

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**74945**

**CORRESPONDENCE**

ANDAs 74-944 (5 mL Single Dose Vial)  
✓74-945 (10 mL multiple dose vial)

Marsam Pharmaceuticals Inc.  
Attention: Steven W. Brown, R.Ph.  
Building 31, Olney Avenue  
P.O. Box 1022  
Cherry Hill, New Jersey 08034

|||||

SEP 22 1997

Dear Sir:

This is in reference to your abbreviated new drug applications dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Atracurium Besylate Injection, 10 mg/mL.

Reference is also made to your amendments dated May 21, July 18 and 23, 1997.

The applications are deficient and, therefore, not approvable under 21 CFR 314.125(b)(13) because the Center for Drug Evaluation and Research (CDER) is unable to find that the methods used in, and the facilities and controls used for, the manufacturing of the drug product by Marsam Pharmaceuticals in Cherry Hill, NJ complies with current good manufacturing practice (CGMP) regulations. This firm is listed in your application as being responsible for manufacturing the drug product.

Our conclusion is based upon the CGMP findings revealed during an inspection of the facility conducted on March 18 to April 17, 1997, by representatives of our New Jersey District Office and subsequent recommendation from our Division of Manufacturing and Product Quality (DMPQ), Office of Compliance.

Until such time that your Cherry Hill, NJ manufacturing facility can demonstrate to the Agency that the CGMP-related issues associated with the manufacturing of Atracurium Besylate Injection have been corrected and the Agency's concerns are otherwise satisfied, your applications cannot be approved.

You should amend these applications when the CGMP-related issues pertaining to the Cherry Hill manufacturing facility have been satisfactorily resolved. Your amendments submitted in response to this not approvable letter will be considered as a MINOR AMENDMENT provided that the amendments contain no significant additional information necessary to remedy the CGMP deficiencies or to address concerns identified by the investigators. Your

amendments should include a statement from a responsible company official informing us that these applications have been recommended for approval by representatives of the New Jersey district. If, as a result of follow-up inspections related to the ongoing evaluation of this or other applications, it is necessary for you to significantly revise your procedures, controls or practices to correct your deficiencies, then the amendments will be considered to represent a MAJOR AMENDMENT.

The file on these applications is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the applications. If you have substantial disagreement with our reasons for not approving these applications, you may request an opportunity for a hearing.

Sincerely yours,

JSI

LS

9/22/97

Frank O. Holcombe, Jr., Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research

ANDA 74-945

Marsam Pharmaceuticals, Inc.  
Attention: Thomas L. Pituk  
Building 31, 24 Olney Avenue  
P.O. Box 1022  
Cherry Hill, NJ 08034

SEP 20 1996

|||||

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Atracurium Besylate Injection, 10 mg/mL, 10 mL  
Multiple-dose Vial

DATE OF APPLICATION: August 21, 1996

DATE OF RECEIPT: August 22, 1996

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod  
Project Manager  
(301) 594-1300

Sincerely yours,

/S/

9/20/96

Jerry Phillips  
Director  
Division of Labeling and Program Support  
Office of Generic Drugs  
Center for Drug Evaluation and Research

505(j)(2)(a) information acceptable  
for filing  
Case Marie H. Weikel 9/9/96

August 21, 1996

APD  
9/17/96

Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
Metro Park, North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2733

**RECEIVED**

AUG 22 1996

**GENERIC DRUGS**

Re: **NEW ANDA**  
Atracurium Besylate Injection, 10 mg/mL  
10 mL Multiple Dose Vial

Dear Sir/Madam:

In accordance with Section 505(j) of the Federal Food, Drug and Cosmetic Act, we are submitting the attached Abbreviated New Drug Application (ANDA) for the above referenced product. The listed drug upon which this application is based is Tracrium<sup>®</sup> Injection (Atracurium Besylate) by Glaxo Wellcome Inc. Please note that a separate ANDA is being submitted concurrently for the unpreserved formulation of this product. Draft labeling is included (Section V) which is based on current approved labeling for Tracrium<sup>®</sup> Injection (Atracurium Besylate). The draft package insert contains both the preserved and unpreserved formulations of Atracurium Besylate Injection, 10 mg/mL; this insert is included in this application and in the ANDA for the unpreserved product.

This submission consists of two (2) volumes. As required, archival and review copies are provided, and a true copy of the ANDA is being sent concurrently to our home district FDA office. (Please refer to Section XXI for the District Copy Certification and Debarment Certification.) In accordance with Policy and Procedure Guide #30-91, we have included two additional separately bound copies of Section XVI, Analytical Methods, since both the raw material and finished product are not USP Articles. A separate table of contents has been provided for this section and is included in both the ANDA binders and separately bound copies. In addition, to facilitate the microbiological review, pertinent information has been placed in Section XI.2 of the ANDA. A request for waiver of bioequivalence testing is located in Section VI.1.

Included in Section XVII are stability data for the product in the 10 mL vial. Based on the data, we are proposing an 18 month expiration date for this product.

During the course of your review of this application, if you have any questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact

Jill Kompa

Phone: (609) 424-5600, Ext. 330

Fax: (609) 751-8784

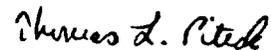
Alternate Contact

Anne Toland

Phone: (609) 424-5600, Ext. 249

Fax: (609) 751-8784

Sincerely,



Thomas L. Pituk  
Director, Regulatory Affairs

Enclosures

cc: FDA Newark District Office (North Brunswick Resident Post)  
120 North Center Drive, North Brunswick, NJ 08902

February 24, 1997

**AMENDMENT**  
*n/ac*

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

Subject: MAJOR AMENDMENT  
ANDA 74-945, Atracurium Besylate Injection  
10 mg/mL, 10 mL vial

Dear Sir/Madam:

In response to your not approvable letter dated January 27, 1997, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments. Additional CMC changes (other than those made in response to the not approvable letter) and revised documents for the referenced product are listed in the section entitled Additional CMC Changes (see Table of Contents). Many of these changes cover observations made by the district office during the pre-approval inspection for the referenced product which were not covered in your not approvable letter.

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

Primary Contact:  
Jill Kompa  
Associate, Regulatory Affairs  
Phone: (609) 489-5330  
Fax: (609) 424-9418

**RECEIVED**

**FEB 27 1997**

**GENERIC DRUGS**

**Alternate Contact:**

Anne M. Toland  
Manager, Regulatory Affairs  
Phone: (609) 489-5249  
Fax: (609) 424-9418

Sincerely,

A handwritten signature in black ink, appearing to read "Davis R. Reese". The signature is fluid and cursive, with a large initial "D" and "R".

Davis R. Reese  
Executive Director,  
Scientific & Regulatory Affairs

**Enclosures**

cc: FDA New Jersey District Office (North Brunswick Resident Post)  
120 North Center Drive, North Brunswick, NJ 08902

*noted  
KRS 6/14/97*

May 21, 1997

*N/A*

*Labeling review  
drafted 7/1/97  
AWJ*

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

RECEIVED

MAY 22 1997

GENERIC LABELS

**SUBJECT: ~~MINOR AMENDMENT~~  
ANDA 74-945, Atracurium Besylate Injection  
10 mg/mL, 10 mL vial**

Dear Sir/Madam:

In response to your not approvable letter dated May 8, 1997, we are submitting this amendment to the Abbreviated New Drug Application for the above referenced product.

We have responded to each deficiency item by restating each comment (in bold) followed by our response and any necessary attachments. As requested, we have also enclosed final printed labels, trays (cartons) and inserts and a side-by-side comparison of the previous version submitted with the revised version where changes have been made.

Additional CMC changes (other than those made in response to the not approvable letter) and revised documents are located in a separate section entitled "Additional CMC Changes". In particular, we are proposing a change regarding closure sterilization. We have included data for a validated closure sterilization cycle of 121 minutes/17 minutes. Based on this validation, we have revised the production cycle parameters to 122 degrees/20 minutes (i.e., safety in temperature and time).

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

We consider this response to adequately address all deficiencies and to provide final printed labeling. Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

*M. Adams  
6/12/97*

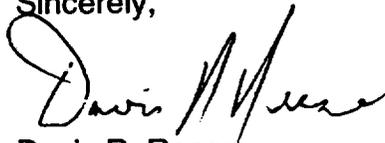
Primary Contact:

Jill Kompa  
Associate, Regulatory Affairs  
Phone: (609) 489-5330  
Fax: (609) 424-9418

Secondary Contact:

Anne Toland  
Manager, Regulatory Affairs  
Phone: (609) 489-5249  
Fax: (609) 489-9418

Sincerely,

A handwritten signature in black ink, appearing to read "Davis R. Reese". The signature is fluid and cursive, with a large initial "D" and "R".

Davis R. Reese  
Executive Director,  
Scientific & Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)  
120 North Center Drive, North Brunswick, NJ 08902

*Labeling satisfactory for  
approval - label review  
drafted 7/31/97 a/b/z*

UPS

July 23, 1997

**AMENDMENT**

*N/A/F*

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**RE: ANDA 74-945, Atracurium Besylate Injection  
10 mg/mL, 10 mL preserved vial  
FACSIMILE AMENDMENT**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations 21 CFR§314.94 for Atracurium Besylate Injection, 10 mg/mL, 10 mL preserved vial.

Reference is also made to your facsimile dated July 9, 1997 requesting additional labeling revisions for the 5 mL container label, carton and insert for ANDA 74-944. However, since the package insert also lists the 10 mL, preserved Atracurium Besylate Injection line item (ANDA 74-945), we are submitting an Amendment to this application for the revised package insert only. The 10 mL label and carton (tray) were not requested to be revised and therefore, no final printed labeling for these are included.

In accordance with 21 CFR§314.96(a), enclosed are twelve copies of final printed package insert labeling that have been revised to be in accordance with your facsimile request. Additionally, in accordance with 21 CFR§314.94(a)(8)(iv), we have included a side-by-side comparison of our proposed labeling with our last submission with all differences annotated and explained.

We consider this response to adequately address all deficiencies and to provide final printed labeling. Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

RECEIVED

*1997 7 24*

**GENERIC DRUGS**

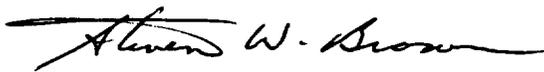
**Primary Contact:**

Jill Kompa  
Senior Regulatory Affairs Associate  
Phone: (609) 489-5330  
Fax: (609) 424-9418

**Secondary Contact:**

Anne Toland  
Manager, Regulatory Affairs  
Phone: (609) 489-5249  
Fax: (609) 489-9418

Sincerely,



Steven W. Brown, R.Ph.  
Director, Regulatory Affairs

Enclosures

**MARSAM**

PHARMACEUTICALS INC.

**UPS OVERNITE**

July 18, 1997

N/AM

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**ANDA ORIG AMENDMENT**

**RE: ANDA 74-944 and ~~74-945~~, Atracurium Besylate Injection  
10 mg/mL, 5 mL unpreserved vial  
10 mg/mL, 10 mL preserved vial  
TELEPHONE AMENDMENT**

Dear Sir/Madam:

In response to a telephone call from Radhika Rajagopalan, Reviewing Chemist, OGD with Jill Kompa, Marsam Pharmaceuticals Inc. on July 16, 1997, we are submitting this telephone amendment to both of the Abbreviated New Drug Applications for the above referenced products.

There are two issues we have addressed in this amendment as requested by Ms. Rajagopalan during this telephone conversation. The first issue is in regard to specific questions on the test procedures used to determine the assay and impurities for both the drug substance and drug product. Specifically, these test methods were submitted to the Philadelphia District Laboratory for method validation studies May 12, 1997 along with the preserved finished product samples. Ms. Rajagopalan has notified us that there are several clarifications requested by the laboratory analyst in order to perform the calculations and complete the validation studies. These questions have been addressed in #1-Test Procedures, and copies of the revised test procedures are also included in this submission.

The second issue is to provide additional information concerning the degradation product at RRT of 0.11 present in the finished product. This issue is discussed in #2-Discussion Related to the Unidentified Peak at RRT 0.11. Finally, we have provided a commitment to investigate this issue in order to determine a positive identification of this peak.

RECEIVED

JUL 21 1997

GENERIC DRUGS

In accordance with 21 CFR 314.96(b), we hereby certify that a true and complete copy of this amendment is being submitted to our home FDA district office (New Jersey District Office, North Brunswick Resident Post).

We acknowledge the labeling deficiency faxed to us July 9, 1997 for Atracurium Besylate Injection, ANDA 74-944. Final printed labeling will be forwarded as soon as it is available.

Should you have any questions or comments regarding this submission, please do not hesitate to contact the following:

Primary Contact:

Jill Kompa  
Senior Regulatory Affairs Associate  
Phone: (609) 489-5330  
Fax: (609) 424-9418

Secondary Contact:

Anne Toland  
Manager, Regulatory Affairs  
Phone: (609) 489-5249  
Fax: (609) 489-9418

Sincerely,



Steven W. Brown, R.Ph.  
Director, Regulatory Affairs

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)  
120 North Center Drive, North Brunswick, NJ 08902

May 23, 1997

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**NEW CORRESP**

*Nc*

**SUBJECT: MINOR AMENDMENT  
ANDA 74-945, Atracurium Besylate Injection  
10 mg/mL, 10 mL vial**

Dear Sir/Madam:

This Amendment corresponds to a Minor Amendment for Atracurium Besylate Injection submitted May 21, 1997. That submission erroneously contained a revised Powder & Filled Container Reconciliation Form in the Additional CMC Changes section. Therefore, please replace it with the revised Liquid Filled Container Reconciliation Form enclosed in this submission. We apologize for any confusion this error may have caused.

If you have any questions or comments which can be addressed via telephone and/or telefax, please do not hesitate to contact the following:

Primary Contact

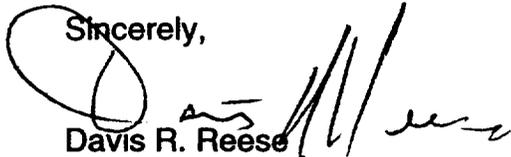
Jill Kompa  
Phone: (609) 489-5330  
Fax: (609) 424-9418

Alternate Contact

Anne Toland  
Phone: (609) 489-5249  
Fax: (609) 424-9418

In accordance with 21 CFR Section 314.96(b), Marsam certifies that a true copy of this Amendment is being submitted concurrently to our home FDA District Office (New Jersey District Office, North Brunswick Resident Post).

Sincerely,



Davis R. Reese  
Executive Director,  
Scientific & Regulatory Affairs

MAY 27 1997

*Madam  
5/23/97*

Enclosure

*noted K8  
2/11/98*

February 5, 1998

**ORIG AMENDMENT**

*U/AM*

Office of Generic Drugs, CDER, FDA  
Document Control Room  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, Maryland 20855-2773

**Re: ANDA 74-945**  
**Atracurium Besylate Injection, 10 mg/mL, 10 mL multiple dose vial**  
**MINOR AMENDMENT**

Dear Sir or Madam:

Reference is made to our abbreviated new drug application dated August 21, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act and in accordance with the provisions of the Regulations 21 CFR§314.94 for Atracurium Besylate Injection, 10 mg/mL, 10 mL multiple dose vial.

Reference is also made to your not approvable letter dated September 22, 1997, stating that the application was deficient and, therefore, not approvable under 21 CFR§314.125(b)(13). Your letter stated that, based on the CGMP findings revealed during an inspection of our facility and subsequent recommendation from the Division of Manufacturing and Product Quality (DMPQ), Office of Compliance, CDER had determined that Marsam was not in compliance with current good manufacturing practice (CGMP) regulations. Your letter stated that, until such time that we can demonstrate that the problems have been corrected, the application cannot be approved. In addition, you directed us to submit a MINOR AMENDMENT in response to the not approvable letter which includes a statement from a responsible corporate official certifying that our facilities have been found to be in compliance with CGMP and cleared for approval of this drug product by representatives of the local FDA District Office.

In accordance with your request and pursuant to 21 CFR§314.96, we are submitting this MINOR AMENDMENT to provide a statement certifying that our facilities have been reinspected and found to be in compliance with CGMP regulations and cleared for approval of this (and all) drug products by representatives of New Jersey District Office. We are also enclosing a copy of the "Profile System" printout that was supplied to us on February 3, 1997, by Mr. Richard T. Trainor, Compliance Officer, of the NJDO.

**RECEIVED**

*Nadine  
2-10-98*

**FEB 06 1998**

**GENERIC DRUGS**

**ANDA 74-945**

**Page 2**

**Atracurium Besylate Injection, 10 mg/mL, 10 mL multiple dose vial  
MINOR AMENDMENT**

We certify that a true copy of this amendment is being sent to our local FDA District Office.

Please advise us if you require any additional information.

Sincerely,  
Marsam Pharmaceuticals Inc.



Steven W. Brown, R.Ph.  
Director, Regulatory Affairs

SWB

Enclosures

cc: FDA New Jersey District Office (North Brunswick Resident Post)  
120 North Center Drive, North Brunswick, NJ 08902

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
 PUBLIC HEALTH SERVICE  
 FOOD AND DRUG ADMINISTRATION  
**APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE  
 OR AN ANTIBIOTIC DRUG FOR HUMAN USE**  
*(Title 21, Code of Federal Regulations, 314)*

Form Approved: OMB No. 0910-0001  
 Expiration Date: December 31, 1995  
 See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

**NOTE:** No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT <b>Marsam Pharmaceuticals Inc.</b>	DATE OF SUBMISSION <b>February 5, 1998</b>
ADDRESS (Number, Street, City, State and Zip Code) <b>Building 31, 24 Olney Avenue, P.O. Box 1022 Cherry Hill, New Jersey 08034</b>	TELEPHONE NO. (Include Area Code) <b>609-424-5600</b>
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) <b>74-945</b>

**DRUG PRODUCT**

ESTABLISHED NAME (e.g., USP/USAN) <b>Atracurium Besylate</b>	PROPRIETARY NAME (If any)
CODE NAME (If any)	CHEMICAL NAME <b>2,2'-[pentamethylenebis(oxycarbonylethelene)]bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-veratrylisoquinolinium) dibenzenesulfonate</b>
DOSAGE FORM <b>Solution for Injection</b>	ROUTE OF ADMINISTRATION <b>Intravenous</b>
	STRENGTH(S) <b>10 mg/mL</b>

PROPOSED INDICATIONS FOR USE  
**Indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.**

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

**RECEIVED**  
**FEB 06 1998**  
**GENERIC DRUGS**

**INFORMATION ON APPLICATION**

TYPE OF APPLICATION (Check one)

- THIS SUBMISSIONS IS A FULL APPLICATION (21 CFR 314.50)     THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG <b>Tracrium® Injection</b>	HOLDER OF APPROVED APPLICATION <b>Glaxo Wellcome Inc.</b>
--	--

TYPE SUBMISSION (Check one)

- PRESUBMISSION     AN AMENDMENT TO A PENDING APPLICATION     SUPPLEMENTAL APPLICATION  
 ORIGINAL APPLICATION     RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) **21 CFR§314.96**

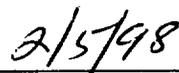
PROPOSED MARKETING STATUS (Check one)

- APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)     APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

**Certification Statement  
Compliance with  
Current Good Manufacturing Practices (CGMP) Regulations**

Marsam Pharmaceuticals Inc. hereby certifies, to the best of our knowledge and belief, that we are in substantial compliance with all of the provisions of the Current Good Manufacturing Practices (CGMP) regulations and that the methods used in, and the facilities and controls used for, the manufacture, processing, packaging, labeling and holding of drug products are in compliance with Current Good Manufacturing Practice regulations contained in 21 CFR Parts 210 and 211.

  
\_\_\_\_\_  
Fakrul Sayeed, Ph.D.  
Vice President  
Scientific and Regulatory Affairs

  
\_\_\_\_\_  
Date