CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:  
NDA 19-732/S-009

Name: Lupron Depot  
leuprolide acetate (7.5 mg)  

Sponsor: TAP Pharmaceuticals, Inc.  

Approval Date: January 26, 1989
**APPLICATION NUMBER:**

NDA 19-732/S-009

**CONTENTS**

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<tr>
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<td>Administrative Document(s)</td>
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<td>Correspondence Document(s)</td>
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-732/S-009

APPROVAL LETTER
TAP Holdings Inc.  
Attention: Aruna Dabholkar, M.D.  
2355 Waukegan Road  
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your December 30, 1994, supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Lupron Depot (leuprolide acetate for depot suspension), 7.5 mg (NDA 19-732);  
- Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg (NDA 19-943);  
- Lupron Depot (leuprolide acetate for depot suspension), 3.75 mg (NDA 20-011); and  
- Lupron Depot (leuprolide acetate for depot suspension), 7.5, 11.25, and 15.0 mg (NDA 20-263).

We acknowledge receipt of your amendments dated May 24, September 1 (NDA 19-732) and September 7 (NDAs 19-943, 20-011, and 20-263), 1995.

These supplemental applications provide for an additional container/closure system (pre-filled, dual-chamber syringe) filled with Lupron Depot and diluent.

We have completed the review of these supplemental applications and they are approved, effective on the date of this letter.

We remind you that you must comply with the requirements for approved NDAs set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.  
Consumer Safety Officer  
(301) 443-3510

Sincerely yours,

Solomon Sobel, M.D.  
Director  
Division of Metabolism and  
Endocrine Drug Products (HFD-510)  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research
cc:
Original NDAs 19-943, 19-732, 20-011, and 20-263
HFD-510
HFD-510/CNiu/YYChiu
HFD-80
DISTRICT OFFICE
HFD-232

drafted: LPauls/October 23, 1995/N19732AP.S09

Concurrences:
CNiu, SMoore 10.23.95

APPROVAL
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ND A 19-732/S-009

CHEMISTRY REVIEW(S)
**CHEMIST'S REVIEW**

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<tr>
<th>1. ORGANIZATION</th>
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<th>3. NAME AND ADDRESS OF APPLICANT</th>
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<tr>
<td>TAP Pharmaceuticals Inc.</td>
</tr>
<tr>
<td>Bannockburn Lake Office Plaza</td>
</tr>
<tr>
<td>2355 Waukegan Road</td>
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<td>Supplement SCP-009</td>
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<td>12/30/94</td>
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<th>6. NONPROPRIETARY NAME</th>
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<tr>
<td>Lupron Depot, 7.5 mg</td>
<td>Leuprolide acetate for depot suspension</td>
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<th>7. SUPPLEMENT PROVIDES FOR:</th>
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<tr>
<td>Additional container-closure system (Pre-filled, Dual-Chamber Syringe) filled with Lupron Depot and diluent.</td>
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<th>8. AMENDMENTS/REPORTS, DATE</th>
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<th>9. PHARMACOLOGICAL CATEGORY</th>
<th>10. HOW DISPENSED</th>
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<tr>
<td>Inhibitor of gonadotropin secretion</td>
<td>RX</td>
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<th>11. DOSAGE FORM</th>
<th>12. POTENCY</th>
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<tbody>
<tr>
<td>Microsphere Depot</td>
<td>7.5 mg</td>
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<th>13. POTENCY</th>
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<tr>
<td>NDA 20-011/S06</td>
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<td>NDA 20-263/S06</td>
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<tr>
<td>5-Oxo-L-prolyl-L-histidyl-L-Tryptophyl-L-seryl-L-Tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate</td>
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<tr>
<th>15. COMMENTS</th>
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<tbody>
<tr>
<td>1. The syringe components are purchased from An authorization letter issued by permitting the FDA to cross reference its DMF on behalf of the sponsor is included.</td>
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<table>
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<tr>
<th>16. CONCLUSIONS AND RECOMMENDATIONS</th>
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<tbody>
<tr>
<td>The supplement is not approvable due to the deficiencies in chemistry and in the sterilization process validation. Also, the cGMP inspection has not been completed. Issue a non-approval letter (see the draft letters in this review and microbiology review).</td>
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</table>

<table>
<thead>
<tr>
<th>17. REVIEWER</th>
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<tr>
<td>Chien-Hua Niu, Ph.D.</td>
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Redacted 16 page(s) of trade secret and/or confidential commercial information from Chemistry Review #1 (S-009)
ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE (Check One)
- Original
- Follow-Up
- FUR

DATE 2/1/95
PHONE NO. 443-3520

REQUESTOR'S NAME
Chien-Hua Niu

APPLICATION AND SUPPLEMENT NUMBER
NDA #19-732 (SCP-009)

BRAND NAME
Lupron Depot

ESTABLISHED NAME
Leuprolide acetate for depot suspension

DOSAGE AND STRENGTH
Microsphere powder, 7.5 mg

STERILE
☑ YES ☐ NO

PROFILE CLASS
Sup

PRIORITY CLASSIFICATION (See SMG CDER-4820.3)

APPLICANT'S NAME
TAP Pharmaceuticals Inc.

ADDRESS
Bannockburn Lake Office Plaza, 2355 Waukegan Rd., Deerfield, IL 60015

COMMENTS
1. Identical requests are made for NDA #20-011 (SCP-006) and NDA #20-263 (SCP-006).
2. The field copy of this submission is kept in my office.

USER FEE DATE 7/3/95

FACILITIES TO BE EVALUATED
(Name and Complete Address)

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<td>Manufacturing</td>
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<td>Osaka Plant (C-71 Building)</td>
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<td>4.</td>
<td>with diluent and microsphere powder.</td>
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<td>5. Abbott Laboratoires</td>
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<td>1400 Sheridan Road</td>
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<td></td>
<td></td>
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<tr>
<td>North Chicago, IL 60064</td>
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**ESTABLISHMENT EVALUATION REQUEST**

- **REQUEST TYPE (Check One)**
  - Original
  - Follow-Up
  - FUR

- **DATE**
  - 2/1/95

- **PHONE NO.**
  - 443-3520

- **REQUESTOR’S NAME**
  - Chien-Hua Niu

- **APPLICATION AND SUPPLEMENT NUMBER**
  - NDA #19-732 (SCP-009)

- **BRAND NAME**
  - Lupron Depot

- **ESTABLISHED NAME**
  - Leuprolide acetate for depot suspension

- **DOSAGE AND STRENGTH**
  - Microsphere powder, 7.5 mg

- **STERILE**
  - Yes

- **PROFILE CLASS**
  - SVP

- **APPLICANT’S NAME**
  - TAP Pharmaceuticals Inc.

- **ADDRESS**
  - Bannockburn Lake Office Plaza, 2355 Waukegan Rd., Deerfield, IL 60015

- **COMMENTS**
  1. Identical requests are made for NDA #20-011 (SCP-006) and NDA #20-263 (SCP-006).
  2. The filed copy of this submission is kept in my office.

---

**FACILITIES TO BE EVALUATED**

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<tr>
<td>3.</td>
<td>Takeda Chemical Industries, Ltd., Osaka Plant (C-71 Building) 17-85 Juso-Hommachi 2-Chome Yodogawa-Ku Osaka, 532, Japan</td>
<td>Manufacturing Pre-filled Single-Chamber Syringes filled with diluent and microsphere powder</td>
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<td>5.</td>
<td>Abbott Laboratoires 1400 Sheridan Road North Chicago, IL 60064</td>
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**FORM FDA 3274 (8/92)**
Distribution: Original and Yellow Copy: HFD-324. Remaining Copies: Requesting Office
Chemistry Review #2 (10/19/95)-
“Microbiologist’s Review #3” under item 16. Conclusions and Recommendations is a typographical error. Should state Microbiologist’s Review #2.
1. ORGANIZATION
DMEDP, HFD-510
2. NDA NUMBER
19,732

3. NAME AND ADDRESS OF APPLICANT
TAP Pharmaceuticals Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

4. SUPPLEMENT NUMBER, DATE
Supplement
SCP-009
12/30/94

5. NAME OF THE DRUG
Lupron Depot, 7.5 mg -
Leuprolide acetate for depot suspension

6. NONPROPRIETARY NAME

8. AMENDMENTS/ REPORTS, DATE
Amendment
5/24/95
9/1/95

7. SUPPLEMENT PROVIDES FOR:
Additional container-closure system (Pre-filled, Dual-Chamber Syringe) filled with Lupron Depot and diluent.

9. PHARMACOLOGICAL CATEGORY
Inhibitor of gonadotropin secretion

10. HOW DISPENSED
RX

11. RELATED IND/NDL/DMF
DMF

12. DOSAGE FORM
Microsphere Depot

13. POTENCY
7.5 mg

NDA 19-943/S02
NDA 20-011/S06
NDA 20-263/S06

14. CHEMICAL NAME AND STRUCTURE
5-Oxo-L-prolyl-L-histidyl-L-Tryptophyl-L-seryl-L-Tyrosyl-D-leucyl-L-Leucyl-L-arginyl-N-ethyl-L-prolinamide acetate

15. COMMENTS
1. The 5/24/95 amendment to NDA #19-732 (Supplement SCP-009) is in response to chemistry deficiencies communicated to the applicant in the non-approval letter dated on April 25, 1995.
2. For other comments, see the next page.

16. CONCLUSIONS AND RECOMMENDATIONS
The sponsor has properly responded the deficiencies in chemistry and the cGMP inspection was acceptable to the Office of Compliance. Moreover, the sterilization validation process has been reviewed by the microbiologist and found to be satisfactory (see microbiologist's review #3 dated 10/4/95). The application can be approved from chemistry viewpoint. Issue an approval letter. In the approval letter, the microbiologist's comments should be communicated to the firm.

17. REVIEWER NAME
Chien-Hua Niu, Ph.D.

SIGNATURE
Date Completed
10/19/95

DISTRIBUTION: ORIGINAL JACKET REVIEWER DIVISION FILE
R/D initialed by:
Disc Supplement/NDA9732.89A

Stephen Wood
10/19/95
Redacted 2 page(s) of trade secret and/or confidential commercial information from Chemistry Review #2 (S-009)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 19-732/S-009

MICROBIOLOGY REVIEW(S)
Consultative Review to HPD-510
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HPD-160

Microbiologist's Review of Supplement
17 March 1995

A. 1. NDA 19-732/S-009
APPLICANT: TAP Pharmaceuticals, Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL  60015

2. PRODUCT NAMES:  Lupron Depot® 7.5 mg, 3.75 mg, and Lupron
Depot-PED® 7.5 mg, 11.25 mg, and 15 mg
formulations (leuprolide acetate for depot
suspension) for Injection.

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Sterile depot suspension for intramuscular injection. The
Supplement provides for packaging the product in a dual-
chambered syringe.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is used for palliative treatment of
advanced prostate cancer.

B. 1. DATE OF INITIAL SUBMISSION:  30 December 1994

2. DATE OF AMENDMENT:  (none)

3. RELATED DOCUMENTS:

Appears This Way
On Original
Table 1. Documents referenced in this Supplement.

<table>
<thead>
<tr>
<th>Document</th>
<th>Subject</th>
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<tbody>
<tr>
<td>NDA 19-010</td>
<td>Manufacture of Lupon Injection</td>
</tr>
<tr>
<td>NDA 19-732</td>
<td>Manufacture of Lupon Depot® 7.5 mg</td>
</tr>
<tr>
<td>NDA 20-011</td>
<td>Manufacture of Lupon Depot® 3.75 mg</td>
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<tr>
<td>NDA 20-263</td>
<td>Manufacture of Lupon Depot-PED® 7.5 mg, 11.25 mg, and 15 mg</td>
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<tr>
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<td>DMF[]</td>
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</table>

4. ASSIGNED FOR REVIEW: 6 February 1995

C. REMARKS: The supplement requests an additional container/closure system (prefilled, dual-chamber syringe) for Lupon Depot® 7.5 mg, 3.75 mg, and Lupon Depot-PED® 7.5 mg, 11.25 mg, and 15 mg formulations. The application also describes the manufacture of the diluent at Takeda’s C-71 (Osaka) site. Unlabelled, pre-filled syringes will be shipped to Abbott Laboratories for labelling and packaging and will be distributed by TAP Pharmaceuticals.

D. CONCLUSIONS: The application is not recommended for approval. Specific comments are provided in "E. Review Notes" and "Microbiologist’s Draft of Letter to Applicant".

Paul Stinavage, Ph.D.

cc: Original NDA 19-732
    HFD-160/Stinavage/Consult File
    HFD-510/Div File/L. Pauls
    Drafted by: P. Stinavage
    R/D initialed by P. Cooney
Redacted ______ page(s)

of trade secret and/or

confidential commercial

information from

Microbiology Review #1

(S-009)
TYPOGRAPHICAL ERROR

Microbiology Review #2 (10/04/95)-
Title, “Microbiologist’s Review #3” is a typographical error. Should state Microbiologist’s Review #2.
A. 1. NDA 19-732/S-009
   APPLICANT: TAP Pharmaceuticals, Inc.
   Bannockburn Lake Office Plaza
   2355 Waukegan Road
   Deerfield, IL  60015

2. PRODUCT NAMES:  Lupron Depot® 7.5 mg (leuprolide acetate for depot suspension) for Injection.

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
   Sterile depot suspension for intramuscular injection. The Supplement provides for packaging the product in a dual-chambered syringe.

4. METHODS OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
   Lupron® Depot 7.5 mg is used for palliative treatment of advanced prostate cancer.

B. 1. DATE OF INITIAL SUBMISSION:  30 December 1994

2. DATE OF AMENDMENT:  1 September 1995
3. RELATED DOCUMENTS:

<table>
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<tr>
<th>Document</th>
<th>Subject</th>
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<tbody>
<tr>
<td>NDA 19-010</td>
<td>Manufacture of Lupron Injection</td>
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<tr>
<td>NDA 19-732</td>
<td>Manufacture of Lupron Depot® 7.5 mg</td>
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<td>NDA 20-011</td>
<td>Manufacture of Lupron Depot® 3.75 mg</td>
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<td>NDA 20-263</td>
<td>Manufacture of Lupron Depot-PED® 7.5 mg,</td>
</tr>
<tr>
<td></td>
<td>11.25 mg, and 15 mg</td>
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Table 1. Documents referenced in the Supplement.

4. ASSIGNED FOR REVIEW: 22 September 1995

C. REMARKS: The amendment is a response to deficiencies found in the 30 June 1995 review of the Supplemental New Drug Application.

D. CONCLUSIONS: The application is recommended for approval. The applicant should be reminded of their commitment to provide information post-approval. See "Draft Letter".

[Signature]

Paul Stinavage, Ph.D.

4 October 1995

CC: Original NDA 19-732
    HPD-160/Stinavage/Consult File
    HFD-510/Div File/L. Pauls
    Drafted by: P. Stinavage, 4 October 1995
    R/D initialed by P. Cooney, 4 October 1995
Redacted  4  page(s)
of trade secret and/or confidential commercial information from Microbiology Review #2 (S-009)
APPLICATION NUMBER:
NDA 19-732/S-009

CORRESPONDENCE
September 1, 1995

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE:   Lupron Depot® 7.5 mg (leuprolide acetate for depot suspension)
NDA   19-732/S-009 (Prefilled Dual Chamber Syringe)
Amendment No. 002 (Response to Deficiency Letter)

Dear Doctor Sobel:

Pursuant to 21 CFR 314.120(a)(1) we are amending the SNDA 009 for
Prefilled Dual Chamber Syringe (additional container/closure system).

Submitted herewith is the complete response to the deficiency letter dated

Attached is the information required to complete this amendment.

Sincerely,

Aruna Dabhokar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp
Attachment

REVIEWED COMPLETED

CSO ACTION:

☐ LETTER  □ N.A.

CSO INITIALS  11/10/95  DATE  11/25/95
May 24, 1995

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 7.5 mg (leuprolide acetate for depot suspension)
NDA 19-732/S-009 (Prefilled Dual Chamber Syringe)
Amendment No. 091 (Response to Deficiency Letter)

Dear Doctor Sobel:

Pursuant to 21 CFR 314.120 (a) (1) and as notified in our letter dated May 1, 1995, we are amending the SNDA 009 for Prefilled Dual Chamber Syringe (additional container/closure system).

Submitted herewith is the complete response to the non-approvable letter dated April 25, 1995.

Some of the additional information requested from [ ], the holder of DMF [ ], required response from Takeda which is also included in this amendment.

Please note that [ ] has-submitted a response to update DMF [ ].

A desk copy of this submission has been sent to Dr. Niu.

Attached is all the information to complete this amendment.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp
Attachment
Tap Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Regulatory Products Manager
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:

Please refer to your December 30, 1994 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Lupron® Depot (leuprolide acetate for depot suspension), 7.5 mg (NDA 19-732);
- Lupron® Depot (leuprolide acetate for depot suspension), 3.75 mg (NDA 20-011); and
- Lupron® Depot PED (leuprolide acetate for depot suspension), (NDA 20-263).

We have completed our review and find the information presented is inadequate, and the supplemental applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

**Manufacturing/Quality Control:**

1. 
2. 
3. 
4. 

**Microbiology:**

1. 
2. 
Redacted 2 page(s) of trade secret and/or confidential commercial information from Correspondence (Non-Approvable Letter - 4/25/95) (S-009)
Please note, additional information has been requested from the [ ], the holder of DMF [ ]. A complete response must be submitted before the review clock can be activated.

Furthermore, these supplemental applications cannot be approved until we receive notification that the establishment is within cGMP compliance.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw these supplemental applications. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.
If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

Solomon Sobel, M.D.
Director
Division of Metabolism and
Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDAs 19-732, 20-011, 20-263
HFD-510
DISTRICT OFFICE
HFD-80
HFD-160/PStinavich/PCooney
HFD-510/CNiu/YYChiu
HFD-510/L.L.Pauls

drafted: LPauls/April 20, 1995/N19732NA.S09

Concurrences:
CNiu, YYChiu 04.24.95

NOT APPROVABLE (NA)
TAP Pharmaceuticals, Inc.
2355 Waukegan Road
Deerfield, IL 60015

Attention: Aruna Dabholkar, M.D.

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lupron Depot 7.5mg

NDA Number: 19-732

Supplement Number: S-009

Date of Supplement: December 30, 1994

Date of Receipt: January 03, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control Room 14B-03
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

[Signature]

Supervisory Consumer Safety Officer
Division of Metabolism and Endocrine Drug Products
Center for Drug Evaluation and Research
December 30, 1994

Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-03
Center for Drugs Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 7.5 mg (leuprolide acetate for depot suspension)
NDA 19-732
Supplemental Application for Prior Approval

Dear Doctor Sobel:

The sponsor, TAP Pharmaceuticals Inc., submits this Supplemental Application under the provisions of Section 505(i) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.70 (b) (2) (vi) and (vii).

This supplement requests for approval of an additional container closure system for Lupron Depot 7.5 mg approved under NDA 19-732.

This supplement consists of 3 volumes labeled as Volume 1.1 - 1.3. The volume 1.1 contains all chemistry, manufacturing and controls information. Volume 1.2 contains information on facilities and process validations for review by CDER's Sterile Products Group. This volume is labeled as "Sterile Process Validation Package." Three copies of each Volume 1.1 and 1.2 are submitted. Four copies of the Methods Validation Package (Volume 1.3) are submitted and are labeled appropriately.

Attached is the information required for this supplement.

Sincerely,

Aruna Dabholkar, M.D.
Regulatory Products Manager
(708) 317-4893

AD/pjp
Attachment