CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:
NDA 20-263/S-012

Name: Lupron Depot-PED
7.5 mg, 11.25 mg, 15 mg
(leuprolide acetate for depot suspension)
&
Lupron Injection
(leuprolide acetate)

Sponsor: TAP Pharmaceuticals, Inc.

Approval Date: August 13, 1999
**APPLICATION NUMBER:**
NDA 20-263/S-012

**CONTENTS**

<table>
<thead>
<tr>
<th>Reviews / Information Included in this Review</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
</tr>
<tr>
<td>Approvable Letter(s)</td>
</tr>
<tr>
<td>Final Printed Labeling</td>
</tr>
<tr>
<td>Medical Review(s)</td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
</tr>
<tr>
<td>EA/FONSI</td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
</tr>
<tr>
<td>Statistical Review(s)</td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
</tr>
<tr>
<td>Clinical Pharmacology/Biopharmaceutics Review(s)</td>
</tr>
<tr>
<td>Administrative Document(s)</td>
</tr>
<tr>
<td>Correspondence Document(s)</td>
</tr>
</tbody>
</table>
APPLICATION NUMBER:
NDA 20-263/S-012

APPROVAL LETTER
NDA 19-732/S-016
NDA 19-943/S-010
NDA 20-011/S-016
NDA 20-263/S-012
NDA 20-517/S-006
NDA 20-708/S-006

TAP Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:


We acknowledge receipt of your submissions dated June 21, 1999 and July 9, 1999.

These supplemental new drug applications provide for a new manufacturing site for the prefilled dual chamber syringe.

We have completed the review of these supplemental applications and they are approved.

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

If you have any questions, contact Jennifer Mercier, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research
cc:
HFD-580/Div. Files
HFD-580/J.Mercier
HFD-580/Raraick/Mann/Rhee/De
HFD-160/Cooney/Vincent
HFD-094/DDMS (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JM/August 13, 1999
final: August 13, 1999

APPROVAL (AP)
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-263/S-012

APPROVABLE LETTER
TAP Holdings, Inc.
Attention: Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Dabholkar:


We acknowledge receipt of your faxed submission dated June 21, 1999.

These supplements propose a new manufacturing site for manufacturing the prefilled dual chamber syringe.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to address the following:

1. [Blank]

2. [Blank]

3. [Blank]
Redacted 1 page(s)
of trade secret and/or
confidential commercial
information from

Approvable Letter
S-012
8.

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 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment 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.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

William Mann, M.D.
Deputy Dir 6/25/97

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products,
(HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Best Possible Copy
cc:
HFD-580/Div. Files
HFD-580/J.Mercier/Rumble
HFD-580/Rarick/Mann/Rhee/De
HFD-95/DDMS
DISTRICT OFFICE

Drafted by: JM/June 25, 1999
final: June 25, 1999
filename:

APPROVABLE (AFV)
APPLICATION NUMBER:
NDA 20-263/S-012

CHEMISTRY REVIEW(S)
CHEMIST REVIEW
OF Supplement

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012
   Letterdate: 12-23-98
   Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES: None
   Letterdate:
   Stampdate:
5. RECEIVED BY CHEMIST: 1-3-99

6. APPLICANT NAME AND ADDRESS:
   TAP Pharmaceuticals Inc.
   2355 Waukegan Road
   Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED®, Lupron®

8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

![Chemical Structure Diagram]

10. DOSAGE FORM(S): Sterile Depot Suspension for Injection

11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml

12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty

13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection

14. RECORDS & REPORTS CURRENT: Yes

15. RELATED IND/NDA/DMF: This is part of a bundled supplements. Related applications include the following:
16. PRIOR APPROVAL SUPPLEMENT PROVIDES FOR: New manufacturing site for manufacturing the prefilled dual chamber syringe

17. COMMENTS:
The prefilled dual chamber syringe was approved as a new container closure system in October 1995 (NDA 19-732/S009). The manufacturing was approved at Osaka plant in Japan. The manufacturer, Takeda Chemical Industries submitted this supplement to add an additional site for filling the syringes at Hikari plant. The diluent used to fill in these syringes will be manufactured at the Hikari plant. The active drug, [ chemical formula ] will be manufactured at the previously approved sites (Shanan plant and Osaka plant). The syringe components, manufacturing method and the final product specifications and testing methods are the same as approved before. The new plant and the manufacturing process are validated. Three months of accelerated and RT stability has been included in the application for one production lot of each of Lupon Depot 3.75 mg, 7.5 mg, 11.25 mg and 15 mg and the results are satisfactory. Quality of the product manufactured at Hikari plant was compared with the corresponding one manufactured at the approved site, Osaka plant and no significant changes have been observed.

The new facility (Hikari plant) should be inspected according to CFR 314.70 and a request had been forwarded through EES on 28-December-1998. Overall recommendation is found 'acceptable' on 6/15/99 based on an inspection performed on 5-19-99.

Since the diluent will be manufactured at the Hikari plant and it needs to be sterile, the application was also reviewed by a microbiologist (Dr. Carol K. Vincent, HFD-805) and it was found deficient.

18. CONCLUSIONS AND RECOMMENDATIONS:
This application is 'approvable' pending satisfactory resolution of the microbiologist's concerned issues as delineated in the draft letter.

Issue "Approvable" letter

19. REVIEWER NAME
Swapan K. De, Ph.D.

SIGNATURE
Swapan K. De

DATE COMPLETED
6/15/99

cc:
Orig. NDA #20-263
HFD-580/Division File
HFD-580/Mercierj
HFD-580/MRhee/SDe

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012
Redacted 1 page(s)
of trade secret and/or confidential commercial information from

Chemistry Review #1
S-012
**Application:** NDA 20263/012

**Stamp:** 28-DEC-1998

**Regulatory Due:** 28-APR-1999

**Applicant:** TAP HOLDINGS

2255 WAUKEEGAN RD

DEERFIELD, IL 60015

**Priority:** 5S

**Org Code:** 580

**Action Goal:**

**District Goal:** 24-MAR-1999

**Brand Name:** LUPRON DEPOT PEDIATRIC KIT

**Estab. Name:**

**Generic Name:** LEUPROLIDE ACETATE

**Dosage Form:** (FOR INJECTION)

**Strength:** (7.5,15,11.25)MG, 5MG/ML

**Application Comment:** SUPPLEMENT PROVIDES FOR NEW MANUFACTURING SITE FOR MANUFACTURING THE PREFILLED DUAL CHAMBER SYRINGE. SAME CHANGES WILL BE APPLICABLE TO NDA 19943-SCM010, 20011-SCM016 AND 19732-SCM016. (on 29-JAN-1999 by S. DE (HFD-580) 301-827-7516)

**FDA Contacts:** S. DE (HFD-580) 301-827-7516, Review Chemist

**Overall Recommendation:** ACCEPTABLE on 15-JUN-1999 by M. EGAS (HFD-322) 301-594-0095

**Establishment:** 9610307

TAKEDA CHEMICAL INDUSTRIES LTD

4720 TAKEDA MITSUI

HIKARI, YAMAGUCHI, JA

**DMF No:**

**Responsibilities:** FINISHED DOSAGE MANUFACTURER

**Profile:** SVS

**OAI Status:** NONE

**Estab. Comment:** TAKEDA CHEMICAL INDUSTRIES PROPOSED THIS NEW SITE TO BE RESPONSIBLE FOR MANUFACTURING THE SYRINGE ASSEMBLY AS WELL AS FILLING THE SYRINGE WITH DRUG PRODUCT FOLLOWING THE PREVIOUSLY APPROVED PROCEDURE. THE DILUENT USED TO FILL THE SYRINGES WILL ALSO BE MANUFACTURED AT THIS NEW SITE (HIKARI PLANT). THE ACTIVE DRUG, [ ] WILL BE MANUFACTURED AT THE PREVIOUSLY APPROVED SITES. THE NEW PLANT AND THE MANUFACTURING PROCESS ARE VALIDATED. BATCH INSTRUCTIONS AND BATCH RECORD FOR ONE LOT ARE SUBMITTED. THREE MONTHS OF ACCELERATED AND RT STABILITY DATA ARE SUBMITTED FOR ONE PRODUCTION LOT EACH OF LUPRON DEPOT 3.75 MG, 7.5 MG, 11.25 MG AND 15 MG. (on 29-JAN-1999 by S. DE (HFD-580) 301-827-7516)

<table>
<thead>
<tr>
<th>Milestone Name</th>
<th>Date</th>
<th>Req. Type</th>
<th>Insp. Date</th>
<th>Decision &amp; Reason</th>
<th>Creator</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUBMITTED TO OC</td>
<td>29-JAN-1999</td>
<td></td>
<td></td>
<td></td>
<td>DES</td>
</tr>
<tr>
<td>SUBMITTED TO DO</td>
<td>29-JAN-1999</td>
<td>PS</td>
<td></td>
<td></td>
<td>FERGUSONS</td>
</tr>
<tr>
<td>ASSIGNED INSPECTION</td>
<td>02-FEB-1999</td>
<td>PS</td>
<td></td>
<td></td>
<td>EGASM</td>
</tr>
<tr>
<td>INSPECTION SCHEDULED</td>
<td>15-APR-1999</td>
<td></td>
<td>19-MAY-1999</td>
<td>ACCEPTABLE</td>
<td>IRIVERA</td>
</tr>
<tr>
<td>INSPECTION PERFORMED</td>
<td>24-MAY-1999</td>
<td></td>
<td>19-MAY-1999</td>
<td>ACCEPTABLE</td>
<td>EGASM</td>
</tr>
<tr>
<td>DO RECOMMENDATION</td>
<td>15-JUN-1999</td>
<td></td>
<td></td>
<td>DISTRICT RECOMMENDATION</td>
<td>EGASM</td>
</tr>
<tr>
<td>OC RECOMMENDATION</td>
<td>15-JUN-1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHEMIST REVIEW OF Supplement CHEMISTRY REVIEW #2

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012
   Letterdate: 12-23-98
   Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES:
   Letterdate: 6/21/99
   Stampdate: 
5. RECEIVED BY CHEMIST: 1-3-99/6-21-99

6. APPLICANT NAME AND ADDRESS:
   TAP Pharmaceuticals Inc.
   2355 Waukegan Road
   Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED\textsuperscript{R}, Lupron\textsuperscript{R}

8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

10. DOSAGE FORM(S): Sterile Depot Suspension for Injection

11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml

12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty

13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection

14. RECORDS & REPORTS CURRENT: Yes

15. RELATED IND/NDA/DMF: This is part of a bundled supplements. Related applications include the following:
16. PRIOR APPROVAL SUPPLEMENT PROVIDES FOR: New manufacturing site for manufacturing the prefilled dual chamber syringe

17. COMMENTS:
The amendment sent by the sponsor on 21-June-1999 was the response of the microbiologist's comments (send to the sponsor on 18 June-1999). The response, as reviewed by the microbiologist (Dr. Carol K. Vincent, HFD-805) is still found to be deficient.

18. CONCLUSIONS AND RECOMMENDATIONS:
This application is 'approvable' pending satisfactory resolution of the microbiologist's concerned issues as delineated in the draft letter of the microbiologist's review.

Issue "Approvable" letter

19. REVIEWER NAME
Swapan K. De, Ph.D.

SIGNATURE
Swapan K. De

DATE COMPLETED
6/24/99

cc:
Orig. NDA #20-263
HFD-580/Division File
HFD-580/Mercier]
HFD-580/MRhee/SDe

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012
CHEMIST REVIEW OF Supplement CHEMISTRY REVIEW #2

1. ORGANIZATION: HFD 580
2. NDA NUMBER: 20-263
3. SUPPLEMENT NUMBERS/DATES: SCM-012
   Letterdate: 12-23-98
   Stampdate: 12-28-98
4. AMENDMENTS/REPORTS/DATES:
   Letterdate: 6/21/99 [fax]; 7/9/99
   Stampdate: 7-12-99
5. RECEIVED BY CHEMIST: 1-3-99/6-21-99/7-14-99

6. APPLICANT NAME AND ADDRESS:
   TAP Pharmaceuticals Inc.
   2355 Waukegan Road
   Deerfield, IL-60015

7. NAME OF DRUG: Lupron Depot-PED®, Lupron®

8. NONPROPRIETARY NAME: leuprolide acetate for depot suspension

9. CHEMICAL NAME/STRUCTURE:

10. DOSAGE FORM(S): Sterile Depot Suspension for Injection

11. POTENCY: 7.5 mg, 15mg, 11.25 mg, 5 mg/ml

12. PHARMACOLOGICAL CATEGORY: Treatment of Central Precocious Puberty

13. HOW DISPENSED: Intramuscular Injection, Subcutaneous Injection

14. RECORDS & REPORTS CURRENT: Yes
15. RELATED IND/NDA/DMF: This is part of a bundled supplements. Related applications include the following:

NDA 19732-scm016
NDA 20011-scm016
NDA 19943-scm010
NDA 20517-scm006
NDA 20708-scm006

16. PRIOR APPROVAL SUPPLEMENT PROVIDES FOR: New manufacturing site for manufacturing the prefilled dual chamber syringe

17. COMMENTS:
The amendment sent by the sponsor on 07-July-1999 was the response of the "approvable" letter from the Agency (send to the sponsor on 25 June-1999). The response is found satisfactory (see attached review) as reviewed by the microbiologist (Dr. Carol K. Vincent, HFD-805).

18. CONCLUSIONS AND RECOMMENDATIONS:
Based on the information provided by the firm and the microbiologist's recommendation, this supplement may be approved.

Issue "Approval" letter

19. REVIEWER NAME
Swapan K. De, Ph.D.

SIGNATURE

DATE COMPLETED 8/12/99

cc:
Orig. NDA #20-263
HFD-580/Division File
HFD-580/Mercierj
HFD-580/MRhee/SDe

R/D Init by: MJ Rhee, Ph.D.

filename: nda20263.scm012a2
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-263/S-012

MICROBIOLOGY REVIEW(S)
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT FOR
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805
FEBRUARY 11, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

NDA / Supplement Number: NDA 19-732 / SCM-016
NDA 20-517 / SCM-006
NB: These supplements are reviewed in tandem.

Drug Product: NDA 19-732 / SCM-016 Lupron Depot® 7.5mg [leuprolide acetate depot suspension]
NDA 20-517 / SCM-006 Lupron Depot®-3 month 22.5mg and -4 month 30mg [leuprolide acetate depot suspension]

Received for Review: January 4, 1999

COMIS User Fee Goal Date: April 28, 1999
COMIS User Fee Due Date: June 26, 1999

Applicant: TAP Pharmaceuticals Inc.
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Manufacturer and Site: Takeda Chemical Industries
4720 Mitsui Aza Takeda
Hikari, Yamaguchi 743-8502
Japan

Supplement Provides For: New manufacturing site in Hikari, Japan for the manufacture of the prefilled dual chamber syringe.

Dosage Form / Route of Administration: Pre-filled syringe; for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

Conclusions and Recommendations: We do not recommend approval of the supplements because inadequate sterilization process validation information for a new manufacturing location has been provided.

See Review Notes, below.

cc:
NDA 19-732 / SCM-016
NDA 20-517 / SCM-006
HFD-580/CKish / SDe-
HFD-160/Consult file/CKVincent [HFD-805]
Drafted by: CKVincent/01-29-99 C:CKV972NDA20517.006

Carol K. Vincent, HFD-805
2-11-99

PHC 2/23/99

JUN 28 1999
Redacted 6 page(s) of trade secret and/or confidential commercial information from Microbiology Review #1 S-012
MICROBIOLOGIST’S REVIEW NO. 2 OF SUPPLEMENT FOR
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805

JUNE 23, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

NDA / Supplement Number:
NDA 19-732 / SCM-016
NDA 19-943 / SCM-010
NDA 20-011 / SCM-016
NDA 20-263 / SCM-012
NDA 20-517 / SCM-006
NDA 20-708 / SCM-006

Drug Product: Lupron Depot® [leuprolide acetate depot suspension]

Document Date: December 23, 1998

Amendment: June 21, 1999 [fax]

Amendment received for review: June 21, 1999

COMIS User Fee Due Date: June 26, 1999 COMIS User Fee Goal Date: April 28, 1999

Name and Address of Applicant: Takeda Chemical Industries
Bannockburn Lake Office Plaza
2355 Waukegan Road
Deerfield, IL 60015

Name and Address of Manufacturer:

Takeda Chemical Industries
4720 Mitsui Aza Takeda
Hikari, Yamaguchi 743-8502
Japan

Supplement Provides For: New manufacturing site in Hakari, Japan for the manufacture of the prefilled dual chamber syringe.

Dosage Form: Pre-filled syringe for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

Conclusions and Recommendations: The subject supplements are approvable pending satisfactory review of sterilization process validation information requested herein. See E:

Review Notes: below.

cc:
NDA 19-732 / SCM-016
NDA 19-943 / SCM-010
NDA 20-011 / SCM-016
NDA 20-263 / SCM-012
NDA 20-517 / SCM-006
NDA 20-708 / SCM-006
HFD-580/Rarick/MRhee/SDe/LPauls/JMercier
HFD-160/Consult file/CKVincent [HFD-805]
Drafted by: CKVincent/06-22-99

CA CKV99 NDA 19732.016

Carol K. Vincent, HFD-805
06-23-99
FAC 6/24/99
Redacted 8 page(s) of trade secret and/or confidential commercial information from

Microbiology Review #2

S-012
MICROBIOLOGIST'S REVIEW NO. 3 OF SUPPLEMENT FOR
DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580
OFFICE OF NEW DRUG CHEMISTRY, MICROBIOLOGY STAFF, HFD-805

AUGUST 11, 1999

Reviewing Microbiologist: Carol K. Vincent, HFD-805

NDA / Supplement Number:
NDA 19-732 / SCM-016
NDA 19-943 / SCM-010
NDA 20-011 / SCM-016
NDA 20-263 / SCM-012
NDA 20-517 / SCM-006
NDA 20-708 / SCM-006

Drug Product: Lupron Depot® [leuprolide acetate depot suspension]

Document Date: July 9, 1999

Received for review: June July 16, 1999

COMIS User Fee Due Date: August 25, 26, 1999

Name and Address of Applicant: Name and Address of Manufacturer:
TAP Pharmaceuticals, Inc. Takeda Chemical Industries
Bannockburn Lake Office Plaza 4720 Mitsui Aza Takeda
2355 Waukegan Road Hikari, Yamaguchi 743-8502
Deerfield, IL 60015 Japan

Supplement Provides For: New manufacturing site in Hakari, Japan for the manufacture of the prefilled dual chamber syringe.

Dosage Form: Pre-filled syringe for injection. Sterile diluent to be mixed with dry drug product powder at point of use.

Conclusions and Recommendations: We recommend approval for the subject supplements.

See E: Review Notes: below.

cc:
NDA 19-732 / SCM-016
NDA 19-943 / SCM-010
NDA 20-011 / SCM-016
NDA 20-263 / SCM-012
NDA 20-517 / SCM-006
NDA 20-708 / SCM-006
HFD-580/Rarick/MRhee/SDe/LPauls/JMercier
HFD-160/Consult file/CKVincent [HFD-805]
Drafted by: CKVincent/08-03-99

C:\CKV99\19732106.3RD

[Signature]
Carol K. Vincent, HFD-805 8-11-99

[Signature]
8/12/99
Redacted ___ page(s)
of trade secret and/or
confidential commercial
information from

Microbiology Review #3
S-012
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 20-263/S-012

CORRESPONDENCE
July 9, 1999

Lisa M. Rarick, MD
Director, Division of Reproductive and Urologic Drug Products (HFD-580)
Attn: Central Document Room 17 B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 19-732/S-016
Lupron Depot * 7.5 mg
(leuprolide acetate for depot suspension)
Amendment to Supplemental Application for New Manufacturing Site (Hikari Plant) for Pre-Filled Dual Chamber Syringe

Dear Dr. Rarick:


The field copy of this amendment is being submitted to the Division. In accordance with 21 CFR 314.5(K)(3), TAP Holdings Inc. certifies that the field copy is a true copy of the information submitted in this amendment to the supplemental application.

Following are the comments from the approvable letter and the responses of TAP Holdings Inc. to those comments:
Redacted __3__ page(s)
of trade secret and/or
confidential commercial
information from

Correspondence (Amendment to Suppl. Application)
S-012
Please do not hesitate to contact me at 847-317-5780 if you have any questions.

Sincerely,

[Signature]

Dean Sundberg
Director, Regulatory Affairs
July 1, 1999

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-011/S-016
19-732/S-016
19-943/S-010
20-263/S-012
20-517/S-006
20-708/S-006

RE: Lupron Depot/Hikari Plant SNDAs

Dear Dr. Rarick,

This is to notify that the sponsor TAP Holdings Inc. intends to file amendments to these supplemental applications as requested in the approvable letter dated June 25, 1999.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs

AD/mea
June 21, 1999

Division of Reproductive and Urologic Drug Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation & Research
Food and Drug Administration
5800 Fishers Lane
Rockville, MD 20857

RE: Lupron Depot® 7.5mg (leuprolide acetate depot suspension)

NDA 19-732, S-016
Amendment No. 001

Dear Dr. Rarick,

The sponsor, TAP Holdings Inc., submits this Amendment to the supplemental Application under the provisions of Section 505(l) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.60 (a).

This amendment includes the data requested by the microbiology reviewer, communicated to the sponsor via a draft letter on June 16, 1999.

Attached is the information required for this amendment.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893 phone
(847) 317-5795 fax

AD/mea

Attachments
NDA 20-263/S-012

Tap Holdings, Inc.
2355 Waukegan Road
Deerfield, IL 60015

Attention: Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs

Dear Dr. Dabholkar:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Lupron Depot-PED® 7.5mg, 11.25mg & 15mg (leuprolide acetate/injection/depot suspension)

NDA Number: 20-263

Supplement Number: S-012

Date of Supplement: December 23, 1998

Date of Receipt: December 28, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 26, 1999, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

[Signature]
Lana Pauls
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research
cc:
Original NDA 20-263/S-012
HFD-580/Div. Files
HFD-580/CSO/C. Kish

SUPPLEMENT ACKNOWLEDGEMENT
December 23, 1998

Division of Reproductive and Urologic Products, HFD-580
Document Control Room 17B-20
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE:  **Lupron Depot-PED® 7.5mg, 11.25mg & 15mg (leuprolide acetate/injection/depot suspension)**

NDA  20-263
Supplemental Application for new manufacturing site for manufacturing the prefilled dual chamber syringe

Dear Dr. Rarick,

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

This supplement requests for approval of a new manufacturing site for the manufacturing of the prefilled dual chamber syringe.

All the required information is submitted under NDA 19-732, in a supplemental application of this date. Attached is the form 356h with this request to cross reference.

Sincerely,

Aruna Dabholkar, M.D.
Associate Director, Regulatory Affairs
(847) 317-4893 phone
(847) 317-5795 fax

AD/mea
Attachment