

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**74945**

**CHEMISTRY REVIEW(S)**

**DIVISION REVIEW SUMMARY**

**ANDA #:** 74-945      **DRUG PRODUCT:** Atracurium Besylate Injection,  
Preserved

**FIRM:** Marsam Pharmaceuticals Inc.

**DOSAGE:** Injection

**STRENGTH:** 10 mg/mL, 10 mL vials

**cGMP STATEMENT/EIR UPDATE STATUS:**

cGMP: GMP Certification is enclosed. (Page 195).

EER: Pending.

**BIO STUDY(ies)/BIOEQUIVALENCE STATUS:**

On 12/23/96 the Division of Bioequivalence issued a no comments letter to the firm.

**METHODS VALIDATION (Including dosage form description):**

The methods were being verified by Philadelphia field laboratories for drug substance and product. The methods are found adequate after incorporation of the comments from the Field labs.

**STABILITY(Conditions, Containers, methods):**

Bio batch

**Evaluation of stability indicating methods:**

**Stability Assays**

Test	Specifications
Appearance	Clear, colorless liquid.
Assay (active)	%
Benzyl alcohol	%
Particulate matter	
pH	

Degradation products	
Total	NMT %
Cp 7110 trans	NMT %
Laudanosine	NMT %
Unknown/unspecified	NMT %
7113	NMT %
7114	NMT %
7115 + 7116	NMT %
7110 cis	NMT %
CP 7185	NMT %
CP 7149	NMT %
Unidentified RRT 0.11	NMT %
Sterility	Complies
Bacterial Endotoxin	EU/MG

Stability studies were done on the bio batch. Containers are the same those listed in the container section. Stability studies are in conformance with the FDA Guidelines.

**LABELING REVIEW STATUS:** Satisfactory dated 7/31/97.

**STERILIZATION VALIDATION (If Applicable):** Acceptable (dated June 10, 1997).

**BATCH SIZES:**

**BIO BATCH:** Lot # 5390

NDS source:

**STABILITY BATCHES** (different from BIO BATCH, manuf. site, process)

Stability batch is the same as the bio-batch

**PROPOSED PRODUCTION BATCH**

L is the proposed production batch size.

Process is the same as the demonstration batch.

**COMMENTS:** Approvable

**CHEMISTRY REVIEWER:**

Radhika Rajagopalan

**DATE:**

April 7, 1998

1. CHEMISTRY REVIEW NO. 5
2. ANDA # 74-945
3. NAME AND ADDRESS OF APPLICANT  
Marsam Pharmaceuticals Inc.  
Attention: Steven W. Brown R.Ph.  
Building 31, 24 Olney Avenue  
Cherry Hill, NJ 08034
4. LEGAL BASIS FOR SUBMISSION  
US Patent No. 4,179,507 for the listed drug will expire on December 18, 1996. Exclusivity I-108 (Expanded Use - For ICU patients undergoing long-term infusion during mechanical ventilation) expired on June 6, 1997.
5. SUPPLEMENT  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Atracurium Besylate
8. SUPPLEMENT PROVIDE FOR:  
N/A
9. AMENDMENTS AND OTHER DATES:

August 21, 1996--	ANDA Original Submission
September 20, 1996--	FDA acknowledgment letter
December 23, 1996--	Division of Bioequivalence issued Bio Waiver
January 27, 1997--	FDA major deficiency letter (chemistry, micro and labeling)
February 24, 1997--	ANDA amendment by firm
April 28, 1997--	Labeling deficiency letter by fax
May 2, 1997--	Micro deficiency (review #2)
May 8, 1997--	Chemistry minor deficiency (#2)
May 21, 1997--	Amendment by firm (chem, micro & label)
May 23, 1997--	New correspondence by firm
June 10, 1997--	Micro review acceptable
July 1, 1997--	Labeling deficiency (review #3)
July 16, 1997--	T-conference initiated by chemist

July 18, 1997-- Amendment by firm (chemistry issues)  
 July 23, 1997-- Amendment by firm  
 September 22, 1997-- Not approvable letter  
 February 5, 1998-- Minor amendment by firm  
 March 2, 1998-- Minor deficiencies to firm (review #4)  
 March 30, 1998-- Amendment by firm

10. PHARMACOLOGICAL CATEGORY  
 Neuromuscular Blocking Agent

11. Rx or OTC  
 Rx

12. RELATED DMF #

13. DOSAGE FORM  
 Injectable, IV  
 Multiple dose

14. POTENCY  
 10 mg/mL; 10 mL  
 (Preserved)

15. CHEMICAL NAME AND STRUCTURE  
 2,2-(pentamethylenebis(oxycaronylethylene))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate

16. RECORDS AND REPORTS  
 N/A

17. COMMENTS  
 Awaiting satisfactory EER.  
 Final acceptable label review satisfactory (7/30/97).  
 Minor amendment (3/30/98) addresses all the deficiencies from the method verification. The firm has also updated drug substance specifications as per USP PF Monograph. Administrative review on this application is already completed. Hence, ANDA can be approved.  
 Bio waiver granted on 12/23/96.

18. CONCLUSIONS AND RECOMMENDATIONS  
 Chemistry is approved.

19. REVIEWER:

DATE COMPLETED:

Radhika Rajagopalan, Ph.D.

4/7/98

1. CHEMISTRY REVIEW NO. 4
2. ANDA # 74-945
3. NAME AND ADDRESS OF APPLICANT  
Marsam Pharmaceuticals Inc.  
Attention: Steven W. Brown R.Ph.  
Building 31, 24 Olney Avenue  
Cherry Hill, NJ 08034
4. LEGAL BASIS FOR SUBMISSION  
US Patent No. 4,179,507 for the listed drug will expire on December 18, 1996. Exclusivity I-108 (Expanded Use - For ICU patients undergoing long-term infusion during mechanical ventilation) expired on June 6, 1997.
5. SUPPLEMENT  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Atracurium Besylate
8. SUPPLEMENT PROVIDE FOR:  
N/A
9. AMENDMENTS AND OTHER DATES:

August 21, 1996--	ANDA Original Submission
September 20, 1996--	FDA acknowledgment letter
December 23, 1996--	Division of Bioequivalence issued Bio Waiver
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May 8, 1997--	Chemistry minor deficiency (#2)
May 21, 1997--	Amendment by firm (chem, micro & label)
May 23, 1997--	New correspondence by firm
June 10, 1997--	Micro review acceptable
July 1, 1997--	Labeling deficiency (review #3)
July 16, 1997--	T-conference initiated by chemist
July 18, 1997--	Amendment by firm (chemistry issues)

July 23, 1997-- Amendment by firm  
September 22, 1997-- Not approvable letter  
February 5, 1998-- Minor amendment by firm

10. PHARMACOLOGICAL CATEGORY  
Neuromuscular Blocking Agent

11. Rx or OTC  
Rx

12. RELATED DMF #

13. DOSAGE FORM  
Injectable, IV  
Multiple dose

14. POTENCY  
10 mg/mL; 10 mL  
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15. CHEMICAL NAME AND STRUCTURE  
2,2-(pentamethylenebis(oxycaronylethylene))bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate

16. RECORDS AND REPORTS  
N/A

17. COMMENTS  
Awaiting satisfactory EER.  
Method validation by field indicated minor deficiencies.  
Minor amendment is required.

18. CONCLUSIONS AND RECOMMENDATIONS  
Not approvable.

19. REVIEWER:

DATE COMPLETED:

Radhika Rajagopalan, Ph.D.

2/18/98

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2/27/98