

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-488**

**Chemistry Review(s)**

**CDER**

**CHEMISTRY REVIEW**

**CDER**

**NDA 21-488**

**ELIGARD™, 30 mg**  
**(Leuprolide acetate for Injectable suspension)**

**ATRIX LABORATORIES INC.**

**SWAPAN K. DE**

**DIVISION OF REPRODUCTIVE & UROLOGIC DRUG**  
**PRODUCTS (HFD-580)**

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# Chemistry Review Data Sheet

1. NDA 21-488
2. REVIEW # 1
3. REVIEW DATE: 10-FEB-2003(revised)
4. REVIEWER: Swapan K. De
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

13-APR-2002

Amendment #003

15-NOV-2002

Amendment #006

14-JAN-2003

Amendment #007

24-JAN-2003

Amendment #008

27-JAN-2003

Amendment #010

07-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.

Address: 2579 Midpoint Drive  
Fort Collins, CO 80525-4417

Representative: Johanna J. Matz

Telephone: (970) 482-5868

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ELIGARD™ 30 mg  
 b) Non-Proprietary Name (USAN): Leuprolide acetate for injectable suspension  
 c) Code Name/# (ONDC only): N/A  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## 10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

## 11. DOSAGE FORM: Injectable suspension

## 13. ROUTE OF ADMINISTRATION: Subcutaneous

## 12. STRENGTH/POTENCY: 30 mg leuprolide acetate

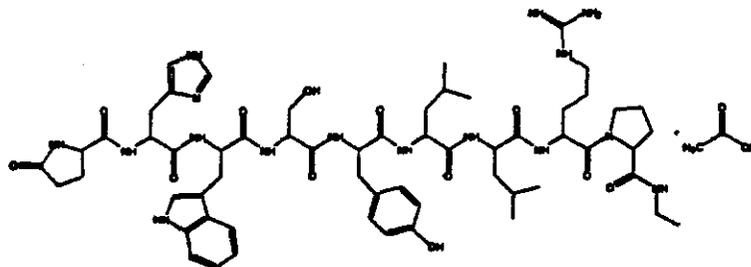
14. Rx/OTC DISPENSED:  Rx  OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

SPOTS product – Form Completed  
 Not a SPOTS product  
 Not a SPOTS product

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

Chemical names: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

Chemical Structure:



**CBER** **CHEMISTRY REVIEW** **CBER**

Chemistry Review Data Sheet

Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide acetate

Molecular formula:  $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$

Relative molecular mass: 1269.48 Daltons (Leuprolide Monoacetate)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
	II		/	3	Adequate	01/17/2000	Reviewed by S.K.De
	II		/	3	Adequate	11/29/01	Reviewed by S.K.De
	II		/	1	Adequate	1/8/03	Reviewed by S.K.De
	II		/	3	Adequate	06/10/02	Reviewed by S.K.De
	II		/	3	Adequate	1/03/02	Reviewed by S.K.De
	III		/	3	Adequate	12/12/01	Reviewed by S.K.De
	III			3	Adequate	2/3/00	Reviewed by



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

		/	'				R. Puttagunta
7092	III		'	3	Adequate	1/10/01	Reviewed By J.D. Vidra
12821	III		'	1	Adequate	1/28/03	Reviewed by S.K.De
11787	III		'	3	Adequate	7/14/00	Reviewed By Young-de Lu
7730	III			3	Adequate	2/17/98	Reviewed by E.G.Pappas

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

1 - DMF Reviewed.

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

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

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

B. Other Documents: IND

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

## ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-FEB-2003	Office of Compliance
Pharm/Tox	Adequate	11-JUN-2002	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	04-FEB-2003	Al-Habet Sayed, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	14-AUG-2002	Hye-Joo Kim, Pharmacist.
EA	Categorical exclusion granted	14-JAN-2002	Swapan K. De, Ph.D.
Microbiology	Adequate	12-DEC-2002	Stephen Langille, Ph.D.

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:

# The Chemistry Review for NDA 21-488

## The Executive Summary

### I. Recommendations

- A. From chemistry, manufacturing, and controls point of view, this NDA may be approved.

### II. Summary of Chemistry Assessments

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

**Dosage form:** Injectable suspension  
**Strength:** 30 mg Leuprolide acetate  
**Route of Administration:** Subcutaneous

#### Description:

The drug product, ELIGARD™, 30 mg is a polymeric matrix formulation and consists of a two syringe mixing system, a 20 gauge 5/8-inch needle, and a silica or silica gel desiccant pouch to control moisture uptake. One syringe (Syringe A) contains the ATRIGEL Delivery System. This delivery system consists of \_\_\_\_\_ g of a sterile, polymeric delivery system solution of \_\_\_\_\_% 75:25 Poly(DL lactide-co-glycolide) (PLG) and \_\_\_\_\_% N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains 35.8 mg of \_\_\_\_\_ leuprolide acetate.

These two syringe assemblies are manufactured at separate locations. The ATRIGEL® Delivery System (75:25 PLGH and NMP; Syringe A) is compounded, filled into syringes, and pouched at Atrix Laboratories Inc. in Fort Collins, CO. This subassembly is then \_\_\_\_\_

acetate is \_\_\_\_\_ An aqueous solution of leuprolide \_\_\_\_\_ in syringes

(Syringe B), and pouched at the \_\_\_\_\_

The final assembly occurs at Atrix Laboratories Inc., in Ft. Collins, CO and consists of a large foil pouch containing two pouched sterile assemblies with the sterile needle and the desiccant. The quality is controlled by tests of both parts of the drug product, Syringe A and Syringe B. Syringe A tests include color, appearance, polymer identification (by NMR), polymer molecular weight, water content, sterility (USP <71>) and endotoxin (USP <85>). Syringe B tests include color, appearance, identification ( \_\_\_\_\_ related substances \_\_\_\_\_), sterility (USP <71>) and endotoxin (USP <85>). Furthermore, the reconstituted product is released by regulatory specifications and is controlled by tests that include color, appearance, polydispersity, leuprolide acetate content and drug release.

The primary packaging of the two syringes that constitute the drug product are performed separately and individually packaged. The ATRIGEL Delivery System is filled into \_\_\_\_\_ syringes \_\_\_\_\_

Executive Summary Section

rod is \_\_\_\_\_ (Syringe A). The plunger tip is \_\_\_\_\_ and the plunger

The Syringe B is constructed of a \_\_\_\_\_ with the syringe tip cap and the plunger tip composed of \_\_\_\_\_ A second plunger tip behind the primary plunger tip is incorporated to ensure a clear zone for the primary tip to travel during product mixing. A \_\_\_\_\_ is installed to assist with injection. The assembled unit is then packaged in \_\_\_\_\_

Both \_\_\_\_\_ pouches are then placed together in a larger pouch with a sterile 20-gauge 5/8-inch needle and a desiccant pouch and \_\_\_\_\_ to enclose all the components. The required DMF's (DMF \_\_\_\_\_ DMF \_\_\_\_\_ and DMF \_\_\_\_\_) for the packaging components are found adequate. From Microbiologist's point of view, container/closure integrity is deemed satisfactory.

Based on the stability data provided, an 18-month expiry date is granted. The tradename, ELIGARD™, 30 mg has been accepted by DMETS, and adequate chemistry information is presented in the labeling and labels of the primary as well as the secondary packaging.

Leuprolide is a synthetic analog of the hormone, leuteinizing hormone releasing hormone (LH-RH). Leuprolide is a nonapeptide and acts as an agonist of naturally-occurring gonadotropin releasing hormone (GnRH). After a short period of up-regulation of the steroidogenesis, sustained leuprolide treatment desensitized anterior pituitary and results in low steroid blood levels. The analog possesses greater potency than the natural hormone.

Leuprolide acetate is manufactured and supplied by three different suppliers: \_\_\_\_\_ synthesizes leuprolide acetate with \_\_\_\_\_

On the contrary,

The major differences in the impurity profile among

The sponsor has provided data to show the comparability of the drug substances among the three suppliers and they are deemed satisfactory. Toxicology and clinical studies qualifies the above impurities and is deemed acceptable.

Leuprolide has the chemical designation 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt). It is white to off-white powder, soluble in water and acetic acid and hygroscopic in nature. The characterization and proof of structure of leuprolide acetate has been determined by \_\_\_\_\_ The tests performed on the starting materials \_\_\_\_\_ has been provided in the respective DMF from \_\_\_\_\_ and are adequate.

## Executive Summary Section

Compliance issued an acceptable recommendation on 10 February, 2003. Thus, considering the provided information, this NDA is deemed satisfactory regarding CMC and may be approved.

**III. Administrative**

/S/

**A. Reviewer's Signature****B. Endorsement Block**

HFD-580/S. K. De, Ph.D.  
HFD-580/D. T. Lin, Ph.D.  
HFD-580/A. Reddy

**C. CC Block**

HFD-580/Division File/NDA 21-488  
HFD-580/S. K. De, Ph.D.  
HFD-580/D. T. Lin, Ph.D.  
HFD-580/A. Reddy

Redacted 2

pages of trade

secret and/or

confidential

commercial

information



**CHEMISTRY REVIEW**



**NDA 21-488**

**ELIGARD™, 30 mg**  
**(Leuprolide acetate for Injectable suspension)**

**ATRIX LABORATORIES INC.**

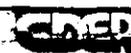
**SWAPAN K. DE**

**DIVISION OF REPRODUCTIVE & UROLOGIC DRUG  
PRODUCTS (HFD-580)**

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<b>V. METHODS VALIDATION .....</b>	<b>79</b>
<b>VI. LABELING.....</b>	<b>80</b>
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# Chemistry Review Data Sheet

1. NDA 21-488
2. REVIEW # 1
3. REVIEW DATE: 10-FEB-2003(revised)
4. REVIEWER: Swapan K. De
5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

13-APR-2002

Amendment #003

15-NOV-2002

Amendment #006

14-JAN-2003

Amendment #007

24-JAN-2003

Amendment #008

27-JAN-2003

Amendment #010

07-FEB-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Atrix Laboratories, Inc.

Address: 2579 Midpoint Drive  
Fort Collins, CO 80525-4417

Representative: Johanna J. Matz

Telephone: (970) 482-5868

## Chemistry Review Data Sheet

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ELIGARD™ 30 mg  
 b) Non-Proprietary Name (USAN): Leuprolide acetate for Injectable suspension  
 c) Code Name/# (ONDC only): N/A  
 d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
  - Submission Priority: S

## 9. LEGAL BASIS FOR SUBMISSION: N/A

## 10. PHARMACOL. CATEGORY: Palliative treatment of prostate cancer

## 11. DOSAGE FORM: Injectable suspension

## 13. ROUTE OF ADMINISTRATION: Subcutaneous

## 12. STRENGTH/POTENCY: 30 mg leuprolide acetate

14. Rx/OTC DISPENSED:  Rx  OTC

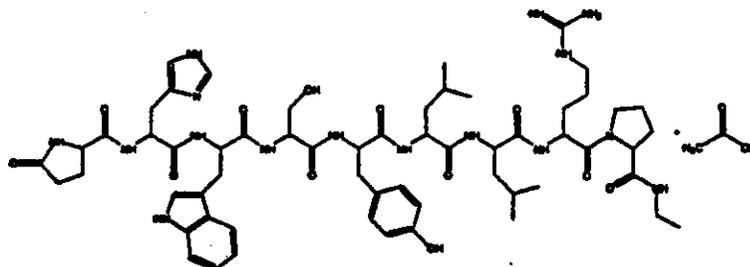
## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note23]:

- SPOTS product – Form Completed  
 Not a SPOTS product  
 Not a SPOTS product

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

Chemical names: 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

## Chemical Structure:



## Chemistry Review Data Sheet

Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide acetate

Molecular formula:  $C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$ 

Relative molecular mass: 1269.48 Daltons (Leuprolide Monoacetate)

## 17. RELATED/SUPPORTING DOCUMENTS:

## A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
-	II	/		3	Adequate	01/17/2000	Reviewed by S.K.De
-	II			3	Adequate	11/29/01	Reviewed by S.K.De
-	II			1	Adequate	1/8/03	Reviewed by S.K.De
-	II			3	Adequate	06/10/02	Reviewed by S.K.De
-	II			3	Adequate	1/03/02	Reviewed by S.K.De
-	III			3	Adequate	12/12/01	Reviewed by S.K.De
-	III			3	Adequate	2/3/00	Reviewed by

**Chemistry Review Data Sheet**

				R. Puttagunta
-	III		3	Adequate 1/10/01 Reviewed By J.D. Vidra
-	III		1	Adequate 1/28/03 Reviewed by S.K.De
-	III		3	Adequate 7/14/00 Reviewed By Young-de Lu
-	III		3	Adequate 2/17/98 Reviewed by E.G.Pappas

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

1 - DMF Reviewed.

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

2 - Type 1 DMF

3 - Reviewed previously and no revision since last review

4 - Sufficient information in application

5 - Authority to reference not granted

6 - DMF not available

7 - Other (explain under "Comments")

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

B. Other Documents: IND

**CHEMISTRY REVIEW**

## Chemistry Review Data Sheet

## 18. STATUS:

## ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	10-FEB-2003	Office of Compliance
Pharm/Tox	Adequate	11-JUN-2002	Krishan Raheja, Ph.D., DVM
Biopharm	Adequate	04-FEB-2003	Al-Habet Sayed, Ph.D.
LNC	N/A		
Methods Validation	Will be initiated		N/A
OPDRA	Adequate	14-AUG-2002	Hye-Joo Kim, Pharmacist.
EA	Categorical exclusion granted	14-JAN-2002	Swapan K. De, Ph.D.
Microbiology	Adequate	12-DEC-2002	Stephen Langille, Ph.D.

The application submission(s) covered by this review was taken in the date order of receipt.  Yes  No If no, explain reason(s) below:



# The Chemistry Review for NDA 21-488

## The Executive Summary

### I. Recommendations

- A. From chemistry, manufacturing, and controls point of view, this NDA may be approved.

### II. Summary of Chemistry Assessments

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

**Dosage form:** Injectable suspension  
**Strength:** 30 mg Leuprolide acetate  
**Route of Administration:** Subcutaneous

#### **Description:**

The drug product, ELIGARD™, 30 mg is a polymeric matrix formulation and consists of a two syringe mixing system, a 20 gauge 5/8-inch needle, and a silica or silica gel desiccant pouch to control moisture uptake. One syringe (Syringe A) contains the ATRIGEL Delivery System. This delivery system consists of — g of a sterile, polymeric delivery system solution of —% 75:25 Poly(DL lactide-co-glycolide) (PLG) and —% N-methyl-2-pyrrolidone (NMP). The other syringe (Syringe B) contains 35.8 mg of \_\_\_\_\_ leuprolide acetate.

These two syringe assemblies are manufactured at separate locations. The ATRIGEL® Delivery System (75:25 PLGH and NMP; Syringe A) is compounded, filled into syringes, and pouched at Atrix Laboratories Inc. in Fort Collins, CO. This subassembly is then \_\_\_\_\_

acetate is \_\_\_\_\_ An aqueous solution of leuprolide \_\_\_\_\_ in syringes

(Syringe B), and pouched at \_\_\_\_\_

The final assembly occurs at Atrix Laboratories Inc., in Ft. Collins, CO and consists of a large foil pouch containing two pouched sterile assemblies with the sterile needle and the desiccant.

The quality is controlled by tests of both parts of the drug product, Syringe A and Syringe B.

Syringe A tests include color, appearance, polymer identification (by NMR), polymer molecular weight, water content, sterility (USP <71>) and endotoxin (USP <85>). Syringe B tests include color, appearance, identification \_\_\_\_\_, related substances \_\_\_\_\_ sterility (USP <71>) and endotoxin (USP <85>). Furthermore, the reconstituted product is released by regulatory specifications and is controlled by tests that include color, appearance, polydispersity, leuprolide acetate content and drug release.

The primary packaging of the two syringes that constitute the drug product are performed separately and individually packaged. The ATRIGEL Delivery System is filled into \_\_\_\_\_ mL \_\_\_\_\_ syringes

Executive Summary Section

rod is \_\_\_\_\_ (Syringe A). \_\_\_\_\_ cover. The plunger tip is \_\_\_\_\_ and the plunger

The Syringe B is constructed of a \_\_\_\_\_ with the syringe tip cap and the plunger tip composed of \_\_\_\_\_. A second plunger tip behind the primary plunger tip is incorporated to ensure a clear zone for the primary tip to travel during product mixing. A \_\_\_\_\_ is installed to assist with injection. The assembled unit is then packaged in \_\_\_\_\_ pouch

Both \_\_\_\_\_ pouches are then placed together in a larger pouch with a sterile 20-gauge 5/8-inch needle and a desiccant pouch \_\_\_\_\_ to enclose all the components. The required DMF's (DMF \_\_\_\_\_ DMF \_\_\_\_\_ and DMF \_\_\_\_\_ for the packaging components are found adequate. From Microbiologist's point of view, container/closure integrity is deemed satisfactory.

Based on the stability data provided, an 18-month expiry date is granted. The tradename, ELIGARD™, 30 mg has been accepted by DMETS, and adequate chemistry information is presented in the labeling and labels of the primary as well as the secondary packaging.

Leuprolide is a synthetic analog of the hormone, leuteinizing hormone releasing hormone (LH-RH). Leuprolide is a nonapeptide and acts as an agonist of naturally-occurring gonadotropin releasing hormone (GnRH). After a short period of up-regulation of the steroidogenesis, sustained leuprolide treatment desensitized anterior pituitary and results in low steroid blood levels. The analog possesses greater potency than the natural hormone.

Leuprolide acetate is manufactured and supplied by three different suppliers: \_\_\_\_\_

\_\_\_\_\_ synthesizes leuprolide acetate with \_\_\_\_\_

On the contrary, \_\_\_\_\_

The major differences in the impurity profile among drug substance batches are:

The sponsor has provided data to show the comparability of the drug substances among the three suppliers and they are deemed satisfactory. Toxicology and clinical studies qualifies the above impurities and is deemed acceptable.

Leuprolide has the chemical designation 5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt). It is white to off-white powder, soluble in water and acetic acid and hygroscopic in nature. The characterization and proof of structure of leuprolide acetate has been determined by \_\_\_\_\_

The tests performed on the starting materials \_\_\_\_\_ has been provided in the respective DMF from \_\_\_\_\_ and are adequate.

## Executive Summary Section

The retest period for leuprolide acetate is determined by the suppliers. The retest period for the leuprolide acetate obtained from \_\_\_\_\_ is \_\_\_\_\_ month when stored at 2-8°C. The retest period for the leuprolide acetate obtained from \_\_\_\_\_ is 24 months when stored at -20°C. The \_\_\_\_\_ product can also be stored at \_\_\_\_\_ to qualify for a \_\_\_\_\_ month retest period.

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

Four month ELIGARD™, 30 mg is supplied as two prefilled sterile syringes and a sterile needle. The product should come to room temperature before use. Prior to administration of the drug product the two syringes are coupled and the contents of the two syringes are mixed by passing the contents from syringe to syringe. It should be mixed for approximately 45 seconds to achieve a uniform suspension. When thoroughly mixed, the suspension will appear as a light tan to tan color. Following mixing, the contents are transferred into syringe B and the syringes are decoupled. A sterile needle is then affixed to the syringe B for patient injection. The total deliverable injection weight is 500 mg including 30 mg of leuprolide acetate. Once mixed the drug product should be administered within 30 minutes.

The drug product is administered subcutaneously and provides continuous release of leuprolide for four months.

The drug product has an 18-month expiry date, when stored at 2-8°C.

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

The sponsor has provided adequate data to demonstrate product quality. Therefore, from a CMC point of view, the data support approval of the NDA.

The sponsor submitted the original submission of this NDA following their other approved products (ELIGARD™, 7.5 mg and ELIGARD™, 22.5 mg) and thus, had minor deficiencies. These deficiencies were sent to the sponsor on January 9, 2003. The sponsor's submission of amendment #006 (14-Jan-2003) includes the response to the deficiencies and was found adequate. Amendment #003 (15-NOV-2002) includes the updated information on stability (to provide more stability data), revised specifications and photostability report (based on ELIGARD™, 7.5 mg and ELIGARD™, 22.5 mg products). Amendment #008 dated 29 January, 2003 includes response on labeling comments sent to the sponsor on January 27, 2003. Some of the major issues and their resolution for this NDA include submission of information to show the comparability among the leuprolide acetate obtained from three suppliers \_\_\_\_\_

\_\_\_\_\_ and addition of stability data on water and polydispersity of the drug product. In response to an IR letter dated January 21, 2003 the sponsor implemented the changes for the post-approval stability commitment and commits to provide method validation packages with samples (amendment #007, dated 24 January, 2003). On February 10, 2003 (amendment #010) the sponsor notified the Agency that they are withdrawing \_\_\_\_\_ of the NDA due to "withhold" recommendation from the district office (Los Angeles) on the site. Following withdrawal of \_\_\_\_\_ the Office of

## Executive Summary Section

Compliance issued an acceptable recommendation on 10 February, 2003. Thus, considering the provided information, this NDA is deemed satisfactory regarding CMC and may be approved.

**III. Administrative****A. Reviewer's Signature****B. Endorsement Block**

HFD-580/S. K. De, Ph.D.  
HFD-580/D. T. Lin, Ph.D.  
HFD-580/A. Reddy

**C. CC Block**

HFD-580/Division File/NDA 21-488  
HFD-580/S. K. De, Ph.D.  
HFD-580/D. T. Lin, Ph.D.  
HFD-580/A. Reddy

Redacted 74

pages of trade

secret and/or

confidential

commercial

information

**Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg**  
**Atrix Laboratories, Inc.**  
**NDA 21-488**

**Environmental Assessment**

A categorical exclusion was granted on 2.14.03 for this NDA application.

OK 2/11/03

# CHEMISTRY REVIEW

## Chemistry Assessment Section

10-FEB-2003

FDA CDER RES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

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Application: NDA 21488/000 Action Goal:  
Stamp: 16-APR-2002 District Goal: 16-DEC-2002  
Regulatory Due: 16-FEB-2003 Brand Name: ELIGARD (LEUPROLIDE  
Applicant: ATRIX Estab. Name: ACETATE) 30MG INJ SUS  
2579 MIDPOINT DR Generic Name: LEUPROLIDE ACETATE  
FORT COLLINS, CO 80525  
Priority: Dosage Form: (INJECTION)  
Org Code: 580 Strength: 30 MG

Application Comment: NDA 21-488 IS FOR THE PALLIATIVE TREATMENT OF PROSTATE CANCER.  
THE DRUG PRODUCT IS ELIGARD 30 MG, CONTAIN LEUPROLIDE ACETATE AS  
API AND A SUSTAINED RELEASE FORMULATION. THE PRODUCT WILL BE  
ADMINISTERED SUBCUTANEOUSLY. (on 31-MAY-2002 by S. DE ( ) )

FDA Contacts: A. REDDY (HFD-580) 301-827-7514 , Project Manager  
S. DE , Review Chemist  
D. LIN (HFD-580) 301-827-4230 , Team Leader

Overall Recommendation: ACCEPTABLE on 10-FEB-2003 by J. D AMBROGIO (HFD-322) 301-827-9054

Establishment: CFW 1722158 FEI 3001237858  
ATRIX LABORATORIES INC  
2579 MIDPOINT DR  
FORT COLLINS, CO 80525

DMF No: AADA:  
Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile: CTL OAI Status: NONE

Estab. Comment: THE FACILITY WILL PERFORM THE CONTROL TESTING OF THE API AND THE  
EXCIPIENTS. IT WILL ALSO PERFORM THE IN PROCESS TESTING AS WELL AS THE  
FINAL DRUG PRODUCT LABELING AND POUCHING. FURTHERMORE, THE FACILITY  
WILL PERFORM THE CONSTITUTED PRODUCT TESTING. (on 31-MAY-2002 by S. DE  
( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
SUBMITTED TO DO	03-JUN-2002	GMP			FERGUSONS
ASSIGNED INSPECTION T	04-JUN-2002	GMP			WSHERER
INSPECTION SCHEDULED	04-JUN-2002		23-AUG-2002		WSHERER
DO RECOMMENDATION	24-JAN-2003			ACCEPTABLE	ESMITHI
OC RECOMMENDATION	24-JAN-2003			INSPECTION	
				ACCEPTABLE	FERGUSONS
INSPECTION PERFORMED	10-FEB-2003		22-OCT-2002	DISTRICT RECOMMENDATION	WSHERER

See Endorsement Text for summary.

# CHEMISTRY REVIEW

## Chemistry Assessment Section

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

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Establishment: FEI 1000153019

DMF No: \_\_\_\_\_ AADA:  
Responsibilities:

Profile: CBN OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
OC RECOMMENDATION	31-MAY-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFM FEI 1000512361

DMF No: \_\_\_\_\_ AADA:  
Responsibilities:

Profile: SVL OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
SUBMITTED TO DO	03-JUN-2002	10D			FERGUSONS
ASSIGNED INSPECTION T	03-JUN-2002	GMP			NGARCIAI
INSPECTION SCHEDULED	09-SEP-2002		15-OCT-2002		GARCIAH
DO RECOMMENDATION	01-OCT-2002			ACCEPTABLE BASED ON FILE REVIEW PROCESS	NGARCIAI
BASED ON EI OF 4/2002 COVERING					
OC RECOMMENDATION	01-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: FEI 1450253

# CHEMISTRY REVIEW

## Chemistry Assessment Section

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FDA CDER HES  
ESTABLISHMENT EVALUATION REQUEST  
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DMF No:  
Responsibilities:

AAAD:

Profile: RSP

OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
OC RECOMMENDATION	03-JUN-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

FBI 2245304

DMF No:  
Responsibilities:

AAAD:

Profile: RSP

OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
OC RECOMMENDATION	03-JUN-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

FBI 1940521

DMF No:  
Responsibilities:

AAAD:

Profile: CSS

OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES



# CHEMISTRY REVIEW



## Chemistry Assessment Section

10-FEB-2003

FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
DETAIL REPORT

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SUBMITTED TO DO 31-MAY-2002 GMP  
DO RECOMMENDATION 10-JUN-2002 ACCEPTABLE  
BASED ON FILE REVIEW  
FERGUSONS  
GBERRYMA

A GMP/PRE-APPROVAL INSPECTION WAS CONDUCTED 2/11-15/02 AND COVERED NDA 21-379 FOR  
LEUPROLIDE ACETATE INJ UNDER PROFILE CLASS "CSN". THE INSPECTION USED THE SYSTEMS  
APPROACH AND COVERED THE QUALITY SYSTEM AND THE PRODUCTION SYSTEM. NO FDA 483 WAS ISSUED  
AND THE INSPECTION FOUND THE FIRM IN SUBSTANTIAL COMPLIANCE WITH cGMPs. KAN-DO  
RECOMMENDS APPROVAL OF THIS APPLICATION UNDER PROFILE CLASS CSN.

OC RECOMMENDATION 11-JUN-2002 ACCEPTABLE  
DISTRICT RECOMMENDATION  
DAMBROGIOJ

Establishment:

FBI

DMP No:  
Responsibilities:

AADA:

Profile:

CTL

OAI Status: NONE

Estab. Comment:

(on 31-MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
OC RECOMMENDATION	03-JUN-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment:

FBI 1000139876

DMP No:  
Responsibilities:

AADA:

Profile:

CTL

OAI Status: NONE

Estab. Comment:

MAY-2002 by S. DE ( ) )

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	31-MAY-2002				DES
OC RECOMMENDATION	03-JUN-2002			ACCEPTABLE BASED ON PROFILE	FERGUSONS

**Eligard™ (leuprolide acetate for injectable suspension) 30.0 mg**  
**Atrix Laboratories, Inc.**  
**NDA 21-488**

**Methods Validation**

Three copies of the Methods Validation section have been requested.

*aw 2/11/03*