

STEPHEN P MILLER  
12/09/2010

I concur - from the CMC perspective, this application can NOT be recommended for approval at this time.

Initial Quality Assessment  
Branch   IV    
Pre-Marketing Assessment Division   II  

**OND Division:** Division of Anti-Infective and Ophthalmology Products  
**NDA:** 22-572  
**Applicant:** Mobius Therapeutics LLC  
**Stamp Date:** June 21, 2010  
**PDUFA Date:** December 21, 2010  
**Trademark:** Optomycin Kit for Ophthalmic Use  
**Established Name:** Mitomycin kit for ophthalmic use  
**Dosage Form:** Sterile lyophilized powder for reconstitution with water for injection  
**Route of Administration:** Topical  
**Indication:** Treatment of refractory glaucoma as an adjunct to ab externo glaucoma surgery by topical application  
  
**PAL:** Linda Ng, Ph.D.

	YES	NO
<b>ONDQA Fileability:</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
<b>Comments for 74-Day Letter</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

## Summary and Critical Issues:

### Summary

Optomycin Kit for Ophthalmic Use is a 5P NDA submitted in eCTD format under 505(b)(2). The applicant also claimed reference to Mutamycin, ANDA 62336, held by Bristol Myers Squibb by a letter of authorization. The non-preserved mitomycin for ophthalmic solution is a lyophilized powder (b) (4). This one strength one size product is for the 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. The related IND is IND 75,734.

A microbiology consult was submitted by the OND PM, Alison Rodgers and Dr. Denise Miller was assigned. The trade name consult was sent directly from the applicant to OSE. The EES evaluation was performed by ONDQA PM Althea Cuff who confirmed sites with the applicant and finalized the request with the CMC reviewer Mark Seggal. A CDRH consult was submitted by Althea Cuff for the non-drug components of the product on July 30, 2010.

The drug substance, mitomycin is manufactured by (b) (4). Mitomycin is (b) (4) manufactured using *streptomyces verticillus Yingtanesis* (b) (4). Some information on synthesis is submitted to the NDA; details are in DMF (b) (4) with letter of authorization dated July 13, 2009.

Thirty-six months RT and six months accelerated data for three batches of the drug substance manufactured by (b) (4) were submitted to support stability. The compound is stored at room temperature 25 °C/60%RH and accelerated 40 °C /75%RH. (b) (4) is the claimed retest period.

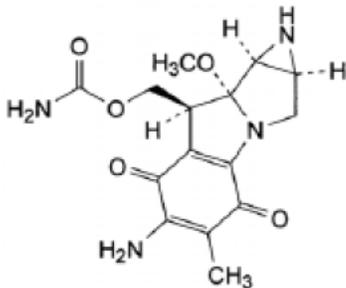
The proposed drug product is a kit that includes (b) (4)

(b) (4)  
Intas  
Pharmaceuticals Ltd, (b) (4) is responsible for manufacturing, packaging, release and stability testing of the lyophilized mitomycin. Synergetics Inc, O'Fallon, MO assembles the kit, (b) (4) and perform release and stability testing.

Mitomycin, formulated with mannitol and water for injection, is lyophilized (b) (4)

The commercial batch size is (b) (4) The stability data included three batches with 3 months accelerated data at 40 °C/75%RH and 12 months room temperature at 25 °C/60%RH. An expiry of 24 months is claimed.

Structural Formula:



Molecular Formula:



Molecular Weight:

334.3

### **Critical issues for review**

- Mitomycin has a USP drug substance monograph. The drug substance reference standard from (b) (4) was tested against the USP reference standard. Reviewer should evaluate qualification studies to ensure acceptability of standards.
- In the drug substance specification, the assay should be a range. It is noted that the applicant is using USP criterion. The Any individual unspecified criterion of the impurity test should meet ICH Q3A
- The drug substance is sensitive to light, moisture, temperature and oxygen. It is stated that (b) (4) The drug product batch record should be evaluated for hold times, and any critical steps to ensure stability of the market product.
- The pH criterion is claimed to be 5 to 8 (b) (4) The proposed range (b) (4) and should be evaluated.
- The reconstitution time is (b) (4) Should be evaluated.
- The particulate matter criteria after dilution should meet Table II of USP <789>
- Residual solvents should be (b) (4) (b) (4) Proposed criteria should be evaluated.
- The drug product specification impurity criteria for Any Individual Unspecified should be (b) (4)
- Assay upper limit of range is (b) (4)
- The dose uniformity criterion should be evaluated. (b) (4)
- Applicant recommends 1 hr storage at room temperature after dilution. Confirm the time for stability and time allowance from clinical perspective.
- Residual solvents in the drug product should be well controlled (b) (4)
- In the drug product, the endotoxin test is based on per mg of mitomycin. In general, the endotoxin is expressed as endotoxin unit per mL of final product solution. Micro will have to comment.
- It is claimed that the drug substance is sensitive to moisture. Reviewer should evaluate if (b) (4)
- All tests should be evaluated for meaningful conditions and criteria for both drug substance and drug product.
- A consult was submitted on July 30, 2010 to CDRH for the non-drug components of the commercial product. Reviewer should follow up
- Reviewer should evaluate if a system suitability test to include a standard at the quantitation limit is included to ensure detectability of impurities at that level. The system suitability test should be included for both drug substance and drug product impurities test.
- Contradictory statements by applicant on storage (b) (4) Reviewer should evaluate.

- Stability protocol states to extend expiration dating period of product from at least 3 production batches. Seems not to understand our guidance.

- **Comments for 74-Day Letter**

CMC comments forwarded to the applicant on July 13, 2010 and applicant responses dated July 20 and 29 have been received.

**D. Review, Comments and Recommendation:**

Acceptable for filing. CMC comments were included in the filing review. Dr. Mark Seggal has been assigned to review this NDA.

\_\_\_\_\_  
Linda Ng, Ph.D.  
Pharmaceutical Assessment Lead

\_\_\_\_\_  
Date

\_\_\_\_\_  
Stephen Miller, Ph.D.  
Acting Branch Chief

\_\_\_\_\_  
Date

Cc: OND PM ARodgers  
ONDQA PM ACuff

**Appendix 1. Composition of the Drug Product**

Name of ingredients	Compendial reference	Function	Qty. / mL in mg
Mitomycin	USP/Ph. Eur.	Active	0.2
Mannitol	USNF/Ph. Eur.	(b) (4)	0.4
Water for Injection	USP/Ph. Eur.	(b) (4)	1 mL

USP: United States Pharmacopoeia  
USNF: United States National Formulary  
Ph. Eur.: European Pharmacopoeia

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

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/s/

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LINDA L NG  
08/16/2010

STEPHEN P MILLER  
08/20/2010

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

**NDA Number:** 22-572

**Established/Proper Name:**  
Optomycin Kit for Ophthalmic  
Use

**Applicant:** Mobius  
Therapeutics, LLC

**Letter Date:** June 21, 2010

**Stamp Date:** June 21, 2010

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

<b>A. GENERAL</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1.	Is the CMC section organized adequately?	x		eCTD
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

<b>B. FACILITIES*</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?		x	List needs clarification. ONDQA PM Althea Cuff will perform the task
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? <b>This question is not applicable for synthesized API.</b>			(b) (4) drug substance

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		<p align="center">Clarification has to be made via communication between ONDQA PM and applicant</p>
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>			<p align="center">Clarification has to be made via communication between ONDQA PM and applicant. Information appeared to be contradictory, e.g., sterilizers vs testing sites</p>

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> <li>• Name of facility,</li> <li>• Full address of facility including street, city, state, country</li> <li>• FEI number for facility (if previously registered with FDA)</li> <li>• Full name and title, telephone, fax number and email for on-site contact person.</li> <li>• Is the manufacturing responsibility and function identified for each facility?, and</li> <li>• DMF number (if applicable)</li> </ul>	x		
10.	<p>Is a statement provided that all facilities are ready for GMP inspection at the time of submission?</p>		x	<p>Unable to locate. ONDQA PM will follow up with applicant.</p>

\* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

<b>C. ENVIRONMENTAL ASSESMENT</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
11.	<p>Has an environmental assessment report or categorical exclusion been provided?</p>	x		<p>M.1.12.14</p>

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

<b>D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
12.	Does the section contain a description of the DS manufacturing process?	x		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		Located in DMF (b) (4)
14.	Does the section contain information regarding the characterization of the DS?	x		
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		36 months room temperature (25°C/60%RH) and 6 months accelerated (40°C/75%RH) for 3 batches at (b) (4) – DMF (b) (4)
17.	Does the application contain Quality by Design (QbD) information regarding the DS?			Not obvious in the NDA
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?			Not obvious in the NDA

**PRODUCT QUALITY (Small Molecule)**  
**FILING REVIEW FOR NDA 22-572 (ONDQA)**

<b>E. DRUG PRODUCT (DP)</b>				
	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		Mitomycin manufactured at Intas Pharmaceuticals, Ahmedadbab, Gujarat, India. Kit put together by Synergetics Inc, O'Fallon, MO
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		Very minimal especially for the kit
21.	Is there a batch production record and a proposed master batch record?	x		Section 3.2.R.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	Not needed for an Ophthalmic solution
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		The kit has many components; CDRH approval references are missing
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		3 batches of mitomycin lyophilized in glass vial with (b) (4) slotted stopper and (b) (4) flip off blue seal – 3 months accelerated (40°C/75%RH) and 12 months room temperature (25°C/60%RH). Summary for accelerated; details for RT. QOS page 111 stability summary on kit 60 °C/50%RH acc & 25°C/60%RH RT. Request (b) (4) expiry on reconstituted solution. Requested 24 months expiry on product/kit
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?			Not obvious
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F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	x		Incorporated in the NDA including Section 3.2.P.3.5

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?		x	Minimal references for 7 items in sterile kit and 3 items non-sterile part of kit. Supplier of pieces mentioned. No DMF/MAF except one for items in kit.

DMF # (b) (4)	TYPE	HOLDER (b) (4)	ITEM REFERENCED	LOA DATE	COMMENTS
	II		Mitomycin	7/13/09	
	II			Feb 2010	
	III			7/15/09	
	III			7/6/09	

**PRODUCT QUALITY (Small Molecule)  
FILING REVIEW FOR NDA 22-572 (ONDQA)**

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	x		PI for kit included. PI for mitomycin from Bristol Myers included (?)
33.	Have the immediate container and carton labels been provided?	x		Mock up for kit but none for the mitomycin bottle

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	<b>IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?</b>	x		Information lack details. A preliminary draft of comments listed below should be forwarded to the applicant at the earliest convenience
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide <b>filing</b> comments to be sent to the Applicant.			N/A
36.	Are there any <b>potential review</b> issues to be forwarded to the Applicant for the 74-day letter?			Very likely

*{See appended electronic signature page}*

Linda Ng, Ph.D.

CMC Lead

Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment

Date

*{See appended electronic signature page}*

Stephen Miller, Ph.D.

Acting Branch Chief

Division of Pre-Marketing Assessment II  
Office of New Drug Quality Assessment

Date

cc: OND PM ARodgers  
ONDQA PM ACuff  
CMC Reviewer MSeggal

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

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/s/

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LINDA L NG  
07/12/2010

STEPHEN P MILLER  
07/13/2010