# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**74496**

# CORRESPONDENCE

ANDA 74-496

Elkins-Sinn Pharmaceuticals
Division of A.H. Robins Company
Attention: Mark Bokelman
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

AUG 28 1996

Dear Sir:

This is in reference to your abbreviated new drug application dated May 6, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lorazepam Injection USP, 2 mg/mL and 4 mg/mL (syringes).

Reference is also made to your amendment dated July 17, 1996.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

> Drug Master File for the drug substance remains deficient and the holder has been notified. Please do not respond until has notified you that they have responded to their deficiencies.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ for 8/27/96

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-496

MAY 19 1994

Elkins-Sinn
Attention: Thelma C. Hilibrand
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated May 6, 1994, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lorazepam Injection USP, 2 mg/mL and 4 mg/mL (syringes).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You have failed to provide a statement as to whether the reference listed drug is entitled to a period of marketing exclusivity. If there is no exclusivity, a statement to that effect should be made [314.94(a)(2)(ii)].

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 5/19/94

Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-496
cc: DUP/Jacket
Division File
HFD-82
File Copy
HFD-600/Reading File
HFD-615/MBennett
Endorsement: HFD-615/GJohnston, Chief date 5/17/94
HFD-615/PRickman, CSO date
HFD-615/WRussell, CSO, date
HFD-6 /Chem Branch date
WP File\Russell\74-496
F/T bcw/5-13-94
ANDA Refuse to File!

5/18/94

ANDA 74-496

Elkins-Sinn
Attention: Barry H. Ballan
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

JUN 9 1994

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.

Reference is also made to our "Refuse to File" letter dated May 19, 1994, and your amendment dated May 24, 1994.

NAME OF DRUG: Lorazepam Injection USP, 2 mg/mL and 4 mg/mL (syringes)

DATE OF APPLICATION: May 6, 1994

DATE OF RECEIPT: May 9, 1994

DATE ACCEPTABLE FOR FILING: May 25, 1994

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:

John Dawson
Consumer Safety Officer
(301) 594-1841

Sincerely yours,

/S/ 6/9/94
Robert W. Pollock
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-496
cc: DUP/Jacket
Division File
Field Copy
HFD-600/Reading File
HFD-82
HFD-615/MBennett

Endorsement: HFD-615/GJohnston, Chief Johnston date 6/7/94
HFD-615PRickman, CSO [signature] date 6/7/94
HFD-615/WRussell, CSO [signature] 6/6/94 date
HFD-629, Supervisory Chemist_____date
WP File\russell\74-496A
F/T bcw/6-6-94
ANDA Acknowledgement Letter!

1.1

ANDA 74-496

Elkins-Sinn
Attention: Thelma C. Hilibrand
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

MAY 23 [illegible]

Dear Madam:

Please refer to your abbreviated new drug application submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Lorazepam Injection USP, 2 mg/mL and 4 mg/mL (syringes).

Reference is also made to the sterilization process employed in the manufacture of the subject drug product. The sterilization data submitted May 6, 1994, have been reviewed and found to be deficient for the following reasons:

1. The description provided in your application of the facilities used for the processing to the drug product were not adequate. Please provide the following information.
   A. A floor plan of the area with designated air cleanliness classes and isolators or barrier systems.
   B. The locations of all critical equipment should be identified on the floor plan.

2. Regarding the sterilization tunnel:
   A. Please proved data summaries which include the range of temperatures, the belt speeds, the recoverable endotoxin and the accumulated lethality (time at temp. or $F_h$) for the three validation runs discuss.
   B. How and when are the HEPA filter functions validated?
   C. What is the output air pressure of the entrance into the area?

3. Regarding the sterilizations: The older data found on pages 323 does not support the conclusion for the sterilization cycle found on page 321. The $F_o$ s are all below the minimum for the max load. This appears to be a different type of bag. Do you still use this bag? Do you use the cycle described on page 321 with it?

4. Please provide validation data summaries for the sterilization of the needles and sheaths.

5. Please provide data summaries which demonstrate that the filters selected to sterilize this product are capable of removing microbial contaminants from it.

6. Please provide data demonstrating the antimicrobial preservative effect for each strength of product at or slightly below the lowest acceptance limit for the preservative in the stability protocol, i.e. 75% of label claim.

7. Although a sterility test is currently acceptable, we strongly recommend that you include a container/closure integrity test at expiry and at the last point of your stability testing plan.

The methods used to assure sterility of this drug product were not sufficiently addressed. The application is therefore not acceptable on the basis of sterility assurance. Please provide responses to clarify these microbiological issues.

Sincerely yours,

/S/ 11/22/94

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA#74-496
Division File
HFD-600/Reading File
Field Copy
HFD-640/JMcVey
Endorsement: HFD-640/JMcVey date 11/21/94
HFD-629/PSchwartz date 11/21/94
HFD-615/PRickman date 11/19/94
WPFile B:\Rickman\74-496
F/T hrw 11-14-94
Micro. Rev!

ANDA 74-496

Elkins-Sinn
Attention: Linda M. Stewart
2 Esterbrook Lane
Cherry Hill, NJ 08003-4099

NOV 13 1995

Dear Madam:

This is in reference to your abbreviated new drug application dated May 6, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Lorazepam Injection USP, 2 mg/mL and 4 mg/mL (syringes).

Reference is also made to your amendments dated March 29, and April 24, 1995, and to your correspondence dated April 20, and May 3, 1995.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies

1. Your 12 months shelf life stability data does not support the claim that the % overage in the active ingredient is needed to maintain the strength over the proposed shelf life of the drug product. Thus the % overage of active ingredient in the formulation of the drug product is not acceptable.

2. Your records indicate that the accelerated stability studies were carried at storage conditions outside the recommended range of relative humidity. Thus the stability data generated under these conditions cannot be used to support tentative expiration period. Please provide shelf life stability data to support the requested expiration period.

3. DMF for Lorazepam USP remains deficient. The holder has been notified of the deficiencies.

B. Microbiology Deficiencies

1. Please provide a summary of the procedures and data collected for the validation of the filtration procedure. What rational is used to

justify the surrogate solution and what filtration parameters were bracketed or duplicated in doing this experiment?

2. Please indicate what methods you are taking to assure the product does not cause degradation of the container closure system and therefore loss of integrity over the expiration period.

B. Labeling Deficiencies

CONTAINER: (1 mL)

Dosette® Cartridge Needle Unit: Satisfactory in final print.

Dosette® Cartridge Assembly and Dosette® Cartridge Blunted Needle Unit: We acknowledge the withdrawal of these line items from the application based on your correspondence dated April 20, 1995.

CARTON: (10 x 1 mL Cartridges)

Dosette® Cartridge Needle Units: Satisfactory in final print.

Dosette® Cartridge Assembly and Dosette® Cartridge Blunted Needle Unit: We acknowledge the withdrawal of these line items from the application based on your correspondence dated April 20, 1995.

INSERT: Satisfactory

Please prepare and submit final printed insert labeling. Should additional information become available relating to the safety and efficacy of this product prior to approval, you may be asked to further revise your labeling accordingly.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered a MINOR amendment and should be so

designated in your cover letter. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 11/3/95

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA #74-496
ANDA #74-496/DUP/Division File
Field Copy
HFD-600/Reading file

Endorsements:

HFD-629/V.Sayeed/7-11-95 Vilayat 11/8/95
HFD-629/JMcVey/10-17-95 J. McVey 11/3/95
HFD-613/A.Payne/10-17-95 A. Payne 11/3/95
HFD-613/J.Phillips/10-19-95 J Phillips 11/2/95
HFD-629/P.Schwartz, Ph.D./10-18-95 P S 11/8/95
HFD-617/AMWeikel, CSO/7-28-95 AMW 11/8/95
X:\wpfile\majors\Sayeed\7449612.ori
F/T by MM 11-2-95
Not Approvable - Minor

ESi LEDERLE

**MINOR AMENDMENT**

August 6, 1998

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

**Lorazepam Injection, USP**
**2 mg/mL and 4 mg/mL**
**Dosette® Sterile Cartridge Needle-Units**
**ANDA #74-496**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL (Dosette® Sterile Cartridge Needle-Units) dated May 6, 1994, and our amendments dated May 24, 1994, March 29, 1995, April 20, 1995, April 24, 1995, July 17, 1996, October 14, 1996, September 3, 1997, October 16, 1997, April 20, 1998, June 12, 1998, and June 26, 1998, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the Agency's letters of January 14, 1997, and July, 20, 1998, requesting that we amend this application when the cGMP-related issues regarding Wyeth-Ayerst ESI Lederle Cherry Hill manufacturing facility had been satisfactorily resolved.

We have been notified by our local District Office that they have recommended to CDER that the application should be placed in an "approvable status." (See attached letter from the New Jersey District Office dated August 5, 1998.)

According to 21 CFR 314.96(b) requiring applicants to submit an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA North Brunswick Resident Inspection Post. We certify that the field copy is a true copy of this amendment to our application.

If you have any questions, please do not hesitate to call. Also, our departmental fax number is (609) 424-1461.

Sincerely,

Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

MCB/mag
Encs.
c: Ms. Regina Brown c/o Ms. Sarah Dellafave
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

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AUG 07 1998
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2 Esterbrook Lane, Cherry Hill, NJ 08003 Tel: (609) 424-3700 Fax: (609) 489-2050

ORIG AMENDMENT

**TELEPHONE AMENDMENT**

June 26, 1998

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

**Lorazepam Injection, USP**
**2 mg/mL and 4 mg/mL**
**Dosette® Sterile Cartridge Needle-Units**
**ANDA #74-496**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL (Dosette® Sterile Cartridge Needle-Units) dated May 6, 1994, and our amendments dated May 24, 1994, March 29, 1995, April 20, 1995, April 24, 1995, July 17, 1996, October 14, 1996, September 3, 1997, October 16, 1997, April 20, 1998, and June 12, 1998, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation of June 15, 1998, between Mr. J. Buccine, CDER/OGD/DLPS and Mr. M. Bokelman, ESI Lederle.

According to the Agency's request of June 15, 1998, we have removed the footnote, "Must meet the requirements of current USP/NF for Injections," from our finished product specifications and testing procedures (SATs). In place of the footnote, we have reformatted the SATs to include the following wording under the Test, Specification, and Method Reference columns listed on the SATs:

| TEST | SPECIFICATION | METHOD REFERENCE |
|---|---|---|
| Other Requirements | Meets current USP/NF requirements for Injections <1>, including particulate matter. | USP |

While we have revised our SAT's Test and Specification for Other Requirements so that "including particulate matter" is specified as you requested, the USP 23 page 1652 [and also similarly USP 23 Supp 5 page 3476] states

> "those small-volume Injections for which the monographs specify such requirements, are subject to the particulate matter limits set forth under *Particulate Matter in Injections* <788> [for the test being applied, unless otherwise specified in the individual monograph]."



In addition, the USP 23 page 1813 and also USP 23 Supp 5 page 3476 states:

> "Injections packaged in prefilled syringes and cartridges are exempt from the requirements, ..."

Since the Lorazepam Injection Monograph does not include any requirement for Particulate Matter testing, we do not intend to perform this test as a requirement for release.

According to 21 CFR 314.96(b) requiring applicants to submit an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA North Brunswick District Office. We certify that the field copy is a true copy of this amendment to our application.

If you have any questions, please do not hesitate to call. Also, our departmental fax number is (609) 424-1461.

Sincerely,

Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

MCB/mag
Encs.
c: Ms. Regina Brown
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

**TELEPHONE AMENDMENT**



June 12, 1998

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

**Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL**
**Dosette® Sterile Cartridge Needle-Units**
**ANDA #74-496**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL (Dosette® Sterile Cartridge Needle-Units) dated May 6, 1994, and our amendments dated May 24, 1994, March 29, 1995, April 20, 1995, April 24, 1995, July 17, 1996, October 14, 1996, September 3, 1997, October 16, 1997, and April 20, 1998 submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our telephone conversations of May 11 and May 26, 1998, with Dr. Allen Rudman, CDER/OGD/DCI.

In accordance with Dr. Rudman's request of May 11, 1998, we have updated our drug product specifications and testing procedures (SATs) in accordance with USP 23, Supplement 8 and have also added the statement, "Meets the current USP/NF requirements for Injections <1>." Previous versions of the SATs were included in our amendment dated October 16, 1997.

In addition, in follow-up to our telephone conversation of May 26, 1998, we have corrected a typographical error that appears in the "Related Compounds" section of USP 23, Supplement 8. This "typo" was confirmed by Dr. Todd Cecil at the USP on May 22, 1998.

The term $r_u$ should have read $r_t$, where $r_t$ is the response of the lorazepam peak in the test preparation. Therefore the calculation in USP 23, Supplement 8 should have been written as $c_u (r_t/r_t)$, not as $c_u (r/r_u)$.

As agreed during our conversation of May 26, 1998, included is a copy of our correspondence dated June 9, 1998, addressed to the USP, requesting that the typographical error in the calculation for related compounds be corrected.

*2 Esterbrook Lane, Cherry Hill, NJ 08003 Tel: (609) 424-3700 Fax: (609) 489-2050*

In accordance with 21 CFR 314.96(b) requiring applicants to submit an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA North Brunswick District Office. We certify that the field copy is a true copy of this amendment to our application.

If you have any questions, please do not hesitate to call. Also, our departmental fax number is (609) 424-1461.

Sincerely,

Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

MCB/mag
Attach.

'/ AF

ESi LEDERLE

**AMENDMENT**

FPL
NDA ORIG AMENDMENT

April 20, 1998 N/AE

ice of Generic Drugs
nter for Drug Evaluation and Research
od and Drug Administration
:tro Park North II
00 Standish Place, Room 150
)ckville, MD 20855

**Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL**
**Dosette® Sterile Cartridge Needle-Units**
**ANDA #74-496**

ear Sir/Madam:

.eference is made to our abbreviated new drug application for Lorazepam Injection, USP, mg/mL and 4 mg/mL (Dosette® Sterile Cartridge Needle-Units) dated May 6, 1994, and our imendments dated May 24, 1994, March 29, 1995, April 20, 1995, April 24, 1995, July 17, 996, October 14, 1996, September 3, 1997, and October 16, 1997, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your facsimile dated January 14, 1998, regarding changes to the labeling of the reference listed drug (Ativan® Injection -- Wyeth Laboratories).

According to your facsimile dated January 14, 1998, we have revised our package insert accordingly.

In addition, we have revised our container and carton labels. According to the Food and Drug Administration Modernization Act of 1997, the container and carton labels have been revised to include the wording "℞ only, " along with some minor editorial changes.

Attached are twelve (12) copies of final printed labeling and labels. To facilitate your review, we have included comparisons of our proposed labeling and labels with the labeling and labels previously submitted on July 17, 1996, and April 24, 1995, respectively.

If you have any questions, please do not hesitate to call. Also, our departmental fax number is (609) 424-1461.

Sincerely,

Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

RECEIVED
APR 21 1998
GENERIC DRUGS

Attach.

*2 Esterbrook Lane, Cherry Hill, NJ 08003 Tel: (609) 424-3700 Fax: (609) 489-2050*

**AMENDMENT**

October 16, 1997

NDA ORIG AMENDMENT
N/HM

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

**Lorazepam Injection, USP**
**2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes)**
**ANDA #74-496**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application for Lorazepam Injection, USP 2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes) dated May 6, 1994 and our amendments dated May 24, 1994, March 29, 1995, April 24, 1995, July 17, 1996, October 14, 1996, and September 3, 1997, submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your comment letter dated January 14, 1997, which outlined that the file on this application was closed pending a recommendation for approval by representatives of the local district office. We now anticipate district review of the application. Therefore, to insure all documents reviewed are amended to our application, we are submitting revised Finished Product, Bulk Solution/In-Process, and Drug Substance Specifications and Testing Procedures (SATs). The changes are described below.

**Revised Finished Product Specifications and Testing Procedures (3291A & 3294A) for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes)**
(Note: Previous versions (3291 & 3294) submitted in ANDA dated May 6, 1994.)

- Adjusted active assay release limits from based on the removal of the % overage from the formulation of the drug product. (See Minor Amendment dated July 17, 1996.)
- Added testing method references to specification pages.
- Added equipment specific parameters to the Heat Tolerance Test.
- Added note to assay standard and sample preparation to minimize time between preparation and injection and to refrigerate samples.
- Added statement to "TEST LABELED SAMPLES ONLY."
- Added USP nomenclature for related compound standards (i.e., Lorazepam Related Compounds B, C, and D) as per USP 23, Supplement 6. (See Assay and Related Compounds sections of enclosed SATs.)
- Added the use of approved house standards for Lorazepam and Lorazepam Related Compounds B, C, and D. (See Assay and Related Compounds sections of enclosed SATs.)
- Revised Related Compounds (Test A) shelf-life specifications from "NMT % Total Impurity" to "NMT % Compound C (WY08480), NMT % Other Individual, and NMT % Total Impurities" to be consistent with the Related Compounds (Test A) specifications stated on our post-approval stability protocols submitted in our Major Amendment dated April 24, 1995. In addition, we have revised the Related Compounds (Test A) release specifications from "NMT % Total Impurity" to "NMT % Compound C (WY08480), NMT % Other Individual, and NMT % Total Impurities," accordingly.

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OCT 17 1997
GENERIC DRUGS

11-21-97

2 Esterbrook Lane, Cherry Hill, NJ 08003 Tel: (609) 424-3700 Fax: (609) 489-2050

**Revised Bulk Solution/In-process Specifications and Testing Procedures (101B)**
(Note: Previous version (101) submitted in ANDA dated May 6, 1994.)

- Adjusted active assay bulk limits from (i.e., the revised finished product active assay release specifications) in accordance with 21 CFR 211.110.
- Added testing method references to specification page.
- Added USP nomenclature for related compound standards as per USP 23, Supplement 6. (See Assay and Related Compounds sections of enclosed SAT.)
- Added typical chromatograms.

**Revised Drug Substance Specifications and Testing Procedures (231C)**
(Note: Previous version (231B) submitted in Major Amendment dated April 24, 1995)

- Added testing method references to specification page.

In addition to the above, we are submitting an amendment to our drug substance impurity report submitted in our ANDA dated May 6, 1994. The data presented for WY-4301 related substances (see p. 977 of the original ANDA, Table 3) were not calculated as WY-8480 as required by the USP method as the report states. An amended Table 3 listing the correct results, as well as the original Table 3 are included. No single impurity was detected at more than % and the total is less than %.

In accordance with 21 CFR 314.96(b) requiring applicants to submit an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA North Brunswick District Office. We certify that the field copy is a true copy of this amendment to our application.

If you have any questions, please do not hesitate to call me. Also, our fax number is (609) 424-1461.

Sincerely,

Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

Encs.
c: Ms. Regina Brown
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

Additional
**AMENDMENT**

NDA ORIG AMENDMENT
AA

September 3, 1997

Noted
JBuccen
9/10/97

RECEIVED
SEP 5 - 1997
GENERIC DRUGS

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

**Lorazepam Injection, USP**
**2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes)**
**ANDA #74-496**

Dear Sir/Madam:

Reference is made to our abbreviated new drug application for Lorazepam Injection, USP 2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes) dated May 6, 1994 and our amendments dated May 24, 1994, March 29, 1995, April 24, 1995, July 17, 1996, and October 14, 1996 submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to your comment letter dated January 14, 1997, which outlined that the file on this application was closed pending a recommendation for approval by representatives of the local district office. In anticipation of the district review, we are submitting revised master production batch records. The majority of the revisions were effected in order to clarify and further define already existing procedures, as well to improve readability and documentation.

In addition to the changes referenced above:

- We have deleted the reference to the manufacturer of the inactive component, Polyethylene Glycol, NF. Only the manufacturer of the active ingredient is listed on the Compounding Logs. The grades of all inactive components, including Polyethylene Glycol, however, are listed on the Compounding Logs. All inactive components used in the manufacture of Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL must comply with all appropriate specifications listed in the current USP/NF.

- As part of our commercialization of the filling process, we re-evaluated our filling machinery process capabilities. Consequently, we have established a filler speed range of 45 - 50 strokes/minute and revised the target and maximum optimum fill ranges from to 1.23 mL and 1.31 mL, respectively. These filling parameters were effected to provide consistent fill values during production and ensure an optimum minimum fill range of mL, the minimum optimum fill range submitted in our original ANDA, ( i.e., label claim plus a 0.15 mL excess as recommended by USP).

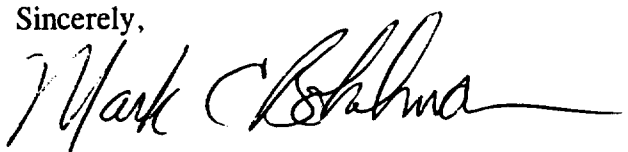
2 Esterbrook Lane, Cherry Hill, NJ 08003 Tel: (609) 424-3700 Fax: (609) 489-2050

Enclosed are side-by-side comparisons of the following documents: (1) Compounding Logs, (2) Compounding Procedures, (3) Filtration and Filling Tickets, and (4) Catching, Inspection and Packaging Tickets (previously titled Inspection Ticket). We have compared and highlighted the differences between the enclosed updated batch records and those previously submitted in ANDA 74-496. In addition, a Sampling Ticket has been added to the master production batch records.

In accordance with 21 CFR 314.96(b) requiring applicants to submit an additional copy of the chemistry, manufacturing and controls section of applications, we are providing a field copy of this amendment directly to the FDA North Brunswick District Office. We certify that the field copy is a true copy of this amendment to our application.

If you have any questions, please do not hesitate to call me. Also, our fax number is (609) 424-1461.

Sincerely,



Mark C. Bokelman
Manager, Regulatory Affairs
ESI Lederle
(609) 489-2121

Encs.

c: Ms. Regina Brown
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
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North Brunswick, NJ 08902

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A division of A. H. Robins Company

NJ 609 424-3700
Phila. 215 925-4559
FAX 609 424-8747

October 14, 1996

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



ANDA 74-496
Lorazepam Injection, USP
2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes)

**MINOR AMENDMENT: Response to Deficiency Letter of August 28, 1996**

Dear Sir/Madam:

We refer to our abbreviated new drug application for Lorazepam Injection, USP 2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes) submitted pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act, as well as the agency's letter of August 28, 1996, which listed the following deficiency with our ANDA:

**"Drug Master File for the drug substance remains deficient and the holder has been notified. Please do not respond until has notified you that they have responded to their deficiencies."**

We were notified via facsimile transmission of October 11, 1996, that responded to the above (see attached). In their reply of September 20, 1996, to the FDA, they stated, "that in the future we will meet the proposed limits for the residual solvents cyclohexane, ethanol and toluene.

This letter responds to all open issues regarding this application, and in accordance with your letter of August 28, 1996, we are designating this response as a Minor Amendment.

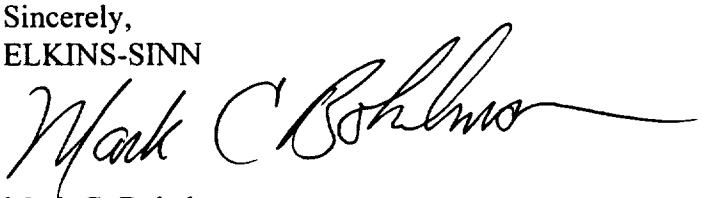
ANDA 74-496 October 14, 1996

In accordance with 21 CFR 314.96 (b), we certify that a true copy of this amendment has been submitted to our home FDA district office.

For your information regarding future correspondence, Elkins-Sinn, ESI Lederle Inc., and Wyeth-Ayerst are affiliated companies under the common ownership and control of American Home Products Corporation.

If you have any questions, please do not hesitate to call.

Sincerely,
ELKINS-SINN



Mark C. Bokelman
Manager, Regulatory Affairs

c: Ms. Regina Brown
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July 17, 1996

RECEIVED
JUL 19 1996
GENERIC DRUGS

approval summary issued 7/25/96

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

AMENDMENT

ANDA 74-496
Lorazepam Injection, USP
2 mg/mL and 4 mg/mL (Dosette® Cartridge Syringes)

**MINOR AMENDMENT: Response to Deficiency Letter of November 13, 1995**

Dear Sir/Madam:

Reference is made to the agency's letter of November 13, 1995, which listed deficiencies with our ANDA for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL (Dosette® cartridge syringes). The agency's requests and our responses are listed below.

**A. Chemistry Deficiencies**

**1. Your 12 months shelf life stability data does not support the claim that the % overage in the active ingredient is needed to maintain the strength over the proposed shelf life of the drug product. Thus the % overage of active ingredient in the formulation of the drug product is not acceptable.**

We have deleted the % overage of active ingredient in the formulation of the drug product. Attached are revised Compounding Logs for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL, 1 mL/2.5 mL Dosette® cartridge syringes. See Addendum 1.

**2. Your records indicate that the accelerated stability studies were carried [*sic*] at storage conditions outside the recommended range of relative humidity. Thus the stability data generated under these conditions cannot be used to support tentative expiration period. Please provide shelf life stability data to support the requested expiration period.**

Attached are shelf life (i.e., 24 months at 5 ± 3°C) stability data for Lorazepam Injection, USP, 2 mg/mL and 4 mg/mL, 1 mL/2.5 mL Dosette® cartridge syringes that support our proposed 24 months expiration dating period. See Addendum 2.

Received 7-17-96

**3. DMF for Lorazepam USP remains deficient. The holder has been notified of the deficiencies.**

We have been notified by the DMF holder ( that FDA has completed the review of the their response of December 22, 1995. In their letter of January 17, 1996, to the DMF holder, FDA noted that, "The response and accompanying documentation are satisfactory and, as such, we are classifying your firm acceptable as a supplier of BPCs." See Addendum 3.

**B. Microbiology Deficiencies**

**1. Please provide a summary of the procedures and data collected for the validation of the filtration procedure. What rationale is used to justify the surrogate solution and what filtration parameters were bracketed or duplicated in doing this experiment?**

Result Summary

A copy of the summary page from the Millipore (i.e., filter vendor) Microbial Retention Validation Report is attached. See Addendum 4.

Surrogate Solution Justification

Lorazepam Injection utilizes an organic, non-aqueous (propylene glycol/polyethylene glycol) vehicle and contains an antimicrobial preservation (benzyl alcohol). As indicated in the 1987 FDA Guideline on Sterile Drug Produced by Processing, paragraph three "Sterilization Operations--Filtration" section, "Addition of *P. diminuta* to products having inherently bactericidal activity or to oil based formulations would not present a meaningful filter challenge." The particular polyethylene glycol solution was recommended by the filter vendor (Millipore), after discussions with FDA as one which simulates product viscosity and other physical characteristics. See Addendum 5.

Filtration Parameters

The challenge conditions were chosen to provide a "worst case" situation, subjecting the filter to a higher pressure, higher viscosity solution for a longer duration than Elkins-Sinn (ESI) procedures.

Process parameters simulated were:

| | Normal ESI | Study |
|---|---|---|
| Pressure | 25 psi max | 60 psi |
| Duration | 16 hours max | 24 hours |
| Surface Area/Volume | 0.08 $cm^2$/mL | 0.4 $cm^2$/mL |
| Temperature | 20-30°C | ambient |
| Viscosity | 24 cps | 100 cps |

**2. Please indicate what methods you are taking to assure the product does not cause degradation of the container closure system and therefore loss of integrity over the expiration period.**

New product submissions which are provided in line items utilizing new and/or different rubber formulations/configurations, container types/sizes, or overseals not previously validated are added to the container/closure test program. This program consists of microbiological and physical components.

To address the microbiological concerns, new packaging systems are evaluated by filling them with trypticase soy broth (TSB) on the filling line in the sterile suite planned for use in the production of the new product. During production, the units are leak tested to assure proper capper head pressure and visually checked for contamination and fill volume accuracy. The units are incubated, inspected, and placed in the container closure program. This includes: bacterial immersion, media viability, leak testing, and aerosol challenges, as well as long-term stability qualification for visual integrity and sterility. In addition to the monitoring of the TSB filled units, product filled units are tested for sterility initially and at expiry.

The Lorazepam 1 mL/2.5 mL Dosette® cartridge syringe system includes 890 S red plungers and 8 mm lined seals. The container closure system was filled with TSB, tested and passed bacterial immersion and media viability effectiveness (see Addendum 6), leak testing (see Addendum 7), and aerosol challenge (see Addendum 8). Long-term stability testing of the media filled units is planned for 48 months and includes visual inspection and sterility time zero, six months and then at yearly intervals. Available data show acceptable results (see Addendum 9). The acceptable sterility results conducted as part of the product stability program have been presented in Addendum 2.

To address the physical compatibility of the container closure system with the product, the product filled units are inspected at every stability interval to assure that there is no deterioration of the closure system. The results of the inspections are included in Addendum 10.

**B.[*sic*]Labeling Deficiencies**

**Container: (1 mL)**

**<u>Dosette® Cartridge Needle Unit</u>: Satisfactory in final print.**

**<u>Dosette® Cartridge Assembly and Dosette® Cartridge Blunted Needle Unit</u>:**

**We acknowledge the withdrawal of these items from the application based on your correspondence dated April 20, 1995.**

**Carton:** **(10 x 1 mL Cartridges)**

**Dosette® Cartridge Needle Units: Satisfactory in final print.**

**Dosette® Cartridge Assembly and Dosette® Cartridge Blunted Needle Unit:**

**We acknowledge the withdrawal of these items from the application based on your correspondence dated April 20, 1995.**

**Insert: Satisfactory**

**Please prepare and submit final printed insert labeling. Should information become available relating to the safety and efficacy of this product prior to approval, you may be asked to further revise your labeling accordingly.**

We acknowledge your comments concerning labeling. As per your request of November 13, 1995, we have attached (see Addendum 11) Final Printed Insert Labeling (12 copies).

In accordance with your letter of November 13, 1995, we are designating this response as a Minor Amendment.

In accordance with 21 CFR 314.96 (b), we certify that a true copy of this amendment (without the Labeling) has been submitted to our home FDA district office.

If you have any questions, please do not hesitate to call.

Sincerely,
ELKINS-SINN

Mark C. Bokelman
Manager, Regulatory Affairs

c: Ms. Regina Brown
Newark District Pre-approval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
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**AIRBORNE**

Noted - AM Weibel
5/31/95
NEW CORRESP
NC

May 3, 1995

Mr. Douglas L. Sporn
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 74-496
Lorazepam Injection, USP

**GENERAL CORRESPONDENCE:** **Correction of Deficiency Response Dated March 29, 1995**

Dear Mr. Sporn:

This letter is to notify you of a typographical error found in our minor amendment to the microbiology deficiency letter of November 23, 1995.

The response to question No. 5, in both the first and second paragraphs, incorrectly identifies the challenge level as The correct number should be $0.8 \times 10^7$ cfu/cm$^2$.

The question and revised response to question No. 5 are attached for clarity.

If there are any questions, please do not hesitate to call.

Sincerely,

ELKINS-SINN

Linda M. Stewart
Regulatory Affairs Associate

LMS/ecc
Attachment

cc: Ms. Heather L. Pederson
Newark District Preapproval Program Manager
Food and Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902

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MAY 0 4 1995
GENERIC DRUGS

5-31-95

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April 24, 1995

Mr. Douglas L. Sporn
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ANDA 74-496
Lorazepam Injection, USP

**MAJOR AMENDMENT: Response to Deficiency Letter of January 13, 1995**

Dear Mr. Sporn:

Reference is made to your letter of January 13, 1995 which listed deficiencies with our ANDA for Lorazepam Injection, USP. Your comments along with our responses follow.

A. Chemistry Deficiencies

1. Your records indicate that a % overage of active ingredient has been used in the formulation of the drug product. Please justify the need for overage.

   Stability studies indicate that a loss of % is likely to occur over the shelf life of the product. Therefore, the % overage has been included to assure that the strength reflects the label claim over the shelf life of the product.

2. Please specify on the master batch record the time the bulk can be held in quarantine before being released for filling. Also, please provide data supporting bulk solution stability for the quarantine period.

   The master batch record compounding procedure has been revised to include "Note: Total time at 5°C not to exceed 24 hours." between steps 11 and 12 of the compounding procedure. (See pages 2-4.)

   Bulk holding time studies were conducted during the manufacture of the pilot batches. Solution held at room temperature for up to five days represents a worst case scenario since the bulk will be held at 5°C. All bulk samples taken prior to filling met bulk SAT specifications.

3. Please specify in the master record the temperature ranges at which each compounding step must be carried out.

   The master batch record compounding procedure has been revised to include a statement under "GUIDELINES" defining the temperature at which all compounding must be carried out. Further revisions have been made at steps 2 and 6a requiring the measurement of the solution temperature at the beginning and end of compounding. (See pages 2-4.)

4. Please establish a test and specification for Microbial Bioburden in the release of the bulk drug product.

   A bioburden test takes five days to complete. Lorazepam bulk drug product must be filled within 48 hours of compounding. Therefore, bioburden test results are not available for bulk release for filling. Based on systems that are in place to minimize and control bioburdens and Microbiological monitoring data of three pilot lots of Lorazepam bulk solution, we conclude that bulk solution processing is microbiologically in control, and bioburden test results are not required for release of the bulk product.

   Measures are taken during the manufacturing process to minimize and control bioburden in the bulk product which include:

   a. Lorazepam raw material is tested for bioburdens and endotoxins which must meet release specifications for use in batches.

   b. Compounding of the bulk is done in Class 10,000 conditions. The compounding environment is monitored for microorganisms daily.

   c. Compounding tanks are cleaned using a Clean In Place system with Water for Injection at 80°C.

   d. Immediately after compounding, the bulk is filtered through a micron filter into a sanitized transfer tank.

   e. During filling operations, the first filtered bulk product is filtered through a filter.

   Additionally, Lorazepam 2 mg/mL and 4 mg/mL formulations pass the USP preservative efficacy test.

Data from Microbiological monitoring of the manufacturing process of the three pilot lots of Lorazepam shows that each of the unfiltered bulk solutions meet the unfiltered bulk bioburden criterium of Not More Than 100 cfu/100 mL. Two lots showed 0 cfu/100 mL and one lot showed 2 cfu/100 mL. Additionally, when the first filtered bulk solutions of these three lots were held for four days in the transfer tank, bioburden test results showed 0 cfu/100 mL. We believe that subsequent lots of Lorazepam manufactured using the same process will exhibit equivalent bioburden profiles.

5. Please establish individual limits for each impurity observed in the profile and include this information in your Product Stability Specification .

   The following impurity, 6-chloro-4(o-chlorophenyl)-2-quinazoline carboxaldehyde, has been assigned the ESI identification number WY 08480. The impurity limits are as follows:

   WY 08480 - NMT %
   Other Individual Impurities - NMT %
   Total Impurities - NMT %

   The Post Approval stability protocols on pages 5-6 have been revised to include impurity limits.

6. Your records indicate that the accelerated stability studies were carried out at 25 ± 2°C, with no reference to relative humidity. Please clarify. The recommended accelerated stability storage conditions for nonaqueous dosage forms, are 15°C higher than the recommended storage condition and 75% RH. Please provide all available refrigerated stability data.

   Our accelerated stability samples are stored at 25°C at ambient humidity which is higher than the recommended label storage condition of "room temperature + 15°C" (i.e., 5°C + 15°C). Referring to a standard psychrometric chart it can be determined that the moisture load of air at 20°C is approximately 80 grains of water per pound of dry air. At 25°C a moisture load of 80 grains corresponds to a typical ambient humidity of approximately 55% relative humidity. It is felt that this comparable moisture load addresses the intent of the high humidity study.

   Stability tables have been updated and are attached on pages 7-12.

7. Your stability protocol does not indicate the orientation in which the samples are stored. Please include this information on the stability data summary form.

   All samples are stored horizontally to provide contact with both elastomeric surfaces. Stability data summaries and post approval protocols have been revised to indicate the orientation in which the samples are stored. (See pages 5-12.)

8. Please provide data to support your contention that the drug product is compatible with the listed diluents for intravenous use.

   Lorazepam is compatible with Sterile Water for Injection, USP; 0.9% Sodium Chloride Injection, USP; and 5% Dextrose Injection, USP. Data is enclosed on pages 13-18.

9. Drug Master File (DMF) for Lorazepam, USP is deficient. The holder has been notified of the deficiencies.

   Deficiencies for Technochemie's Drug Master File for Lorazepam, USP have been addressed. Enclosed on page 19 is a confirmation letter from the manufacturer.

In addition we are submitting a revised raw material SAT (pages 20- 35) for Lorazepam, USP to include the following changes:

A single impurity requirement was added to the Related Compounds procedure.

Bioburden and bacterial endotoxin tests were added to the SAT.

B. Labeling Deficiencies

As per your request the following changes have been made:

**CONTAINER**

Dosette® Cartridge Needle Unit

1. Graduations have been provided to 2.5 mL.

2. Route of administration has been revised to read:

   For IM use
   For IV use see directions.

3. Space permits the statement "Must dilute before IV use" to remain.

4. Lot number and expiration will be located in the upper right corner next to the company name and address.

5. Enclosed is final printed labeling for the container labeling which shows a differentiation between strengths through contrasting colors.

Dosette® Cartridge Blunted Needle Unit

Not Applicable - See amendment dated April 20, 1995.

Dosette® Cartridge Assembly

Not Applicable - See amendment dated April 20, 1995.

**CARTON**

Dosette® Cartridge Needle Units

1. Route of administration has been revised to read:

   For IM use
   For IV use see directions.
   Lot number and expiration will be embossed on the flap below the company name and address.

   Enclosed is final printed labeling for the carton labeling which shows a differentiation between strengths through contrasting colors.

2. Quantity expression has been revised to read "1 mL fill in 2.5 mL cartridge" to be in accordance with the innovator.

3. PROTECT FROM LIGHT statement was retained since this is a uniform statement throughout all of our labeling.

4. The following statement was added, "Each Dosette® ... before injection."

Dosette® Cartridge Blunted Needle Units

Not Applicable - See amendment dated April 20, 1995.

Dosette® Cartridge Assemblies

Not Applicable - See amendment dated April 20, 1995.

**INSERT**

GENERAL COMMENT

It is our policy to capitalize Lorazepam since it is the name of our product, i.e., a proper name.

CLINICAL PHARMACOLOGY

We have revised the first line of the fourth paragraph to read:

Clinically employed doses of lorazepam injection do not ... .

PRECAUTIONS

We have deleted the word following lorazepam in the areas listed below:

GENERAL, second paragraph, line 1
INFORMATION FOR PATIENTS, second paragraph, line 1
INFORMATION FOR PATIENTS, third paragraph, line 3
LABORATORY TESTS, line 2

PREGNANCY section has been revised to read:

PREGNANCY
*Teratogenic Effects*: Pregnancy Category D. (see WARNINGS.)

NURSING MOTHERS section revised to read:

Lorazepam injection should not be ... .

OVERDOSAGE

The third paragraph has been revised as the Agency's letter of January 20, 1995 as requested.

HOW SUPPLIED

The established name has been included.

PROTECT FROM LIGHT statement was retained since this is a uniform statement throughout all of our labeling.

Enclosed are twelve (12) copies of final printed container labels and carton labeling and four copies of draft insert labeling.

All points of your January 13, 1995 letter have been addressed. We are designating this response as a major amendment.

If there are any questions, please do not hesitate to call.

Sincerely,

ELKINS-SINN

Linda M. Stewart

Linda M. Stewart
Regulatory Affairs Associate

LMS:hk
Encs.
cc: Ms. Heather L. Pedersen
Newark District Preapproval Program Manager
Food and Drug Administration
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March 29, 1995

Mr. Douglas L. Sporn
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N | NS
AMENDMENT

ANDA 74-496
Lorazepam Injection, USP

**MINOR AMENDMENT: Response to Letter of November 23, 1994**

Dear Mr. Sporn:

Reference is made to your letter of November 23, 1994 regarding the sterilization process described in our ANDA for Lorazepam Injection, USP. Your comments along with our responses follow.

1. The description provided in your application of the facilities used for the processing to the drug product were not adequate. Please provide the following information.

   A. A floor plan of the area with designated air cleanliness classes and isolators or barrier systems.

   B. The locations of all critical equipment should be identified on the floor plan.

      The floor plan of the area with designated air cleanliness classes with the locations of all critical equipment is attached. (See pages 2, 3 and 4).

2. Regarding the sterilization tunnel:

   A. Please provide data summaries which include the range of temperatures, the belt speeds, the recoverable endotoxin and the accumulated lethality (time at temp. or $F_h$) for the three validation runs discussed.

      Data summaries which include the range of temperatures, belt speed, recoverable endotoxin, and the accumulated lethality (time at temp. or $F_h$) for the three validation runs discussed are included on page 5.

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MAR 31 1995
GENERIC DRUGS

B. How and when are the HEPA filter functions validated?

HEPA filters are validated by an outside certification service every six months by testing for particle leakage using an Emory 3004 smoke generator and photometer. Additionally, particle measurements are made to assure a class 100 environment. The service also tests each unit for air velocity. Maintenance is performed as required. Validation records for all units are provided by the service and maintained in the Microbiology Department.

C. What is the output air pressure of the entrance into the area?

The output air pressure of the entrance into the area is negative to both the area and the sterilizing section of the tunnel.

3. Regarding the sterilizations: The older data found on pages 323 does not support the conclusion for the sterilization cycle found on page 321. The $F_o$s are all below the minimum for the max load. This appears to be a different type of bag. Do you still use this bag? Do you use the cycle described on page 321 with it?

The older data on page 323 was included only to show studies of preliminary runs to determine the cold spots in the load configuration. The bag indicated in the heading of this data sheet is no longer in use. A new bag identical in size, but having the breather strip at the top of the bag rather than in the center, was validated in 1993. The cycle described on page 321 is the cycle used with the bag currently in use. We have summarized all data pertinent to the sterilization validation for the components in bags currently in use on pages 6 and 7.

4. Please provide validation data summaries for the sterilization of the needles and sheaths.

Validation data summaries from for the radiation sterilization of the 22 x 1-1/4" needle assembly unit is attached on pages 8-18.

5. Please provide data summaries which demonstrate that the filters selected to sterilize this product are capable of removing microbial contaminants from it.

   Testing done at in August, 1994 to validate the Durapore (10") hydrophobic filter for bacterial retention indicates that the filter is effective and can be qualified against a challenge level of $0.8 \times 10^6$ cfu/cm$^2$. [NOTE: Due to antagonism from the test solution (PEG 8000), the challenge did not reach the original protocol specified level of $1 \times 10^7$ cfu/cm$^2$.]

   However, we believe that the nominal difference in the actual post test challenge to the filter ($0.8 \times 10^6$ cfu/cm$^2$ compared to $1.0 \times 10^7$ cfu/cm$^2$) is insignificant. Please note that we use

   These measures effectively insure there will be no challenge to the filter at any level near that which was tested.

6. Please provide data demonstrating the antimicrobial preservative effect for each strength of product at or slightly below the lowest acceptance limit for the preservative in the stability protocol, i.e. 75% of label claim.

   Data has been provided for Lorazepam Injection 2 mg/mL and 4 mg/mL containing no preservative (i.e., 0% of label claim). Both of these formulations pass the USP preservative efficacy test. (See pages 19-23 respectively.) Data for the 2 mg/mL and 4 mg/mL formulations with 100% preservative has previously been supplied. By showing effectiveness of both formulations with 100% preservative and in the absence of preservative, all concentrations of preservative below 100% are therefore acceptable.

7. Although a sterility test is currently acceptable, we strongly recommend that you include a container/closure integrity test at expiry and at the last point of your stability testing plan.

   Please note we currently have a container/closure program which tests the long term integrity of each container/closure system. Media filled units are checked for sterility at 0, 6, 12, 24, 36 and 48 months. The 48 month storage is longer than any expiry period of any of our products.

All points of your November 23, 1994 letter have been addressed. We are designating this response as a minor amendment.

If there are any questions, please do not hesitate to call.

Sincerely,

ELKINS-SINN

Linda M Stewart

Linda M. Stewart
Regulatory Affairs Associate

LMS:hk
Encs.
cc: Ms. Heather L. Pedersen
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Food and Drug Administration
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May 24, 1994

Mr. Douglas L. Sporn
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Metro Park North II
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Rockville, MD 20855-2773

ANDA 74-496
Lorazepam Injection, USP
2 mg/mL and 4 mg/mL (syringes)

**AMENDMENT: Exclusivity Statement**

Dear Mr. Sporn:

Enclosed is a revised Patent Certification and Exclusivity Statement amending our ANDA 74-496 for Lorazepam Injection, USP 2 mg/mL and 4 mg/mL (syringes).

This amendment answers all issues raised in your letter of May 19, 1994.

We look forward to confirmation of your acceptance to file our application.

Please feel free to call if you have any questions.

Sincerely,
ELKINS-SINN

Barry H. Ballan
Manager, Regulatory Affairs

RECEIVED
MAY 25 1994
GENERIC DRUGS

BHB:hk
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Desk Copy: Mr. Robert W. Pollock
Director, Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Mr. William Russell
Consumer Safety Officer
Office of Generic Drugs
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ORIGINAL

esi
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May 6, 1994

Mr. Douglas L. Sporn
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

**SUBJECT: SUBMISSION OF ANDA - LORAZEPAM INJECTION, USP**

Dear Mr. Sporn:

Elkins-Sinn is herewith submitting a two-volume ANDA for Lorazepam Injection, USP (2 mg/mL and 4 mg/mL). It is being presented as a 1 mL fill cartridge-syringe.

Wyeth Laboratories' Ativan® is the listed drug. The labeling is patterned on the Ativan® insert revised October, 1993. A letter from Wyeth Laboratories (our sister company) authorizing FDA to reference their NDA #18-140 in support of our ANDA is included in Section XXI.

Our raw material manufacturer is
An authorization letter to reference their DMF is also included in Section XXI.

We have enclosed complete executed batch records for the two production facility batches we have manufactured. One is for a liter batch, 2 mg/mL strength (#P123296) and the other is for a liter batch, 4 mg/mL strength (#P123282). These batches are the same size as those we plan for our maximum size production batch. The enclosed data on these batches demonstrate good stability after 3 months at 25°C. (This is a refrigerated product.) We are requesting 24 months expiration dating.

In addition to the standard cartridge-syringe needle unit, we have included two other configurations in the application; one with a blunted needle and one without any needle. Both of these (the latter with an adapter) may be used with several "needle-free" access ports currently on the market. (Please see the Container / Closure and Labeling sections for complete information.)

We are enclosing a separate desk copy of the microbiological portion of the application.

As directed in the September 8, 1993 *Federal Register* and in the FDA letter dated February 28, 1994, we are sending what we certify to be a true copy of the application (without the labeling section) to our FDA district office.

If any questions arise that can be handled by phone, we'd appreciate a call. We will respond promptly.

Sincerely,

ELKINS-SINN

Thelma C Hilibrand

Thelma C. Hilibrand
Director, Regulatory Affairs

TCH/LMS:hk
Enc.
cc: Ms. Heather L. Pedersen
Newark District Pre-approval Program Manager
U. S. Food & Drug Administration
North Brunswick Resident Post
120 North Center Drive
North Brunswick, NJ 08902