

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER  
21-379**

**ADMINISTRATIVE DOCUMENTS**

**2.5. Patent Information**

The undersigned declares that the patents listed below in Table 4 cover the formulation, composition and/or method of use of LA-2550 22.5 mg. This product is the subject of this application for which approval is being sought:

*Richard L. Dunn*

Richard L. Dunn, PhD  
Senior Vice President, Drug Delivery

<b>Table 4. List of LA-2550 22.5 mg Patents</b>		
<b>Patent Number</b>	<b>Description</b>	<b>Expiration</b>
B1 4,938,763	Methods for forming an implant in-situ in the body using a syringeable liquid biodegradable polymer system.	10-03-2008
5,278,201	Compositions for forming a solid biodegradable implant in-situ in the body using a liquid polymer system.	1-11-2011
5,324,519	Compositions and methods for forming a solid or gelatinous microporous implant in-situ in the body using a liquid thermoplastic or thermosetting biodegradable polymer system.	10-20-2011
5,599,552	Compositions and methods for forming a solid microporous implant in-situ in the body using a liquid thermoplastic or thermosetting biodegradable polymer system.	2-04-2014
5,733,950	Compositions and methods for forming a solid biodegradable implant in-situ in the body using a flowable thermoplastic polymer system.	10-03-2008
5,739,176	Compositions and methods for forming a solid biodegradable implant in-situ in the body using a liquid thermoplastic biodegradable polymer system.	10-03-2008

EXCLUSIVITY SUMMARY for NDA # 21-379 SUPPL #  
Trade Name Eligard 22.5 mg  
Generic Name leuprolide acetate for injectable suspension  
Applicant Name Atrix Laboratories, Inc.  
HFD- 580  
Approval Date June 24, 2002

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES /  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type (SE1, SE2, etc.)?

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /  / NO /  /

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /X/ NO /\_\_\_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /\_\_\_/ NO /X/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /\_\_\_/ NO /X/

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

3. Is this drug product or indication a DESI upgrade?

YES /\_\_\_/ NO /X/

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /\_\_\_/ NO /\_\_\_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /\_X\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /\_X\_/      NO /\_\_\_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /\_\_\_/      NO /\_X\_/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /\_\_\_/      NO /\_\_\_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /\_\_\_/ NO /\_X\_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # AGL 9802

Investigation #2, Study # AGL 9904

Investigation #3, Study # AGL 9909

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /\_\_\_/ NO /\_X\_/

Investigation #2 YES /\_\_\_/ NO /\_X\_/

Investigation #3 YES /\_\_\_/ NO /\_X\_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1                      YES /\_\_\_/                      NO /\_X\_/

Investigation #2                      YES /\_\_\_/                      NO /\_X\_/

Investigation #3                      YES /\_\_\_/                      NO /\_X\_/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

NDA # \_\_\_\_\_ Study #

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation # 1, Study # AGL 9802

Investigation # 2, Study # AGL9802

Investigation # 3, Study # AGL 904

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND #      YES /\_X\_/ ! NO /\_\_\_/ Explain:

!  
!  
!  
!

Investigation #2 !  
!  
IND #      YES /\_X\_/ ! NO /\_\_\_/ Explain:

!  
!  
!  
!

Investigation #3 !  
!  
IND #      YES /\_X\_/ ! NO /\_\_\_/ Explain:

!  
!  
!  
!  
!

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES /\_\_\_/ Explain \_\_\_\_\_ ! NO /\_\_\_/ Explain \_\_\_\_\_  
! \_\_\_\_\_ ! \_\_\_\_\_  
! \_\_\_\_\_ ! \_\_\_\_\_  
!

_____	!	_____
	!	
Investigation #2	!	
	!	
YES /___/ Explain _____	!	NO /___/ Explain _____
	!	
_____	!	_____
	!	
_____	!	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /\_\_\_/                      NO /\_X\_/

If yes, explain: \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

/S/

<u>Archana Reddy, M.P.H.</u>	<u>07/23/02</u>
Signature of Preparer	Date
Title: <u>Project Manager</u>	

/S/

<u>Daniel Shames, M.D.</u>	<u>7/24/02</u>
Signature of Office or Division Director	Date

CC:

Archival NDA 21-379

HFD-580/Division File

HFD- 580/Reddy

HFD-093/Mary Ann Holovac

HFD-104/PEDS/T.Crescenzi

Form OGD-011347

Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**2.6. Claimed Exclusivity 314.50 j**

LA-2550 22.5 mg is a unique and novel drug product for sustained release of leuprolide acetate intended as a palliative treatment for prostate cancer. Although leuprolide acetate is a well characterized drug, the safety and efficacy of LA-2550 22.5 mg is dependent on the ATRIGEL® Delivery System which differs from the delivery systems utilized in currently approved leuprolide acetate products. The new clinical investigation reported in this application (AGL9909) is essential to the approval of LA-2550 22.5 mg and was conducted by Atrix Laboratories, Inc. Atrix Laboratories, Inc. was named as the sponsor on the Form FDA-1571 submitted to IND for this study. To the best of Atrix's knowledge, no other clinical studies have been performed using 22.5 mg of leuprolide acetate in the ATRIGEL® Delivery System. Therefore, pursuant to FDCA §505(c)(3)(D)(iii) and 21 CFR §314.108(b)(4), Atrix is claiming marketing exclusivity for three years following the approval date of the LA-2550 22.5 mg.

**2.7. Financial Certification or Disclosure Statement (Part 54)**

APPEARS THIS WAY  
ON ORIGINAL

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this page is the manifestation of the electronic signature.**  
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/s/

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Daniel A. Shames  
7/24/02 05:10:08 PM

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 21-379

Supplement Type (e.g. SE5):

Supplement Number:

Stamp Date: September 26, 2001

Action Date: July 24, 2002

HFD Trade and generic names/dosage form: Eligard 22.5 mg  
(leuprolide acetate for injectable suspension)

Applicant: Atrix Laboratories, Inc. Therapeutic Class: 3s

Indication(s) previously approved: Palliative treatment of advanced prostate cancer

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Palliative treatment of advanced prostate cancer

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see*

*Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_ kg \_\_\_\_ mo. \_\_\_\_ yr. \_\_\_\_ Tanner Stage \_\_\_\_

Max \_\_\_\_ kg \_\_\_\_ mo. \_\_\_\_ yr. \_\_\_\_ Tanner Stage \_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/ yy): \_\_\_\_\_

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_ kg \_\_\_\_ mo. \_\_\_\_ yr. \_\_\_\_ Tanner Stage \_\_\_\_

Max \_\_\_\_ kg \_\_\_\_ mo. \_\_\_\_ yr. \_\_\_\_ Tanner Stage \_\_\_\_

Comments:

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_ Archana Reddy, M.P.H. \_\_\_\_

Regulatory Project Manager

cc: NDA

HFD-960/ Terrie Crescenzi

(revised 1-18-02)

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301/594-7337**

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this page is the manifestation of the electronic signature.**  
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/s/

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Daniel A. Shames  
7/24/02 09:11:13 AM

**2.8. Debarment Certification**

Atrix Laboratories, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

**2.9. Pediatric Labeling Waiver**

Atrix is requesting a full waiver from the pediatric use labeling information required under CFR §314.55 for LA-2550 22.5 mg in the palliative treatment of prostate cancer. Atrix certifies that LA-2550 22.5 mg does not represent a meaningful therapeutic benefit over existing treatment for pediatric patients and is not likely to be used in a substantial number of pediatric patients since prostate cancer is not a pediatric disease. Moreover, the established pharmacology of leuprolide acetate indicates that the drug product would be neither effective nor safe in all pediatric age groups at the proposed dose of 22.5 mg.

**2.10. Agency's Comment Letter Dated March 10, 2000**

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-379

### Supervisory Medical Officer's Memorandum

**Date submitted:** September 25, 2001

**Date received:** September 27, 2001

**Memo draft completed:** July 15, 2002

**Drug product (tradename):** ELIGARD™ 22.5 mg

**Drug product (non-proprietary):** leuprolide acetate for injection

**Dose:** 22.5 mg every 3 months

**Route:** subcutaneous injection

**Indication:** palliative treatment of advanced prostate cancer

**Sponsor:** Atrix Laboratories, Fort Collins, CO

**Related INDs/NDAs:** IND # — (3-month formulation) and IND # — and NDA 21-343 (1-month formulation).

#### I. Executive summary:

The purpose of this medical team leader's memo is to provide a regulatory recommendation for NDA 21-379. I recommend that ELIGARD 22.5 mg should be approved for the indication of palliative treatment of advanced prostate cancer *pending successful negotiation of a few minor revisions to the package insert and to the Syringe A labeling.*

Upon resolution of these matters (which I do anticipate occurring), this team leader will write a brief "wrap-up" memorandum for this NDA.

#### II. Clinical and regulatory background:

ELIGARD 22.5 mg is the second drug product in this sponsor's "leuprolide product line". ELIGARD 7.5 mg, a novel subcutaneous formulation of leuprolide intended for palliative treatment of men with advanced, hormonally-sensitive prostate cancer, was approved under Atrix' NDA 21-343 in January, 2002.

The 1-month product was launched in the United States on May 28, 2002. Approval of the 3-month formulation would allow prescribers the option of using ELIGARD in a manner similar to TAP's Lupron Depot® and AstraZeneca's Zoladex®; specifically, patients will be started on the 1-month formulation and then will continue treatment with the 3 or 4-month formulation. It should be noted that Lupron Depot® is an intramuscular injection and Zoladex® is a subcutaneous "implant". Atrix contends that ELIGARD may be an improvement upon these formulations since it is a subcutaneous suspension able to be delivered with a fine-gauge, fairly short needle. The one-month and three-month ELIGARD formulations differ primarily in the ratio of lactide to glycolide subunits and the molecular weights of their co-polymers.

Leuprolide is a leutinizing hormone releasing hormone analogue (LHRH) that acts by initially stimulating the production of LH from the pituitary and later downregulating this production. Ultimately, testosterone secretion from the testes is reduced to “castrate levels”. Currently, the Division accepts a total serum testosterone concentration of less than or equal to 50 ng/dL as evidence of medical “castration”. The Division uses this surrogate marker to determine efficacy for these types of products.

Given the extensive clinical experience with leuprolide in the treatment of prostate cancer, the Division recommends that clinical drug development programs for this type of product (for this indication) may consist of a single Phase 3 trial. This trial usually consists of approximately 100 to 120 patients and is supported by a small pharmacokinetics study or by a pharmacokinetic “sub-study” within the body of the larger protocol. Atrix conducted their clinical development program for ELIGARD 3-month in accordance with such guidance from DRUDP. In that regard, Phase 3 protocol AGL 9909 was discussed at an End-of-Phase 2 (EOP2) meeting dated March 10, 2000.

The clinical results submitted included data from this single, multicenter, open-label, Phase 3 study (AGL 9909) in approximately 117 men with prostate cancer treated for 6 months (two dosage administrations), from a pharmacokinetic “sub-study” conducted in 22 patients, and from the previous study reports submitted for ELIGARD 7.5 mg.

### **III. Clinical results in brief:**

#### **1. Efficacy**

Study AGL9909 enrolled 117 patients. The protocol called for the administration of two doses of 22.5 mg to each patient, separated by an interval of 3 months.

Of these 117 patients, 115 (98%) achieved castrate T levels by Day 28. One patient (#1801) was inappropriately administered an inadequate dose of study medication and never achieved castrate T level. He was withdrawn from the study on Day 74. The other patient achieved castrate T level on Day 35, not prior to or on Day 28. Therefore, 115 of 116 patients who received the appropriate per-protocol dose (99%) achieved castrate T levels by Day 28, and 116 of these 116 patients (100%) achieved castrate T levels by Day 35.

Of the 116 patients who suppressed to castrate levels, ALL remained suppressed while on study EXCEPT for one patient (#1710). This particular patient suppressed to a T level below 50 ng/dL on Day 21 and experienced breakthrough on Day 49 (T was measured as 112 ng/dL on that day and subsequently rose to a maximum of 557 ng/dL on Day 85, the day after his second injection). This patient’s T level then declined to 27 ng/dL on Day 98 and remained suppressed thereafter.

The total number of patients who actually completed the entire trial on a per-protocol basis was 111. In addition to Patient #1801 who was described above (inappropriately

low dose administered), another five patients withdrew prior to completing the trial. These are herein described in detail:

1. Patient #3401 was withdrawn due to an adverse event on Day 155. All his previous T levels were castrate including the final T drawn on Day 154. He was withdrawn due to exacerbation of pre-existing COPD/CHF.
2. Patient #0102 withdrew of his own volition on Day 71. All his previous T levels were castrate including the final T drawn on Day 63. He described transportation problems that precluded further participation.
3. Patient #2002 withdrew of his own volition on Day 134. All his previous T levels were castrate including the final T drawn on Day 126. He moved his residence some distance away from the study center.
4. Patient #2402 was withdrawn due to clinical disease progression on Day 64. He described an increase in bone pain on Day 14. All his previous T levels were castrate including the final T drawn on Day 56.
5. Patient #2602 was withdrawn due to clinical disease progression on Day 78. Of his own volition, this patient sought a second opinion at the \_\_\_\_\_ shortly after his first injection. \_\_\_\_\_ advised the patient to undergo pelvic radiotherapy for “locally recurrent” disease. The site investigator decided to withdraw this patient. All his previous T levels were castrate including the final T drawn on Day 70.

Therefore, none of the premature discontinuations were related to failure of the formulation to induce or maintain medical castration.

The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.9 days (19.7 days in the pK sub-study of 22 patients).

There was no evidence of acute rises in the serum testosterone upon repeated dosing (the so-called “acute-on-chronic” phenomenon).

The sponsor also analyzed the results of AGL9909 using a serum total T concentration cut-point for “castration” of 20 ng/dL (rather than 50 ng/dL). Of 117 original patients, 98 patients (84%) achieved this lower threshold by Day 28 and 108 patients (92%) achieved this level by Day 42. After Day 42, the proportion of patients with T <20 ng/dL remained fairly stable at each subsequent visit with a total of 104 of 111 completers (94%) achieving this level. While the clinical data from this NDA confirms these findings, it is not clear that 20 ng/dL represents any clinically relevant improvement over 50 ng/dL. Nor is it clear whether similar results would be obtained for the currently approved products if such post-hoc data analyses were conducted. Therefore, this claim will not be allowed in labeling.

## 2. Safety

Medical castration by GnRH analogue is usually accompanied by an initial rise in serum T level for 1-2 weeks followed by a decline to castrate levels in about one month. This initial rise can occasionally cause a “flare” phenomenon whereby the patient might experience transient worsening of symptoms (bone pain, obstructive urinary symptoms). In rare instances, ureteral obstruction and spinal cord compression have been reported.

While no “flares” were reported in this NDA, this potential adverse reaction is a labeled warning for all drugs of this class.

GnRH analogues can also potentially induce antibody formation and hypersensitivity reactions. These were not reported in this NDA but they are also labeled for the class.

In this specific NDA, for this novel 3-month leuprolide preparation, such known drug-class adverse events as hot flashes, fatigue/lethargy/weakness, urinary frequency, testicular atrophy/pain, diminished libido, and impotence were reported. The incidences and severity of these events were generally in line with that expected for the class.

Additionally, since ELIGARD 22.5 mg is a novel subcutaneous preparation, the sponsor conducted extensive injection site assessments. While burning (22% of all injections), stinging (6% of all injections), pain (3.5% of all injections), bruising (1.7% of all injections), erythema (<1% of all injections) and itching (0.4% of all injections) at the injection site were commonly reported adverse events, the majority were graded as mild in severity. The majority of reports of burning, stinging and pain were very short in duration (e.g. minutes). There were rare reports of mild pain lasting for up to two days. In the two patients with localized erythema, this event resolved within 6 days. In the single patient reporting itching, the event resolved in seven days. All of the reported events resolved spontaneously without sequelae. No patient was discontinued for a local adverse event.

#### **IV. Relevant issues from other disciplines**

##### **1. Chemistry**

The draft chemistry review provided to me by Dr. De recommends the following:

*“From chemistry, manufacturing and controls point of view, this NDA may be approved.”*

Here, I believe it is appropriate to note that the drug product will be supplied in two separate syringes. Syringe A will contain the Atrigel Delivery System. This delivery system consists of 0.44 grams of a sterile polymer (75:25 lactide-co-glycolide [PLG] and 1% N-methyl-2-pyrrolidone [NMP]). Syringe B will contain 28.2 milligrams (1%) of lyophilized leuprolide acetate. Prior to drug administration, these syringes are connected and the contents are mixed by pushing the contents back and forth for 45 seconds using the syringe plungers. The mixed suspension is then injected into the patient, delivering a leuprolide dose of 22.5 milligrams.

The relevant chemistry sections of the label were reviewed by Dr. De and found to be generally acceptable. Very minor revisions (e.g. changing the total amount delivered from 375 mg to 37.5 mg) were made and sent to the sponsor. At this time, we await the sponsor’s reply regarding final labeling.

All FDA-proposed modifications to the container and carton labeling have been made by sponsor except for one. The sponsor believes that the syringe A label and syringe A pouch label should \_\_\_\_\_ and that it should not contain the statement: \_\_\_\_\_

At this time, the Division believes strongly that these labels should contain the latter statement. This negotiation is ongoing.

The manufacturing sites were deemed acceptable by the Office of Compliance.

The microbiology consultant ultimately recommended approval (see Dr. Languille's final review dated June 17, 2002).

The major chemistry review issues have been fully discussed with sponsor and all have been acceptably resolved except one (Item #5 below). These included:

1. Stability: The sponsor accepted an initial 18-month expiration date for the drug product. \_\_\_\_\_
2. Residual solvents: The sponsor agreed to add a residual solvent test, specifications, and acceptance criterion for residual solvents for PLG.
3. Acceptance criteria for NMP: The sponsor agreed to change the upper end of the acceptance criteria for NMP.
4. Polydispersity: A test for "polydispersity" has been added and will also constitute a specification.
5. In-vitro release test: As described for their previous NDA (21-343), the sponsor's release test method was revised during stability testing of the primary batches. Thus there has been little experience with the method. The results from the recent primary stability batches were not consistent with the results from the clinical batches. The sponsor initially addressed this inconsistency by widening the test acceptance criteria. This was not acceptable to the Division. DRUDP and sponsor discussed tightening one of the acceptance criteria for the in vitro release test during teleconferences on July 1 and July 11, 2002. Written agreement to the FDA-proposed acceptance criteria for the 18-hour sampling timepoint was received on July 12, 2002.

## 2. Clinical Pharmacology

OCPB found the submission "acceptable". Minor labeling comments have been conveyed to the sponsor and their response to these is pending. There were no major review issues noted in the written review and none were brought up at the time of the OCPB Briefing.

In her review, Dr. Kim noted that:

1. The pharmacokinetics and pharmacodynamics of leuprolide after each of two dose administrations were evaluated in a subset of 22 patients in AGL 9909. The procedures for these assessments were acceptable. She noted rapid absorption and 100% bioavailability.
2. The formulation used in AGL 9909 was identical to the to-be-marketed formulation.
3. No acute-on-chronic responses were seen in these 22 patients after the second dose administration.
4. Drug exposure tended to be lower in patients of larger weights, but this had no clinical impact on efficacy.
5. There were two different lots used in AGL 9909. The leuprolide acetate used for these lots was from two different manufacturers \_\_\_\_\_ and these lots delivered the same mass of leuprolide and polymer. She notes that “both formulations used in the Phase 3 study (AGL 9909) were identical.”
6. The DRUDP-proposed acceptance criterion for the 18-hour timepoint for the in-vitro release test is \_\_\_\_\_ %.

### 3. Pharmacology/toxicology

Pharmacology recommended approval of ELIGARD 22.5 mg based upon the

“the review and recommended approval of NDA 21-343 for Leuprogel one-month formulation for the palliative treatment of advanced prostate cancer.”

The reviewer noted that this 3-month formulation has the same components and the same intended use as the previous one-month formulation. NO new studies were reviewed within this submission.

Previously, the reviewer had noted that there was a long regulatory and clinical usage history for leuprolide and an acceptable review of the literature and the relevant DMF and toxicity studies for the excipient, N-methyl-2-pyrrolidone (NMP).

Along with PLG, NMP serves to prolong delivery of leuprolide via the Atrigel Delivery System for a duration of approximately one-month. NMP is approved as an excipient in the drug Atridox, which is used for the treatment of periodontal disease. In that formulation, NMP is delivered as a single dose of 450 mg. Under NDA 21-343, the reviewer commented that the daily dose of NMP from ELIGARD amounting to approximately \_\_\_\_\_ milligrams, an amount considered very low compared to doses used safely in toxicology and toxicokinetic studies. The daily NMP dose is not different in this 3-month formulation.

### 4. Biometrics

A brief review of the efficacy data-set for AGL9909 was conducted for this open-label trial by Biometrics. This review confirmed the sponsor’s presentation of the study

results. While the reviewer comments that the study results are completely descriptive, this is acknowledged and is consistent with guidance for conducting these sorts of trials.

#### 5. ODS

ODS consultation was obtained for purposes of tradename and container/carton safety review. There was no objection to the use of the proprietary name “ELIGARD 22.5 mg”.

ODS had no comments relevant to the actual package insert. However, there were several recommendations relevant to revising the carton and container labels.

1. As per ODS, the carton label was revised to make “22.5 mg every 3 months” more prominent.
2. As per ODS, the outer pouch label was also revised to make “22.5 mg every 3 months” more prominent.
3. ODS commented that the outer pouch label was confusing regarding the amount of ATRIGEL. It is true that the amount of ATRIGEL that is actually contained in Syringe A (440 mg) and the amount of ATRIGEL that is actually delivered (352.5 mg) do differ. While ODS has asked us to further clarify this difference on the outer pouch label, I do not think any further clarification of this issue on the pouch label is either possible or necessary.
4. As per ODS, the statement “for subcutaneous injection” was deleted from syringe A pouch label.
5. ODS recommends that the syringe B label contains the statement “For subcutaneous use” if space permits. Sponsor and chemistry do not believe that space permits. Therefore, this statement will not appear on this syringe label and I concur.
- 6.
7. ODS recommends that all inactive ingredients should appear on the syringe A label. The syringe A label is not sufficiently large to contain all inactive ingredients. I believe there is already sufficient information on the syringe and pouch labels.
8. ODS recommends that the proprietary name on the syringe A label (Eligard 22.5 mg) should be removed since the contents of that syringe are all inactive. As long as the syringe A label states that the contents contain the ATRIDOX delivery system and that syringe A does not contain active leuprolide, then I believe that “Eligard 22.5 mg” may remain at the top of the syringe label.

Therefore, I am of the opinion that all ODS container/carton comments have been sufficiently managed except one and that one (#6 above) is under active negotiation.

#### 6. DSI

Data on twenty (20) patients from one site from Pivotal Study AGL9909 was considered acceptable and useful in support of this NDA.

## 7. DDMAC

DDMAC labeling review was conducted for the previously submitted Atrix NDA 21-343 (ELIGARD 7.5 mg). Since the label for ELIGARD 22.5 mg mirrored the previous ELIGARD 7.5 mg label, a DDMAC review pre-approval was not considered necessary. All previous DDMAC comments were considered during labeling negotiations for this NDA.

## **V. Other relevant issues**

### 1. Financial Disclosure

There was no disclosure of financial interests that could bias the outcome of the trials.

### 2. Pediatrics

ELIGARD 22.5 mg will be indicated for the palliative treatment of advanced prostate cancer. A waiver for conducting pediatric studies is considered appropriate.

### 3. Phase 4 commitments

No Phase 4 commitments were requested and none are considered necessary.

## **VI. Medical team leader's summary statement**

Pending successful completion of labeling negotiation ELIGARD 22.5 mg is considered safe and effective for the palliative treatment of advanced prostate cancer and should be approved for marketing. It offers another option for patient care in these unfortunate patients.

/s/

Mark S. Hirsch M.D.  
Medical Team Leader  
Division of Reproductive and Urologic Drug Products  
Arch NDA 21-379  
cc: HFD-580/Div File  
HFD-580/DShames/ABatra/AReddy

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/s/

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Mark S. Hirsch  
7/14/02 05:13:03 PM  
MEDICAL OFFICER

Daniel A. Shames  
7/17/02 05:48:39 PM  
MEDICAL OFFICER

**MEMORANDUM****DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: October 17, 2001

From: Jeanine Best, M.S.N., R.N.  
Senior Regulatory Associate  
Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: NDA 21-379

I have reviewed the financial disclosure information submitted by Atrix Laboratories in support of their NDA 21-379 for LA-2550 22.5 mg (leuprolide acetate for injectable suspension).

One pivotal study was conducted to assess the safety and efficacy of LA-2550 22.5 mg (leuprolide acetate for injectable suspension). This product is indicated for the palliative treatment of advanced prostate cancer. The study number and the results of the review of financial disclosure documents is summarized below:

<b>Study Number/Title</b>	<b>Study Status</b>	<b>Financial Disclosure Review</b>
Study AGL9909 / "A Six-Month, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics, and Endocrine Efficacy of Monthly Doses of Two Doses of LA-2550 22.5 mg in Patients with Advanced Prostate Cancer"	Study Start: July 1, 2000  Study Complete: April 7, 2001	Appropriate documentation received, no financial disclosure submitted.

**Documents Reviewed:**

- FDA Form 3454, Certification: Financial Interests and Arrangements of Clinical Investigators
- Clinical Study Report

**Study AGL9909**

There were 95 principal and subinvestigators (investigators) at 26 sites in this trial, enrolling 117 patients. Three sites had subinvestigators (3 total) that left the employment of the site during the conduct of the study. These subinvestigators provided financial disclosure information at the study start; none had any disclosable information at the study start. Complete financial disclosure information was received for the remaining principal and subinvestigators; none had any disclosable information.

**Conclusion:**

Adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials.

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/s/

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Jeanine Best  
10/17/01 01:33:06 PM  
CSO

**Division of Reproductive and Urologic Drug Products (HFD-580)**

**ADMINISTRATIVE REVIEW OF APPLICATION**

**Application Number:** 21-379

**Name of Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Sponsor:** Atrix Laboratories, Inc.

**Material Reviewed:** NDA Submission

**Submission Date:** September 25, 2001

**Receipt Date:** September 26, 2001

**Filing Date:** November 25, 2001

**User-Fee Goal Date(s):** July 26, 2001 (10-Month)

**Proposed Indication:** Palliative treatment of advanced prostate cancer

**Other Background Information:** none

**Regulatory Project Manager Review**

**PART I: OVERALL FORMATTING<sup>a</sup> and REGULATORY REQUIREMENTS**

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Cover Letter (original signature)	X		Vol. 1.1
2. Form FDA 356h (original signature)	X		Vol. 1.1, pgs. 2-3
a. Reference to DMF(s) & Other Applications	X		Vol. 1.1, pgs. 4-5
3. Patent information & certification	X		Vol. 1.1, pg. 12
4. Debarment certification (note: must have a definitive statement)	X		Vol. 1.1, pg. 24
5. Financial Disclosure	X		Vol. 1.1, pgs. 14-23
6. Comprehensive Index	X		Vol. 1.1, pgs. xli-xlix

7. Pagination	X	Okay throughout NDA
8. Has the applicant submitted a complete Environmental Assessment, that addresses 21 CFR 25.31 or provided a request for categorical exclusion under 21 CFR 25.24?	X	Vol. 1.13, pg. 283
9. On its face, is the NDA legible?	X	
10. Has the sponsor submitted all special Studies/ data requested during Presubmission discussions?		NA
11. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with Part 58 or a statement why it has not complied?	X	Vol. 1.59
12. If required, has the applicant submitted carcinogenicity studies?		NA
13. On its face, does the application contain at least two adequate and well-controlled clinical trials?	X	(1) uncontrolled trial as agreed upon
14. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	X	Vol. 1.61
15. Have all articles/ study reports been submitted either in English or translated into English?	X	Vols. 1.61-1.92
16. Summary Volume	X	Vol. 1.1

17. Review Volumes	X		Vols. 1.1-1.92
18. Labeling (PI, container, & carton labels)	X		Vol. 1.1
a. unannotated PI	X		Vol. 1.1
b. annotated PI	X		Vol. 1.1
c. immediate container	X		Vol. 1.1
d. carton	X		Vol. 1.1
e. foreign labeling (English translation)			NA
19. Foreign Marketing History			NA
20. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Electronic
21. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Electronic

Y=Yes (Present), N=No (Absent)

## PART II: SUMMARY<sup>b</sup>

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Vol. 1.1, pgs. 56-58
2. Summary of Each Technical Section	X		Vol. 1.1

a. Chemistry, Manufacturing, & Controls (CMC)	X	Vol. 1.1, pgs. 58-73
b. Nonclinical Pharmacology/Toxicology	X	Vol. 1.1, pgs.74-90
c. Human Pharmacokinetic & Bioavailability	X	Vol. 1.1, pgs. 90-104
d. Microbiology	X	Vol. 1.1, pgs. 58-73
e. Clinical Data & Results of Statistical Analysis	X	Vol. 1.1, pg. 105
3. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X	Vol. 1.1, pg. 122
4. Summary of Safety	X	Vol. 1.1, pg.119
5. Summary of Efficacy	X	Vol. 1.1, pg. 108

Y=Yes (Present), N=No (Absent)

### PART III: CLINICAL/STATISTICAL SECTIONS<sup>c</sup>

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. List of Investigators	X		Vol. 1.61, pg. 1
2. Controlled Clinical Studies			NA-Studies were Uncontrolled
a. Table of all studies	X		Vol. 1.61
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Vol. 1.61
c. Optional overall summary & evaluation of data from controlled			NA-Studies were Uncontrolled

clinical studies			
3. Integrated Summary of Efficacy (ISE)	X		Vol. 1.61, pgs. 45-58
4. Integrated Summary of Safety (ISS)	X		Vol. 1.61, pgs. 59-114
5. Drug Abuse & Overdosage Information	X		Vol. 1.61, pg. 114
6. Integrated Summary of Benefits & Risks of the Drug	X		Vol. 1.61, pg. 115
7. Gender/Race/Age Safety & Efficacy Analysis Studies	X		Vol. 1.61, pg. 57

Y=Yes (Present), N=No (Absent)

#### PART IV: MISCELLANEOUS

Y=Yes (Present), N=No (Absent)

	Y	N	COMMENTS (list volume & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Waiver Request Vol. 1.1, pg.24
2. Diskettes	X		EDR
a. Proposed unannotated labeling in MS WORD 8.0	X		
b. Stability data in SAS data set format		X	
c. Efficacy data in SAS data set format	X		
d. Biopharmacological information & study summaries in MS WORD 8.0	X		
e. Animal tumorigenicity study data in SAS data set format		X	
3. User-fee payment receipt		X	Payment sent with NDA; verified against User Fee and Arrears List

Y=Yes (Present), N=No (Absent)

<sup>a</sup>“GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS” (FEBRUARY 1987) and 21 CFR 314.100(d)

<sup>b</sup>“GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS” (FEBRUARY 1987).

<sup>c</sup>“GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS” (JULY 1988)

**Additional Comments: None.**

**Conclusions: NDA is filable.**

*{See appended electronic signature page}*

  
Senior Regulatory Associate

cc:

Original NDA

HFD-580/Div. Files

HFD-580/PM/Best

HFD-580/Shames

HFD-580/Reviewers

draft:JAB/October 17, 2001

r/d Initials:

final:JAB/October 17, 2001

**ADMINISTRATIVE REVIEW**

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/s/

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Jeanine Best  
10/17/01 03:42:46 PM  
CSO

**NDA FILEABILITY CHECKLIST**

**NDA Number: 21-379**

**Applicant: ATRIX LABORATORIES INC.**

**Stamp Date: 09/26/01**

**Drug Name: LA-2550 22.5 mg**

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes\_X\_ No\_)**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		DMF number and authorization letter has been provided
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

NDA is fileable from a manufacturing and controls perspective.

Review Checked:  Swapan K. De, Ph. D.

Date: 11/15/01

Team Leader: David Lin, Ph. D.

Date: 11/15/01

cc:

Original NDA 21-379

HFD-580/Division File

HFD-580/Chem/De/Lin

HFD-580/PM/JBest

HFD-580/DivDir/DShames

## Teleconference Minutes

**Date:** June 17, 2002      **Time:** 11:00 – 11:15 PM      **Location:** Parklawn; 17B-45

**NDA 21-379 Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** Clinical

**Meeting Chair:** Ashok Batra, M.D.

**External Participant Lead:** Soe Than, M.D., Ph.D.

**Meeting Recorder:** Archana Reddy, M.P.H.

**FDA Attendees:**

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

**External Participants:**

Soe Than, M.D., Ph.D., Vice President, Clinical Research

J. Steven Garrett, DDS, MS, FACD, Senior Vice President

Larry Tamura, Director, Regulatory Affairs

Graham Carron, Biostatistics Supervisor

Barbara Pons, Data Management Specialist

Johanna Matz, Regulatory Affairs Project Leader

**Meeting Objective:** To seek clarification regarding clinical issues for the Eligard™ 22.5 mg label.

**Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

**Discussion:**

- 1) Identify the race of the "1 Other" that appears in the Race subsection of the Pharmacokinetics section of the proposed package insert.

The Case Report Form describes the race for this patients as Other (Puerto Rican) Atrix will contact the investigator site for this patient in order to gain more information.

**Decision Reached:** The sponsor will confirm the race of this individual and send this information in a fax response.

- 2) In the pivotal trial, two patients withdrew from the study due to disease progression.

**Decision Reached:** The sponsor should provide any further follow-up information on these two patients beyond what was reported in the NDA application.

- 3) In the Systemic Adverse Events subsection of the proposed package, it is reported that less than 2 % of the patients experienced possibly or probably treatment-related sweating and hypotension/hypertension. DRUDP requested that the sponsor identify if the patients who experienced these events are the same and did any patient experience anaphylaxis.

**Atrix Response:** In the list of possibly or probably related systemic adverse events reported by fewer than 2 % of patients (i.e., reported by only one patient), are clamminess, night sweats, sweating increased (all in the Skin Body System), and hypertension and hypotension (both in the Vascular Body System). The adverse events for these patients can be found in more detail in the NDA submission, in Appendix 2.7.1 of the study report. No patient experienced anaphylaxis in this study.

**Action Item:**

The PM will fax the minutes of this teleconference to the sponsor within 30 days.

  
\_\_\_\_\_  
Signature, Meeting Chair

See appended electronic signature page

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/

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Ashok Batra  
7/10/02 11:19:52 AM

## Teleconference Minutes

**Date:** July 1, 2002      **Time:** 11:00 – 11:30 PM      **Location:** Parklawn; 17B-43

**NDA 21-379 Drug:** Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** Guidance (Chemistry)

**Meeting Chair:** David Lin, Ph.D.

**External Participant Lead:** Soe Than, M.D., Ph.D.

**Meeting Recorder:** Archana Reddy, M.P.H.

### **FDA Attendees:**

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II  
(DNDC II) @ Division of Reproductive and Urologic Drug Products (HFD-580)  
Swapan De, Ph.D., Chemistry Reviewer, DRUDP (HFD-580)  
Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

### **External Participants:**

Mike Duncan, Vice President, Technical Operations  
Mark Sweeney, Vice President, Quality Assurance  
Elyse Wolff, MT (ASCP), Director, Technical Affairs  
Cody Yarborough, Director, Process Development  
Lori Nowaldy, Packaging Manager  
Brent Coonts, Manager, Analytical Methods Development and Services  
Stanley Young, Ph.D., Senior Scientist, Analytical Methods Development and Services  
Larry Tamura, Director, Regulatory Affairs  
Johanna Matz, Regulatory Affairs Project Leader

**Meeting Objective:** To discuss acceptance criteria of PLG molecular weight range and dissolution acceptance criterion for Eligard™ 22.5 mg.

### **Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-

dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

**Discussion:**

1) Acceptance criteria of PLG molecular weight range.

Based on the molecular weight range for clinical batches, DRUDP recommends that Atrix set a [redacted] PLG molecular weight range; sponsor is using a [redacted] range for PLG and argued that pre-clinical data shows good correlation between dogs and humans for efficacy; this point would need further discussion with the Pre-clinical reviewer if clinical efficacy is being connected to pre-clinical efficacy; the broad molecular weight range is of concern to DRUDP; Atrix argued that the risk is on the low-end of the molecular weight range and not on the high-end of the molecular weight range

**Decision Reached:** Atrix should submit an argument to DRUDP for review and the CMC reviewer will discuss this with the Pre-clinical and clinical reviewers.

2) Dissolution acceptance criterion.

a) 6 hours – The means range from 6.9 to 19.8 % with exception of batch 1831 [redacted] %).

DRUDP agreed that the proposed acceptance criterion of up to [redacted] % for the 6-hour timepoint is acceptable.

b) 18 hours – The means range from 27 to 49 %

DRUDP recommends that the sponsor change the dissolution acceptance criterion from [redacted] to [redacted]. The acceptance criteria for individual units should also change accordingly.

c) 48 hours – Atrix's proposed dissolution acceptance criterion is acceptable.

**Decision Reached:** The sponsor will provide data and an argument on why the DRUDP proposed acceptance criterion for the 18-hour time point is not acceptable. The sponsor should take into consideration that if the requirements are not met in Tier 1 testing, Tier 2 testing can be performed.

**Action Item:**

The PM will fax the minutes of this teleconference to the sponsor within 30 days.

\_\_\_\_\_  
Signature, Meeting Chair  
See appended electronic signature page

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

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/s/  
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David T. Lin  
7/9/02 02:39:32 PM  
I concur.

## Teleconference Minutes

**Date:** July 11, 2002      **Time:** 12:30 – 1:00 PM      **Location:** Parklawn; 17B-43

**NDA 21-379 Drug:** Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** Guidance (Chemistry)

**Meeting Chair:** Mark Hirsch, M.D.

**External Participant Lead:** Johanna Matz

**Meeting Recorder:** Archana Reddy, M.P.H.

### **FDA Attendees:**

Mark Hirsch, M.D., Medical Team Leader, Division of Reproductive and Urologic Drug Products (HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)

Swapan De, Ph.D., Chemistry Reviewer, DRUDP (HFD-580)

Ameeta Parekh, Ph.D., Biopharmaceutics/Clinical Pharmacology Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Myong-Jin Kim, Pharm.D., Biopharmaceutics Reviewer (OCPB) @ DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

### **External Participants:**

Elyse Wolff, MT (ASCP), Director, Technical Affairs

Brent Coonts, Manager, Analytical Methods Development and Services

Stanley Young, Ph.D., Senior Scientist, Analytical Methods Development and Services

Bhagya Chandrashekar, Scientist I, Drug Delivery

Larry Tamura, Director, Regulatory Affairs

Johanna Matz, Regulatory Affairs Project Leader

**Meeting Objective:** To discuss acceptance criterion for the PLG molecular weight range and dissolution acceptance criterion for Eligard™ 22.5 mg.

### **Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a

polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

**Discussion:**

- 1) Acceptance criterion for the PLG molecular weight range.

**Decision Reached:** Atrix agrees to use the PLG polymer molecular weight acceptance criterion recommended by DRUDP in the June 26, 2002, information request letter.

- 2) Dissolution acceptance criterion.

- a) DRUDP recommended to sponsor that Atrix narrow their acceptance criterion for the 18-hour sampling timepoint from  $\text{--- \%} - \text{--- \%}$  to  $\text{--- \%} - \text{--- \%}$ .

**Decision Reached:** Atrix agreed to change the acceptance criteria for the 18-hour sampling timepoint from  $\text{--- \%} - \text{--- \%}$  to  $\text{--- \%} - \text{--- \%}$ . Also, Atrix will revise the instructions to clarify that Tier 2 testing will be performed if any of the three conditions (mean % of individual units, NLT 5 of 6 units are within  $\pm 10\%$  of mean specification value) fail to meet the acceptance criteria. The sponsor can report individual and mean release assay results as integers rather than to one decimal place. Atrix will submit the revised acceptance criteria.

**Action Item:**

The PM will fax the minutes of this teleconference to the sponsor within 30 days.

  
\_\_\_\_\_  
Signature, Meeting Chair  
See appended electronic signature page

**Note to sponsor:** These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Meeting Minutes

Page 3

Cc:

Arch NDA 21-379

HFD-580/Division Files

HFD-580/Reddy/Lin/De/Hirsch/Batra/Parekh/Kim/Raheja

Created by: Archana Reddy, July 18, 2002

Concurrence: sd/July 18, 2002, 2002, mk/July 18, 2002, sd/July 18, 2002, mk/July 18, 2002, dtl/July 18, 2002

Finalized: ar/July 23, 2002

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/s/

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Mark S. Hirsch  
7/23/02 02:27:55 PM

# Meeting Minutes

**Date:** June 14, 2002

**Time:** 3:00 – 3:30 PM

**Location:** Parklawn; 17B-43

**NDA 21-379 Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** 9-Month Status Meeting

**Meeting Chair:** Mark Hirsch, M.D.

**Meeting Recorder:** Archana Reddy, M.P.H.

**FDA Attendees:**

Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Ashok Batra, M.D., Medical Officer, DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Myong-Jin Kim, Pharm.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

**Meeting Objective:** 8-Month Status Meeting

**Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel<sup>®</sup> Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

**Discussion:**

**Pharmacology/Toxicology**

- Review signed off in DFS; recommend approval
- No changes to the label

### **Clinical**

- Review underway
- Will hold discussion with sponsor to clarify following issues:
  - "hypotension, clamminess, sweaty" if it was a case of anaphylaxis?"
  - CAP Progression and inevaluable patients.
  - Race : Define "other"

### **Clinical Pharmacology/Biopharmaceutics**

- Draft review is complete
- Review of dissolution data is complete pending review by OCPB (at briefing)
- Label review complete; minor changes to labeling on N drive done
- OCPB briefing will be held in last week of June, Dr. Batra will attend as well

### **Chemistry**

- CMC IR letter sent to the sponsor
- DMF review is complete; all DMFs are acceptable
- Review complete pending response to minor chemistry deficiencies
- Label the same as for the Eligard™ 7.5 mg drug product and minor changes already made to the N drive

### **Microbiology**

- Review complete; recommend approvable action
- List of microbiology deficiencies conveyed to sponsor; pending reply from sponsor

### **Regulatory Issues:**

- OPDRA Tradename Review complete; tradename is acceptable, minor carton and container label changes recommended
- DSI audit complete; report complete and site data is acceptable

### **Action Items:**

- 1) The PM will forward the action package to the Medical Team Leader for review by July 3, 2002.
- 2) The reviewers will finalize their draft reviews by July 3, 2002.
- 3) The PM will finalize all changes to the label and forward revised draft labeling to the sponsor.

- 3) The PM will finalize all changes to the label by June 14, 2002 and forward revised draft labeling to the sponsor, based upon all reviewers making changes to their sections by that date.

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NDA 21-379  
Meeting Minutes  
Page 4 of 4

Cc:  
Arch NDA 21-379  
HFD-580/Division Files  
HFD-580/Hirsch/Batra/Raheja/Jordan/Parekh/Kim/Welch/

Created by: Archana Reddy, May 28, 2002  
Concurrence: mjk/June 11, 2002, mh/June 20, 2002, 2002, dtl/June 11, 2002,  
kr/June 11, 2002, sd/June 11, 2002  
Finalized: ar/June 21, 2002

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Mark S. Hirsch  
6/30/02 03:27:59 PM

# Meeting Minutes

**Date:** May 28, 2002      **Time:** 12:00 – 12:30 PM      **Location:** Parklawn; 17B-43

**NDA 21-379 Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** 8-Month Status Meeting

**Meeting Chair:** Mark Hirsch, M.D.

**Meeting Recorder:** Archana Reddy, M.P.H.

## **FDA Attendees:**

Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Zili Li, M.D., Medical Officer, DRUDP (HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)

Swapam De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Myong-Jin Kim, Pharm.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

**Meeting Objective:** 8-Month Status Meeting

## **Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 mg is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel<sup>®</sup> Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

## **Discussion:**



NDA 21-379  
Meeting Minutes  
Page 3 of 3

Cc:  
Arch NDA 21-379  
HFD-580/Division Files  
HFD-580/Hirsch/Batra/Raheja/Jordan/Parekh/Kim/Welch/

Created by: Archana Reddy, May 28, 2002  
Concurrence: mjk/June 18, 2002, ab/, 2002, sd/June 21, 2002, mh/June 21, 2002,  
dtl/June 20, 2002, kr/June 17, 2002  
Finalized: ar/June 21, 2002

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Mark S. Hirsch  
6/30/02 03:31:43 PM

# Meeting Minutes

**Date:** April 22, 2002      **Time:** 11:00 – 12:00 PM      **Location:** Parklawn; 17B-43

**NDA 21-379 Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** Status Meeting

**Meeting Chair:** Mark Hirsch, M.D.

**Meeting Recorder:** Archana Reddy, M.P.H.

## **FDA Attendees:**

Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Myong-Jin Kim, Pharm.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

Archana Reddy, M.P.H., Project Manager, DRUDP (HFD-580)

**Meeting Objective:** 7-Month Status Meeting

## **Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel<sup>®</sup> Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

## **Discussion:**

### **Pharmacology/Toxicology**

- Review complete awaiting team leader sign-off; recommend approval

### **Clinical**

- Six month open-label, two dose, fixed-dose study conducted to investigate the safety and hormonal efficacy in 117 patients and pharmacokinetics studied in a subset of 25 patients
- 14 non-related adverse events reported
- No related adverse events reported
- Review underway; electronic data shows acceptable risk/benefit ratio
- Medical officer will look into how local adverse events were assessed

### **Clinical Pharmacology/Biopharmaceutics**

- Review is about 75 % complete
- Subset of 22 patients studied for clinical pharmacology
- No acute-on-chronic events reported; no accumulation after the second dose
- Review of dissolution data pending
- Label review pending
- *In-vitro* release rate the same as dissolution; this issue will be discussed at OCPB briefing
- there was no breakthrough response seen in 22 PK patients

### **Chemistry**

- ratio of the polymer in the formulation (22.5 mg) is different from the 7.5 mg approved formulation (NDA 21-343); DMF holder of this polymer ~~\_\_\_\_\_~~ promised to send the updated information by second week of May, 2002; this DMF should be adequate to support the NDA
- Sponsor amending stability data on April 26, 2002
- Sponsor has responded to all chemistry deficiencies
- EES inspections are complete; recommendation pending

### **Microbiology**

- Review pending

### **Regulatory Issues:**

- OPDRA Tradename Review pending
- DSI audit complete; report pending

### **Action Items:**

- 1) The PM will forward the action package to the Medical Team Leader for review by July 3, 2002.
- 2) The reviewers will finalize their draft reviews by July 3, 2002.
- 3) Decision about the approvability of the drug product will be reached by the next status meeting (May 28, 2002).

- 4) Labeling negotiations should begin immediately after the next status meeting.

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NDA 21-379  
Meeting Minutes  
Page 4 of 4

Cc:  
Arch NDA 21-379  
HFD-580/Division Files  
HFD-580/Hirsch/Batra/Raheja/Jordan/Parekh/Kim/Welch/

Created by: Archana Reddy, May 3, 2002  
Concurrence: mk/May 10, 2002, ab/May 13, 2002, ad/May 14, 2002, mh/May 20, 2002,  
dtl/May 15, 2002  
Finalized: ar/May 21, 2002

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Mark S. Hirsch  
5/28/02 12:40:43 PM

# Meeting Minutes

**Date:** November 14, 2001      **Time:** 3:00-3:45 PM      **Location:** Parklawn; 17B-43

**NDA 21-379    Drug:** LA-2550 22.5 mg (leuprolide acetate for injectable suspension)

**Indication:** Palliative treatment for advanced prostate cancer

**Sponsor:** Atrix Laboratories, Inc.

**Type of Meeting:** Filing Meeting

**Meeting Chair:** Mark Hirsch, M.D.

**Meeting Recorder:** Jeanine Best, M.S.N., R.N.

**FDA Attendees:**

Mark Hirsch, M.D., Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

David Lin, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)

Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Mike Welch, Ph.D., Statistical Team Leader, Division Of Biometrics II (DBII) @ DMIRDP (HFD-160) and DRUDP (HFD-580)

Swapan De, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)

Myong-Jin Kim, R.Ph., Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

Krishan Raheja, D.V.M., Ph.D., Pharmacologist, DRUDP (HFD-580)

Connie Lewin, Ph.D., Pharmacologist, Division of Scientific Investigations (DSI; HFD-45)

Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

**Meeting Objective:** To determine the fileability of this New Drug Application (NDA) 21-379, submitted September 25, 2001; 10-month PDUFA date is July 26, 2002.

**Background:**

LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. LA-2550 22.5 is prefilled and supplied in two separate syringes whose contents are mixed just prior to administration. One syringe contains leuprolide acetate and the other syringe contains the Atrigel® Delivery System (a polymeric delivery system consisting of poly DL-lactide-co-glycolide [PLGH] that is dissolved in N-methyl-2-pyrrolidone [NMP]). There was one, 6-month, open-label, fixed-dose, pivotal Phase 3 trial performed in 117 patients (113 patients completed the trial, and 11 patients were evaluable) to demonstrate safety and efficacy in the palliative treatment of men with advanced prostate cancer.

**Discussion:**

**Clinical:**

- the sponsor performed one pivotal study (AG-9909) and used the two studies from the LA-2550 7.5 mg NDA as supportive studies to support the safety and efficacy of this product; the one Phase 3 pivotal trial (an open-label, fixed-dose in 117 men) demonstrated a 100% castrate rate at Month 6 with 94% of the men achieving the new threshold testosterone (T) castrate level of 20 ng/dL at Month 6
- the most common reported Adverse Event (AE) were hot flushes (56%), an expected event with this class of products, no injection site reactions were noted but this will be a review issue; there is a potential bone safety concern with the new low T threshold levels
- DSI inspections are requested for one site for this application; all sites are in the U.S., and are the same sites as used in the LA-2550 7.5 mg NDA which is undergoing DSI inspection at this time
- adequate Financial Disclosure data was supplied by the sponsor; no disclosable information was reported
- no tradename was submitted by the sponsor for OPDRA review; the sponsor is awaiting OPDRA decision for the LA-2550 7.5 mg product because a similar name will be given to this product; an OPDRA consult will be initiated when the sponsor submits a tradename for consideration
- NDA is fileable

**Chemistry:**

- The formulation is identical to the LA-2550 7.5 mg formulation with the exception of increased amounts of leuprolide acetate (22.5 mg), NMP ( — mg), and PLG ( — mg, polymer formulation), and a change in the ratio of lactide and co-glycolide (75:25 instead of — which changes the release pattern
- the drug substance is made by — who use different methods of synthesis; both suppliers' drug substances were used in the clinical trials
- the product is supplied in two syringes which are — ' together for mixing of the contents; the product becomes a solid biodegradable implant upon injection and is slowly released over time
- in vitro release is being done for quality purposes using an organic solvent, this will be a review issue
- facility inspection requests have been submitted to EER
- NDA is fileable

**Microbiology:**

- A microbiology consult was sent; reviewer assignment is pending

**Biopharmaceutics and Clinical Pharmacology:**

- The sponsor has evaluated Pk/PD parameters in a subset of 22 patients from the Phase 3 trial
- the to-be-marketed formulation is the same as that used in the clinical trials
- the in vitro release testing will be reviewed
- the release pattern with this product is different than that observed with Lupron Depot®; there are two peaks observed during the first week after injection as opposed to one peak observed with Lupron Depot®; the significance of the second peak, if any, will be reviewed
- NDA is fileable

**Pharmacology/Toxicology:**

- The information supplied in this NDA is identical to that supplied with the LA-2550 7.5 mg NDA; there is sufficient information to support the additional amount of the excipient
- NDA is fileable

**Statistics:**

- no issues, a formal statistical review is not required; a memo will be provided as a final review
- NDA is fileable

**Decisions made:**

- NDA is fileable

**Action Items:**

- J. Best will forward memo to DSI for inspection request
- reviewers to have filing memos in DFS by 60-day filing date, November 25, 2001

JS

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Minutes Preparer

JS

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Concurrence, Chair

cc:

Original NDA

HFD-580/DivFile

HFD-580/PM/Best

HFD-580/ Hirsch/Lin/De/Parekh/Kim/Welch

HFD-45/Lewin

drafted:JAB/November 16, 2001/N21379Filmtg111401.doc

concurrence:Hirsch,11.16.01/Welch,11.16.01De,11.19.01/Raheja,11.20.01/Kim,11.21.01/  
Parekh,11.27.01

final:JAB/ November 28, 2001

MEETING MINUTES

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/s/

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Mark S. Hirsch  
12/3/01 05:07:30 PM

NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Advisory Committee Meeting**

This NDA application was not the subject of an advisory committee meeting.

*CR 7/10/02*

**APPEARS THIS WAY  
ON ORIGINAL**

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ON ORIGINAL**

NDA 21-379  
Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Federal Register Notice**

This NDA application was not the subject of a Federal Register Notice.

*EM 7/05/02*

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**CONSULTATION RESPONSE**  
**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT**  
**OFFICE OF DRUG SAFETY**  
**(ODS; HFD-400)**

**DATE RECEIVED:** 03/13/02      **DUE DATE:** 06/07/02      **ODS CONSULT:** 02-0042

**TO:** Daniel Shames, M.D.  
Acting Director, Division of Reproductive and Urologic Drug Products  
HFD-580

**THROUGH:** Archana Reddy  
Project Manager  
HFD-580

<p><b>PRODUCT NAME:</b></p> <p>Eligard 22.5 mg  (Leuprolide Acetate For Injection)  22.5 mg</p> <p><b>NDA #:</b> 21-379</p>	<p><b>MANUFACTURER:</b> Atrix Laboratories, INC.</p>
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**SAFETY EVALUATOR:** Hye-Joo Kim, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), the Division of Medication Errors and Technical Support conducted a review of the proposed proprietary name "Eligard 22.5 mg" to determine the potential for confusion with approved proprietary and established names as well as pending names.

**DMETS RECOMMENDATION:** DMETS has no objection to the use of the proprietary name Eligard 22.5 mg. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

*DMETS decision* is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

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Carol Holquist, R.Ph.  
Deputy Director  
Division of Medication Errors and Technical Support  
Office Drug Safety  
Phone: 301-827-3242 Fax: (301) 443-5161

Jerry Phillips, R.Ph.  
Associate Director  
Office of Drug Safety  
Center for Drug Evaluation and Research  
Food and Drug Administration

Division of Medication Errors and Technical Support  
Office of Drug Safety (ODS)  
HFD-400; Parklawn Building Room 15B-32  
Center for Drug Evaluation and Research

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** May 22, 2002  
**NDA NUMBER:** 21-379  
**NAME OF DRUG:** **Eligard 22.5 mg**  
(Leuprolide Acetate For Injection)  
22.5 mg  
**NDA SPONSOR:** \_\_\_\_\_

**I. INTRODUCTION**

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the proprietary name, *Eligard 22.5 mg* for their proposed product that delivers “22.5 mg of leuprolide acetate at a controlled rate over a three-month period.” The syringe labels, foil outer pouch labeling, and package insert labeling were reviewed for possible interventions in minimizing medication errors.

The sponsor, Atrix, currently markets Eligard in the following strength and dosage form:

Eligard (Leuprolide Acetate Injection: 7.5 mg)

**PRODUCT INFORMATION**

Eligard 22.5 mg, which is a polymeric matrix formulation of leuprolide acetate for subcutaneous injection, delivers 22.5 mg of leuprolide acetate at a controlled rate over a three-month period. Eligard 22.5 mg is indicated for the palliative treatment of advanced prostate cancer. The usual dose is 22.5 mg subcutaneously every three months. The proposed product is supplied in a kit that consists of a two-syringe mixing system and a 20-gauge half-inch needle. One syringe contains the ATRIGEL® Delivery System. The ATRIGEL® Delivery System is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable, ~% poly (DL-lactide-co-glycolide) (PLGH), polymer formulation dissolved in a biocompatible solvent, ~% N-methyl-2-pyrrolidone (NMP). PLGH is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains 22.5 mg of leuprolide acetate. The contents of two separate syringes are mixed immediately before administration.

## II. RISK ASSESSMENT

The standard DMETS proprietary name review was not conducted for this consult because the proprietary name “Eligard” has been utilized in the U.S. marketplace since January 2002. An Expert Panel discussion was conducted to address concerns with the use of the proprietary name Eligard 22.5 mg for their proposed product that delivers “22.5 mg of leuprolide acetate at a controlled rate over a three-month period.” In addition, the Adverse Event Reporting System (AERS) database was searched to determine if there is any confusion with the use of the proprietary name “Eligard.”

### A. EXPERT PANEL DISCUSSION

A discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Eligard 22.5 mg. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS’s Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The panel had concerns with the use of the modifier “22.5 mg” in conjunction with the proprietary name Eligard for this proposed product. In order to prevent potential medication errors between the proposed Eligard 22.5 mg and the currently available Eligard 7.5 mg, distinctive labels/labeling should be used to differentiate Eligard 22.5 mg from Eligard 7.5 mg.
2. DDMAC did not have any concerns about the name with regard to promotional claims.

### B. AERS DATABASE SEARCH

We searched the *FDA Adverse Event Reporting System (AERS)* database for all postmarketing safety reports of medication errors associated with Eligard. The Meddra Preferred Term (PT), “Medication Error” and the drug name “Eligard%” were used to perform the search. The search resulted in one potential medication error report involving Eligard. The following is the summary of this medication error report:

ISR# 3890401-2 (Date of Report 02/26/02):

The reporter wanted to express concerns over the recently released drug product names, Elidel (Pimecrolimus) and Eligard (Leuprolide). Although the two products are very different and are for different indications, the reporter was concerned that both are newly released and may be unfamiliar to healthcare professionals.

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### C. SAFETY EVALUATOR RISK ASSESSMENT

Eligard was approved by the Agency on January 3, 2002. Since then, DMETS received only one potential medication error report involving name confusion between Eligard and Elidel. Therefore, there is insufficient evidence at this time to conclude that the proprietary name, Eligard, has significant potential for name confusion. However, since Eligard was recently approved, DMETS will continue to monitor post-marketing medication errors in association with the proprietary name, Eligard.

Eligard 22.5 mg contains the same active ingredient, leuprolide acetate, as the currently marketed Eligard 7.5 mg. In addition, Eligard 22.5 mg uses the same ATRIGEL® Delivery System as the currently available product Eligard 7.5 mg to deliver leuprolide acetate subcutaneously. However, the ATRIGEL® Delivery System for Eligard 22.5 mg consists of PLGH that is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. ATRIGEL® Delivery System for Eligard 7.5 mg, on the other hand, consists of PLGH that is a co-polymer with a 50:50 molar ratio of DL-lactide to glycolide containing carboxyl end groups. Eligard 7.5 mg is “designed to deliver 7.5 mg of leuprolide acetate at a controlled rate over a one month period” while Eligard 22.5 mg is “designed to deliver 22.5 mg leuprolide acetate at a controlled rate over a three-month period.” Consequently, the use of the proprietary name Eligard for this proposed product is appropriate.

Additionally, DMETS has no objection to the use of the modifier, “22.5 mg”, in conjunction with the proprietary name Eligard. In general, we discourage the use of numbers as a part of the proprietary name. However, numbers have been successfully used with certain products, such as the oral contraceptive drug products (e.g., 1/35 and 1/50). Similarly, the numerical suffix “22.5 mg” will assist in distinguishing the proposed product from the existing product, Eligard 7.5 mg and prevent potential selection errors between Eligard 22.5 mg and Eligard 7.5 mg.

We acknowledge that there is a potential risk where “Eligard 22.5 mg” will be inappropriately dispensed instead of “Eligard 7.5 mg” and “Eligard 22.5 mg” may be administered instead of Eligard 7.5 mg. Therefore, “Eligard 22.5 mg” may be prone to more frequent administrations than the recommended 3-month interval. Consequently, we recommend increasing the prominence of the usual dosage statement, “22.5 mg subcutaneously every 3 months” by placing it on the front panel of the outer pouch and carton labeling. We also recommend careful monitoring and sufficient education regarding the difference between Eligard 7.5 mg and Eligard 22.5 mg upon the launch of this product.

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### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the syringe labels, foil outer pouch labeling, and insert labeling of 22.5 mg, DMETS has focused on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

#### A. General Comments

In our previous consult for Eligard (ODS Consult 01-150), DMETS only reviewed the *draft* labels and labeling. In reviewing the *final* printed labels and labeling for Eligard 7.5 mg, DMETS refers the sponsor to our comments for Eligard 22.5 mg.

#### B. SYRINGE A LABEL (22.5 mg)

1. Please delete the proprietary (Eligard 22.5 mg) and established name (leuprolide acetate for injectable suspension) of the product. Since Syringe A contains only 440 mg of Atrigel Delivery System, the label should reflect the contents of the syringe. Please revise the proprietary name and ATRIGEL Delivery System as follows to prevent potential user error:

440 mg ATRIGEL Delivery System  
(Diluent for Eligard 22.5 mg)

2. If space permits, inactive ingredients are required to appear on the container label in accordance with 21 CFR 201.100 (b) (5).
3. We recommend adding the following statement to the Syringe A label, \_\_\_\_\_  
\_\_\_\_\_ to prevent potential errors.

#### C. SYRINGE B LABEL (22.5 mg)

If space permits, please include the statement "For Subcutaneous Use" in accordance with 21 CFR 201.100 (b) (3).

#### D. SYRINGE A POUCH LABELING (22.5 mg)

1. Please delete the statement "For Subcutaneous Injection" since Syringe A \_\_\_\_\_  
\_\_\_\_\_ leuprolide acetate and will not be used to inject the medication.

2. See comments under SYRINGE A LABEL

#### E. SYRINGE B POUCH LABELING (22.5 mg)

No comments.

F. OUTER POUCH LABELING (22.5 mg)

1. Please clarify the statement ‘ 22.5 mg Atrigel Delivery System containing...’. This statement is not consistent with the Syringe Label, which states that the proposed product contains 22.5 mg of Atrigel System.
2. Please increase the prominence of the statement “...delivers 22.5 mg leuprolide acetate.” Please see Syringe B Pouch Labeling as an example.
3. We recommend adding the usual dose statement to "Usual Dosage: 22.5 mg subcutaneously every 3 months" to minimize potential errors with the use of this product.

G. CARTON LABELING (7.5 mg and 22.5 mg)

1. We recommend revising the usual dose statement to "Usual Dosage: 22.5 mg subcutaneously every 3 months" to minimize potential errors with the use of this product. Please relocate the usual dose statement to the front panel to increase the prominence.
2. See comments under OUTER POUCH LABELING.

H. PACKAGE INSERT

No comments.

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**IV. RECOMMENDATIONS:**

1. DMETS has no objection to the use of the proprietary name, Eligard 22.5 mg.
2. DMETS recommends the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

*DMETS decision* is considered tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

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Hye-Joo Kim, Pharm.D.  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety (ODS)

Concur:

/S/

---

Alina R. Mahmud, RPh.  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Hye-Joo Kim  
6/5/02 04:26:30 PM  
PHARMACIST

Alina Mahmud  
6/6/02 10:32:25 AM  
PHARMACIST

Carol Holquist  
6/7/02 03:44:34 PM  
PHARMACIST

Jerry Phillips  
6/7/02 03:51:44 PM  
DIRECTOR

NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Application Integrity Policy**

This NDA application is not the subject of the AIP.

OR 710102

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NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Advertising**

Advertising will be requested once the application is approved.

*CR 7/6/102*

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NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Post Marketing Commitments**

No Phase IV commitments.

*our 7/10/102*

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NDA 21-379  
Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Press Office Information**

No press release or talk paper issued.

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NDA 21-379

Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

**Micro Efficacy Review**

No review required.

*cm 2/01/02*

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pages of trade

secret and/or

confidential

commercial

information

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-379	Efficacy Supplement Type SE-	Supplement Number N/A
Drug: Eligard 22.5 mg (leuprolide acetate for injectable suspension)		Applicant: Atrix Laboratories, Inc.
RPM: Reddy	HFD- 580	Phone # 7-5424
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name): NDA 21-343, Eligard 7.5 mg (leuprolide acetate for injectable suspension)
<b>❖ Application Classifications:</b>		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3S
• Other (e.g., orphan, OTC)		N/A
<b>❖ User Fee Goal Dates</b>		
		July 26, 2002
<b>❖ Special programs (indicate all that apply)</b>		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
<b>❖ User Fee Information</b>		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
<b>❖ Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
<b>❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.</b>		
		<input checked="" type="checkbox"/> Verified
<b>❖ Patent</b>		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	X
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Project Manager (October 17, 2001)
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	See OPDRA Tradename Review (6/07/02)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	X
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	X
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other	7-month, 8-month, 9-month, 10-month status meetings, clinical tcon (June 17, 2002), chemistry tcon

	(July 1, 2002); CMC tcon (July 11, 2002)
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	N/A
<i>Summary Review</i>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Refer to summary memoranda section
<i>Clinical Review</i>	
❖ Clinical review(s) (indicate date for each review)	X (7/01/02)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Refer to Medical Officer's Review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) (indicate date for each review)	No review required (only descriptive stats); See Stats Memo
❖ Biopharmaceutical review(s) (indicate date for each review)	X (July 22, 2002)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Complete; acceptable
• Bioequivalence studies	N/A
<i>CMC Review</i>	
❖ CMC review(s) (indicate date for each review)	X (July 22, 2002)
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	Granted (July 22, 2002)
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	X (July 22, 2002)
❖ Facilities inspection (provide EER report)	Date completed: June 6, 2002 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested (X) Not yet requested
<i>Nonclinical Review</i>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X (April 30, 2002)
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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/s/

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Archana Reddy  
7/23/02 04:53:41 PM

# USER FEE COVER SHEET

**See Instructions on Reverse Side Before Completing This Form**

1. APPLICANT'S NAME AND ADDRESS

Atrix Laboratories, Inc.  
2579 Midpoint Drive  
Fort Collins, CO 80525-4417

3. PRODUCT NAME

LA-2550 22.5 mg

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE  
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.  
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY  
REFERENCE TO \_\_\_\_\_  
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( 970 ) 482-5868

5. USER FEE I.D. NUMBER

4147

6. LICENSE NUMBER / NDA NUMBER

N021379

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

### FOR BIOLOGICAL PRODUCTS ONLY

- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See reverse side if answered YES)

**A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.**

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Hubert H. Humphrey Building, Room 531-H  
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Washington, DC 20201

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

TITLE

Senior Vice President,  
Research and Development

DATE

September 24, 2001