CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
NDA 21-856

CHEMISTRY REVIEW(S)
CMC Memo to File

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<td>Uloric (febuxostat)</td>
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<td>Subject:</td>
<td>Approval recommendation</td>
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<td>Reviewer:</td>
<td>Dr. Olen Stephens</td>
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Pursuant the overall "acceptable" recommendation given on Jan 16, 2009 of the manufacturing facilities by the Office of Compliance, CMC recommends that NDA application 21-856 be approved.

HFD-/Division File
HFD-170
HFD-170/M. Sullivan

Olen Stephens, Ph.D.
Chemistry Reviewer

Ali Al-Hakim, Ph.D.
Branch II Chief, ONDQA
NDA 21-856

Uloric
(febuxostat tablets)

TAP Pharmaceutical Products Inc.

Olen M. Stephens
Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division I, Branch II
for the
Division of Anesthesia, Analgesia and
Rheumatology Products
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### Chemistry Review Data Sheet

1. NDA 21-856

2. REVIEW #: 4

3. REVIEW DATE: 18-Dec-2008

4. REVIEWER: Olen M. Stephens

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7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 N. Field Drive
         Lake Forest, IL 60045
Representative: Binita Kwankin, Assistant Director, Regulatory Affairs
Telephone: (847) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

   a) Proprietary Name: Uloric
   b) Non-Proprietary Name (USAN): febuxostat tablets
   c) Code Name/# (ONDC only): TMX-67, TEI-6720, A-319198.0
   d) Chem. Type/Submission Priority (ONDC only):
      • Chem. Type: 1 (new molecular entity)
      • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 40 mg and 80 mg per tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED:  ✔ Rx    _ OTC
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

   - [ ] SPOTS product – Form Completed
   - [x] Not a SPOTS product

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

   2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

   ![Chemical Structure](image)

   C_{16}H_{16}N_{2}O_{3}S  \quad MW 316.37

17. **RELATED/SUPPORTING DOCUMENTS:**

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CHEMISTRY REVIEW

Chemistry Review Data Sheet

*See page 78 of Review #1 under container closure system for details.

1 Action codes for DMF Table:
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Other codes indicate why the DMF was not reviewed, as follows:
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II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

A. Labeling & Package Insert

Response to FDA Discipline Review Letter Dated June 14, 2006

The Agency’s comments are in bold.

The Applicant’s response is in normal font.
_____ Page(s) Withheld

/  Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Olen Stephens
1/6/2009 10:15:11 AM
ENV ASSESSMENT
Revised Labeling Review

Ali Al-Hakim
1/6/2009 12:57:40 PM
CHEMIST
NDA 21-856

Uloric
(febuxostat tablets)

TAP Pharmaceutical Products Inc.

Olen M. Stephens

Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division I, Branch II
for the
Division of Anesthesia, Analgesia and
Rheumatology Products
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III. List Of Deficiencies To Be Communicated ....................................................... Error! Bookmark not defined.
Chemistry Review Data Sheet

1. NDA 21-856

2. REVIEW #: 3

3. REVIEW DATE: 14-Oct-2008

4. REVIEWER: Olen M. Stephens

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   Resubmission (AZ)  17-Jul-2008

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b(4)
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The Chemistry Review for NDA 21-856

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, the NDA is recommended for approval, pending an "Acceptable" Office of Compliance recommendation.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

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

(1) Drug Substance
(No changes to the drug substance sections in the current submission.)

The USAN and INN name for the active pharmaceutical ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance characterization, manufacturing and controls was provided in the original NDA and has been previously reviewed. The drug substance is produced as [b(4)] which is consistently manufactured by [b(4)]

Febuxostat solubility is highly pH dependent. At pH ≤ 5.5 solubility is minimal — [b(4)], and exceeds — [b(4)] mg/mL in pH 6.8 phosphate buffer.

Febuxostat is stable [b(4)] for 36 months at 25°C/60% RH and 6 months at 40°C/75% RH. Furthermore, stress testing at 70°C, in packages ranging in protective properties, showed no change [b(4)] The stability data show no increase in impurities, nor trends in other attributes, and therefore support the proposed retest period of [b(4)]

(2) Drug Product

The drug product is an immediate release film-coated tablet containing febuxostat in two strengths: 40 mg and 80 mg. Except for the color (Opadry II, Green
coating the tablets, all the excipients are pharmacopeial (USP/NF). Critical parameters in the manufacturing process were identified as: The 40 mg tablets are packaged in 30, 90, and 500 count bottles and 100 count blisters (10 cards x 10 tablets). The 80 mg tablets are packaged in 30, 100, and 1000 count bottles and 3 and 100 count blisters (10 cards x 10 tablets). The two dosage forms are supported by real time stability data in both commercial packaging configurations.

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

Febuxostat tablets will be dispensed by prescription only for the management of hyperuricemia in patients with gout. The recommended dose is 40 mg or 80 mg QD.

C. Basis for Approvability or Not-Approval Recommendation

Chemistry, Manufacturing and Controls deficiencies for the drug substance and the drug product have been communicated to the applicant during the previous review cycles and have been sufficiently addressed and resolved, except for the discriminatory ability of the proposed dissolution method, for the two strengths (see CMC reviews #1 and #2). In the current resubmission, the dissolution method and acceptance criterion have been amended to conditions that can discriminate between the 40 mg and 80 mg tablets by changing the pH of the media used in the method. The new method validation has been reviewed and deemed adequate.

All labeling comments from review #1 have been conveyed to the applicant in the Agency 6/14/06 “Approvable” letter. New labeling has been re-submitted.

There are no changes in the manufacturing facilities for febuxostat. The Office of Compliance found all the facilities used in the manufacture and control of the drug substance and drug product acceptable on 8/1/05 (Chemistry Review #1), and on 6/14/06 (Chemistry Review #2). The facilities have been resubmitted for re-evaluation to the Office of compliance and are pending inspection.
III. Administrative

A. Reviewer's Signature: electronically signed in DFS
   Olen M. Stephens

B. Endorsement Block: electronically signed in DFS

C. CC Block: entered electronically in DFS
9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Olen Stephens
10/30/2008 01:51:46 PM
ENV ASSESSMENT

Ali Al-Hakim
10/31/2008 09:51:08 AM
CHEMIST
NDA 21-856

Uloric
(febuxostat tablets)

TAP Pharmaceutical Products Inc.

Sue-Ching Lin
Review Chemist

Office of New Drug Quality Assessment
Pre-Marketing Division III, Branch V
for
Division of Anesthesia, Analgesia, and
Rheumatology Products
Chemistry Review Data Sheet

1. NDA 21-856

2. REVIEW #: 2

3. REVIEW DATE: 14-July-2006

4. REVIEWER: Sue-Ching Lin

5. PREVIOUS DOCUMENTS:

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<td>Amendment (BC) (control of excipients and comparability protocol for DP scale-up)</td>
<td>28-Jan-2005</td>
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<td>Amendment (BL)</td>
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7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 N. Field Drive
         Lake Forest, IL 60045
Representative: Binita Kwankin, Assistant Director, Regulatory Affairs
Telephone: (847) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPe:

a) Proprietary Name: Uloric
b) Non-Proprietary Name: febuxostat tablets
c) Code Name/# (ONDQA only): TMX-67, TEI-6720
d) Chem. Type/Submission Priority (ONDQA only):
   • Chem. Type: 1 (new molecular entity)
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients
    with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: √Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ____SPOTS product – Form Completed
    √____Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(3-cyano-4-(2-methylpropoxy)phenyl)-4-methylthiazole-5-carboxylic acid

```
CH3
CH3
CH3
CH2-O

CH3

C16H16N2O3S    MW 316.37
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

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*See page 78 of Review #1 under for details.

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

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

B. Other Documents:

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The Chemistry Review for NDA 21-856

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC review perspective, this NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

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

(1) Drug Substance

The active ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance was provided in the NDA. The drug substance is produced as manufactured by controlling

[Redacted]

Solubility of febuxostat is highly pH dependent. Up to pH 5.5, the solubility is minimal —mg/mL, while in pH 6.8 phosphate buffer, solubility exceeds —mg/mL.

Febuxostat was shown to be stable for —— months at 25°C/60%RH and 6 months at 40°C/75% RH in the commercial container

[Redacted]. Furthermore, stress testing at up to 70°C, in packages ranging in protective properties, showed no change ———. The submitted stability data, which also show no increase in impurities, support the proposed retest period of
(2) Drug Product

The drug product is an immediate release tablet containing febuxostat in two strengths: 80 mg and 120 mg. With the exception of the color (Opadry II, Green used in coating tablets, all the excipients are USP/NF materials. The critical parameters in the manufacturing process were identified as The tablets are packaged in bottles and blisters.

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

Febuxostat tablets will be dispensed by prescription only. The drug product is indicated for the management of hyperuricemia in patients with gout. The recommended dose is

The submitted drug product stability data include long-term stability data for 18 months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. The supportive data include 18 months of data for febuxostat 20 mg and 12 months of data for 40 mg tablets. The supportive lots were manufactured using the same formulation as the proposed commercial product. The stability data support the proposed expiration period for the drug product stored at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

As stated in the executive summary of chemistry review #1 of this NDA, the only pending CMC issue was related to the drug product dissolution method and acceptance criteria. The deficiency was included in the FDA 10/14/05 “approvable” letter. In response, the applicant revised the dissolution method and acceptance criteria as requested by the FDA. The response is adequate.

All the labeling comments from review #1 have been conveyed to the applicant in the 6/14/06 letter.

All the facilities used in the manufacture and control of the drug substance and drug product were found to be acceptable by the Office of Compliance on 8/1/05, as indicated in Chemistry Review #1. Establishment evaluation was requested again for this resubmission. The Office of Compliance issued an “acceptable” recommendation again on 6/14/06 for all the sites used in the manufacture and control of the drug substance and drug product.
III. Administrative

A. Reviewer’s Signature: electronically signed in DFS
   Sue-Ching Lin

B. Endorsement Block: electronically signed in DFS
   Ravi Harapanhalli

C. CC Block: entered electronically in DFS
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Sue Ching Lin
7/17/2006 11:54:39 AM
CHEMIST

Ravi Harapanhalli
7/18/2006 02:54:07 PM
CHEMIST
NDA 21-856

Uloric (Febuxostat) Tablets, 80, 120 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant:

TAP Pharmaceutical Products, Inc.
675 North Field Drive
Lake Forest IL

Indication: Management of Hyperuricemia in pts with gout

Presentation: Bottles as 30, 100, 1000 count, and in — blisters as 100 count and

EER Status: Acceptable 1-AUG-2005

Consults: Trade name review - acceptable as Uloric, 25-FEB-2005
Statistics – NA
OCPB – dissolution method and AC not acceptable
EA – no consult - waiver requested – granted

Post Approval Agreements/Commitments: None

The original NDA was dated 14-DEC-2004.

The febuxostat drug substance is manufactured in

[b(4)]
Drug substance packaging is adequate, and stability studies support retest. The stability protocol and commitment are adequate.

**Conclusion**

Drug substance is satisfactory.

The Uloric drug product is a film coated immediate release tablet of 80 and 120 mg manufactured at Abbott Laboratories, Abbott Park, IL (CFN# 1415939).

The formulation is as follows

<table>
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<tr>
<th>Strength</th>
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Note that 3 different formulations were used through the phase I – II trials, but the differences are not considered to be significant with respect to performance attributes.

The manufacturing method is a conventional

Batch size is with comparability protocol to increase batch size to

Controls of critical processes are considered adequate. The specification is considered adequate after addition of individual specified and total degradation product
tests and acceptance criteria. The testing will on a "skip-lot” basis and then if there is shown to be no need for the testing it will be "sun-set”. The dissolution method and acceptance criteria are yet to be fully agreed upon. The firm is requested to revise the acceptance criteria to $Q_\infty$ at $t=15$ min.

Room temperature stability data for all presentations and strengths were provided through 18 months. These data, along with supportive data are considered adequate to support a representative expiry. The stability protocol (matrix design) and commitment are acceptable following revisions in accord with FDA recommendations.

All associated DMFs are acceptable

The overall Compliance recommendation is pending as of 11-JUL-2005.

**Overall Conclusion**
From a CMC perspective the application is recommended for an approvable action.

Eric P. Duffy, PhD
Director, DNDC II/ONDC
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Eric Duffy
10/12/2005 11:12:40 AM
CHEMIST
NDA 21-856

Uloric
(febuxostat tablets)

TAP Pharmaceutical Products Inc.

Sue-Ching Lin

Review Chemist

Division of Anesthesia, Analgesia, and Rheumatology Products
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### II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1

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Chemistry Review Data Sheet

1. NDA 21-856
2. REVIEW #: 1
3. REVIEW DATE: 19-Sep-2005
4. REVIEWER: Sue-Ching Lin
5. PREVIOUS DOCUMENTS:

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7. NAME & ADDRESS OF APPLICANT:

Name: TAP Pharmaceutical Products Inc.
Address: 675 N. Field Drive
         Lake Forest, IL 60045
Representative: Binita Kwankin, Assistant Director, Regulatory Affairs
Telephone: (847) 582-3263

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Uloric
b) Non-Proprietary Name: febuxostat tablets
c) Code Name/# (ONDC only): TMX-67, TEI-6720
d) Chem. Type/Submission Priority (ONDC only):
   • Chem. Type: 1
   • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Management of hyperuricemia in patients with gout (xanthine oxidase/xanthine dehydrogenase inhibitor)

11. DOSAGE FORM: tablets

12. STRENGTH/POTENCY: 80 mg and 120 mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: √ Rx     ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
    ____ SPOTS product – Form Completed
    √___ Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

2-(3-cyano-4-(2-methylpropoxy)phenyl]-4-methylthiazole-5-carboxylic acid

\[
\text{C}_{16}\text{H}_{16}\text{N}_{2}\text{O}_{3}\text{S} \quad \text{MW 316.37}
\]

17. RELATED/SUPPORTING DOCUMENTS:

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<td></td>
<td>*See page 78</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>4</td>
<td>N/A</td>
<td></td>
<td>*See page 78</td>
</tr>
<tr>
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<td></td>
<td></td>
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<td>4</td>
<td>N/A</td>
<td></td>
<td>*See page 78</td>
</tr>
<tr>
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<td>4</td>
<td>N/A</td>
<td></td>
<td>*See page 78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>N/A</td>
<td></td>
<td>*See page 78</td>
</tr>
</tbody>
</table>

*See page 78 of this review under for details.

1 Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 – Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available  
7 – Other (explain under "Comments")  

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

B. Other Documents:  

<table>
<thead>
<tr>
<th>DOCUMENT</th>
<th>APPLICATION NUMBER</th>
<th>DESCRIPTION</th>
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<tr>
<td>IND</td>
<td>58,229</td>
<td>TMX-67</td>
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18. STATUS:

**ONDC:**  

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<tr>
<th>CONSULTS/CMC RELATED REVIEWS</th>
<th>RECOMMENDATION</th>
<th>DATE</th>
<th>REVIEWER</th>
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<tr>
<td>Biometrics</td>
<td>N/A</td>
<td></td>
<td></td>
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<tr>
<td>EES</td>
<td>Acceptable</td>
<td>8/1/05</td>
<td>J. D. Ambrogio</td>
</tr>
<tr>
<td>Pharm/Tox</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopharm</td>
<td>Dissolution method and acceptance criteria need revision</td>
<td>See Biopharm review in DFS and page 65 of this review.</td>
<td>Lei Zhang</td>
</tr>
<tr>
<td>LNC</td>
<td>N/A</td>
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<td></td>
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<td>Methods Validation</td>
<td>N/A, according to the current ONDC policy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office of Drug Safety</td>
<td>The proposed proprietary name Uloric is acceptable*</td>
<td>2/25/05 (DMTES) &amp; 8/31/05 (DDMAC)</td>
<td>Linda Wisniewski, Dennis Toyer, &amp; Carol Holquist (DMETS) Suzanne Berkman (DDMAC)</td>
</tr>
<tr>
<td>EA</td>
<td>Categorical exclusion (see review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microbiology</td>
<td>N/A</td>
<td></td>
<td></td>
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</table>

* The proposed proprietary name “Uloric” has been consulted to DDMAC (Division of Drug Marketing, Advertising, and Communications) and DMETS (Division of Medication Errors and Technical Support) of the Office of Drug Safety. Both DDMAC and DMETS had no objections to the use of the proposed name, Uloric (refer to the DMETS memo dated 2/25/05 and DDMAC 8/31/05 e-mails in the DFS). However, DDMAC recommended...
The Chemistry Review for NDA 21-856

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry review perspective, this NDA is approvable pending satisfactory response to the deficiencies in dissolution method and acceptance criterion.

Please refer to the clinical pharmacology reviewer’s recommendation on the analytical procedure and acceptance criterion for the dissolution test. The labeling comments will need to be conveyed to the applicant, if there is a resubmission to this NDA (see the next page under Basis of Approvability).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

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

(1) Drug Substance

The active ingredient is febuxostat, which is a new molecular entity. Detailed information regarding the drug substance was provided in the NDA. The drug substance is produced .s consistently manufactured by controlling

Solubility of febuxostat is highly pH dependent. Up to pH 5.5, the solubility is minimal mg/mL), while in pH 6.8 phosphate buffer, solubility exceeds mg/mL.

Febuxostat was shown to be stable for for 36 months at 25°C/60%RH and 6 months at 40°C/75% RH in the commercial container . Furthermore, stress testing at up to 70°C, in packages ranging in protective properties, showed no change . The submitted stability data, which also show no increase in impurities, support the proposed retest period of
(2) Drug Product

The drug product is an immediate release tablet containing febuxostat in two strengths: 80 mg and 120 mg. With the exception of the color (Opadry II, Green used in coating tablets, all the excipients are USP/NF materials. The critical parameters in the manufacturing process were identified as: The tablets are packaged in bottles and blisters.

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

Febuxostat tablets will be dispensed by prescription only. The drug product is indicated for the management of hyperuricemia in patients with gout. The recommended dose is

The submitted drug product stability data include long-term stability data for 18 months and accelerated stability data for 6 months on three primary stability batches manufactured at the proposed commercial manufacturing site. The supportive data include 18 months of data for febuxostat 20 mg and 12 months of data for 40 mg tablets. The supportive lots were manufactured using the same formulation as the proposed commercial product. The stability data support the proposed expiration period for the drug product stored at controlled room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The dissolution method and acceptance criterion remained unresolved at the completion of this review, after FDA information request letters, telephone conferences between the applicant and the FDA, and the applicant’s revisions in the amendments. Refer to clinical pharmacology review and page 65 of this review for details.

The Division has decided that this NDA will not be approved due to major clinical deficiencies and thus there will be no labeling negotiations with the applicant. However, the labeling comments, as appeared on pages 88 to 90 of this review, will need to be communicated to the applicant if there is a resubmission to this NDA.
III. Administrative

A. Reviewer's Signature: electronically signed in DFS
B. Endorsement Block: electronically signed in DFS
C. CC Block: entered electronically in DFS
47 Page(s) Withheld

/  

_____ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sue Ching Lin
9/22/2005 05:12:41 PM
CHEMIST

John Smith
9/22/2005 05:19:28 PM
CHEMIST
### NDA FILEABILITY CHECKLIST

**NDA Number:** 21-856  
**Applicant:** TAP Pharmaceutical Products Inc.  
**Stamp Date:** 12/15/04  
**Drug Name:** Uloric (febuxostat) Tablets

**IS THE CMC SECTION OF THE APPLICATION FILABLE?**  Yes

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Yes</th>
<th>No</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 On its face, is the section organized adequately?</td>
<td>✔</td>
<td></td>
<td>eCTD format</td>
</tr>
<tr>
<td>2 Is the section indexed and paginated adequately?</td>
<td>✔</td>
<td></td>
<td>eCTD format</td>
</tr>
<tr>
<td>3 On its face, is the section legible?</td>
<td>✔</td>
<td></td>
<td>eCTD document</td>
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<tr>
<td>4 Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?</td>
<td>✔</td>
<td></td>
<td>Module 1, Regional, Forms, 356 H</td>
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<td></td>
<td></td>
<td></td>
<td>Module 3, Section 3.2.S.2.1</td>
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<tr>
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<td></td>
<td></td>
<td>Module 3, Section 3.2.P.3.1</td>
</tr>
<tr>
<td>5 Is a statement provided that all facilities are ready for GMP inspection?</td>
<td>✔</td>
<td></td>
<td>Module 1, Regional, Forms, 356 H</td>
</tr>
<tr>
<td>6 Has an environmental assessment report or categorical exclusion been provided?</td>
<td>✔</td>
<td></td>
<td>Module 1, Section 1.12.14, categorical exclusion</td>
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<tr>
<td>7 Does the section contain controls for the drug substance?</td>
<td>✔</td>
<td></td>
<td>Module 3, Section 3.2.S.4</td>
</tr>
<tr>
<td>8 Does the section contain controls for the drug product?</td>
<td>✔</td>
<td></td>
<td>Module 3, Section 3.2.P.5</td>
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<tr>
<td>9 Has stability data and analysis been provided to support the requested expiration date?</td>
<td>✔</td>
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<td>Module 3, Section 3.2.P.8</td>
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<tr>
<td></td>
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<td></td>
<td>18-month and 12-month long-term data for 80 mg and 120 mg tablets respectively and 6-month accelerated data on 3 full production batches to support expiration period.</td>
</tr>
<tr>
<td>10 Has all information requested during the IND phase, and at the pre-NDA meetings been included?</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 Have draft container labels been provided?</td>
<td>✔</td>
<td></td>
<td>Module 1, Section 1.14.1.1.</td>
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<tr>
<td>12 Has the draft package insert been provided?</td>
<td>✔</td>
<td></td>
<td>Module 1, Section 1.14.1.3.</td>
</tr>
<tr>
<td>13 Has an investigational formulations section been provided?</td>
<td>✔</td>
<td></td>
<td>Sections 2.7.1.1, 3.2.P.1, 3.2.P.2.2, and 3.2.P.2.2.1.2. The proposed commercial formulation was used in pivotal and other clinical trials as well as for the registration lots.</td>
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<tr>
<td>14 Is there a Methods Validation package?</td>
<td>✔</td>
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<td>Module 3, Section 3.2R</td>
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<td>15 Is a separate microbiological section included?</td>
<td>✔</td>
<td></td>
<td>N/A</td>
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</tbody>
</table>

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

**Reviewing Chemist:** Sue-Ching Lin  
**Date:** 1/21/05

**Team Leader:** John Smith, Ph.D.  
**Date:** 1/25/05
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Sue Ching Lin
1/25/05 04:54:38 PM
CHEMIST

John Smith
1/26/05 07:14:14 AM
CHEMIST
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21856/000
Stamp: 15-DEC-2004
Regulatory Due: 18-JAN-2009
Applicant: TAKEDA PHARMS NA
ONE TAKEDA PKY
DEERFIELD, IL 60015
Priority: 1S
Org Code: 170

Action Goal: 
District Goal: 19-NOV-2008
Brand Name: ULORIC (FEBUXOSTAT)
Estab. Name: 80/120MG TABLETS
Generic Name: FEBUXOSTAT
Dosage Form: (TABLET)
Strength: 40 AND 80 MG TABLET

Application Comment: RESUBMISSION

PLEASE UPDATE OVERALL OC RECOMMENDATION FOR THE APPLICATION.
NOTE THAT BUILDING — AT THIS ADDRESS PERFORMS DRUG PRODUCT RELEASE AND STABILITY TESTING. (on 15-JAN-2009 by D. CHRISTODOULOU (301-796-1342)

FDA Contacts: M. SULLIVAN (HFD-170) 301-796-1245 , Project Manager
O. STEPHENS (HFD-170) 301-796-3901 , Review Chemist
D. CHRISTODOULOU 301-796-1342, Team Leader

O all Recommendation: ACCEPTABLE on 16-JAN-2009 by H. KIEL (HFD-323)301-796-3246
ACCEPTABLE on 14-JUN-2006 by DAMBROGIOJ
ACCEPTABLE on 01-AUG-2005 by DAMBROGIOJ
Establishment: CPN 1411365 FEI 1411365

ABBOTT LABORATORIES
14TH & SHERIDAN RD
NORTH CHICAGO, IL 60064

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
                      DRUG SUBSTANCE RELEASE TESTER
                      DRUG SUBSTANCE STABILITY TESTER
                      FINISHED DOSAGE OTHER TESTER
                      FINISHED DOSAGE RELEASE TESTER
                      FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE

Estab. Comment: THIS SITE WILL DO DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY TESTING OF DRUG SUBSTANCE, RELEASE AND STABILITY TESTING OF DRUG PRODUCT, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS FOR DRUG PRODUCT. (on 18-JAN-2005 by S. LIN () 301-796-1403)

Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator
----------------|------|------|------------|-------------------|--------
SUBMITTED TO OC 18-JAN-2005  LINS
SUBMITTED TO DO 18-JAN-2005 PS  DAMBROGIOJ
ASSIGNED INSPECTION T 27-JUN-2005 PS  LJARRELL
DO RECOMMENDATION 29-JUL-2005 ACCEPTABLE  LJARRELL

PREVIOUS INSPECTION OF THIS SITE FOR PROFILE CLASS CSN WAS CONDUCTED ON 2/17/04 AND WAS FOUND ACCEPTABLE.
OC RECOMMENDATION 01-AUG-2005 ACCEPTABLE  DAMBROGIOJ
DISTRICT RECOMMENDATION

SUBMITTED TO OC 13-JUN-2006 LINS
OC RECOMMENDATION 14-JUN-2006 ACCEPTABLE  DAMBROGIOJ

SUBMITTED TO OC 06-AUG-2008 ALHAKIMA
SUBMITTED TO DO 07-AUG-2008 GMP FERGUSONS
ASSIGNED INSPECTION T 04-SEP-2008 PS LJARRELL
INSPECTION PERFORMED 30-SEP-2008 30-SEP-2008 LJARRELL

THIS INSPECTION REVEALED FIRM DEMOLISHED THE BUILDINGS WHERE THE API WAS MANUFACTURED.
THEY INTEND TO BUT HAVE NOT UPDATED THE APPLICATION.
INSPECTION SCHEDULED 20-OCT-2008 30-SEP-2008 b(4) LJARRELL
DO RECOMMENDATION 20-OCT-2008 WITHHOLD LJARRELL

SER COMMENTS UNDER INSPECTION MILESTONE
OC RECOMMENDATION 20-OCT-2008 WITHHOLD CRUZC

FIRM INTENDS TO , BUT HAVE NOT UPDATED THE APPLICATION.
SUBMITTED TO OC 14-JAN-2009 CHRISTODOUL
OC RECOMMENDATION 16-JAN-2009 ACCEPTABLE KIEL
Establishment:  CFN  1415939  PBI  1415939
ABBOTT LABORATORIES
100/200 ABBOTT PARK RD
ABBOTT PARK, IL  60064

DMF No:  AADA:
Responsibilities:  FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER

Profile:  TCM  OAI Status:  NONE

Estab. Comment:  THIS SITE WILL DO DRUG PRODUCT MANUFACTURING, PACKAGING, AND TESTING OF
COMPONENTS AND CONTAINER CLOSURE SYSTEMS.  (on 18-JAN-2005 by S. LIN)
301-796-1403)

Milestone Name  Date  Type  Insp. Date  Decision & Reason  Creator

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</table>
NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483 ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED VAI.

DO RECOMMENDATION 29-JUL-2005

INSPECTION CONDUCTED 7/13-29/05.

OC RECOMMENDATION 01-AUG-2005

SUBMITTED TO OC 13-JUN-2006

OC RECOMMENDATION 14-JUN-2006

SUBMITTED TO OC 06-AUG-2008

SUBMITTED TO DO 07-AUG-2008 PS

ASSIGNED INSPECTION T 04-SEP-2008 PS

INSPECTION PERFORMED 01-NOV-2008 01-NOV-2008

NO SIGNIFICANT GMP ISSUES FOUND.

DO RECOMMENDATION 07-JAN-2009

INSPECTION CONDUCTED 10/29 - 11/5/08.

OC RECOMMENDATION 08-JAN-2009
ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 21856/000
Action Goal: 

Stamp: 15-DEC-2004
District Goal: 22-JUN-2006

Regulatory Due: 21-AUG-2006
Brand Name: ULORIC (PSTUOOSTAT)

Applicant: TAP PHARM
Estab. Name: 80/120MG TABLETS

675 NORTH FIELD DR
Generic Name: FEZUOSTAT
LAKE FOREST, IL 60045

Priority: 1S
Dosage Form: (TABLET)

Org Code: 170
Strength: 80 MG & 120 MG

Application Comment:

FDA Contacts:
J. DEAN 301-796-1202 , Project Manager
S. LIN 301-796-1403 , Review Chemist
J. SMITH 301-796-1757 , Team Leader

-----------------------------------------------------

Overall Recommendation: ACCEPTABLE on 14-JUN-2006 by J. D AMBROGIO(HFD-322)301-827-
9049

ACCEPTABLE on 01-AUG-2005by J. D AMBROGIO(HFD-322)301-827-
9049

-----------------------------------------------------

Establishment: CFN 1411365 FEI 1411365
ABBOTT LABORATORIES
14TH & SHERIDAN RD
NORTH CHICAGO, IL 60064

DMP No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CSN OAI Status: NONE
Establishment Comment: THIS SITE WILL DO DRUG SUBSTANCE MANUFACTURING, RELEASE AND STABILITY TESTING OF DRUG SUBSTANCE, RELEASE AND STABILITY TESTING OF DRUG PRODUCT, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS FOR DRUG PRODUCT. (on 18-JAN-2005 by S. LIN ( ) 301-796-1403)

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<td>DAMBROGIOJ</td>
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<td>LJARRELL</td>
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<td>Acceptable</td>
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BASED ON FILE REVIEW

Previous inspection of this site for profile class CSN was conducted on 2/17/04 and was found acceptable.

<table>
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<tr>
<th>OC Recommendation</th>
<th>01-AUG-2005</th>
<th>Acceptable</th>
<th>DAMBROGIOJ</th>
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Submitted To OC 13-JUN-2006 LINS
OC RECOMMENDATION 14-JUN-2006 ACCEPTABLE DAMBREGIOJ
BASEx ON PROFILE

Establishment: CFN 1415939 FEI 1415939
ABBOTT LABORATORIES
100/200 ABBOTT PARK RD
ABBOTT PARK, IL 60064

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGER
Profile: TCM OAI Status: NONE

Estab. Comment: THIS SITE WILL DO DRUG PRODUCT MANUFACTURING, PACKAGING, AND TESTING OF
COMPONENTS AND CONTAINER CLOSURE SYSTEMS. (on 18-JAN-2005 by S. LIN ()
301-796-1403)

<table>
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<th>Milestone Name</th>
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<td>ASSIGNED INSPECTION T</td>
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<td>29-JUL-2005</td>
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<td>LJARRELL</td>
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NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483
ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED
VAI.

COMMENDATION 29-JUL-2005 ACCEPTABLE LJARRELL
INSPECTION

INSPECTION CONDUCTED 7/13--29/05.

OC RECOMMENDATION 01-AUG-2005 ACCEPTABLE DAMBREGIOJ
DISTRICT RECOMMENDATION
**ESTABLISHMENT EVALUATION REQUEST**

**DETAIL REPORT**

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<td>Regulatory Due:</td>
<td>15-OCT-2005</td>
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<td>675 NORTH FIELD DR</td>
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<td>LAKE FOREST, IL 60045</td>
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<td>Priority:</td>
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<td>Org Code:</td>
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**Action Goal:**

**District Goal:** 16-AUG-2005

**Brand Name:** ULORIC (FEBUXOSTAT)

**Estab. Name:** 80/120MG TABLETS

**Generic Name:** FEBUXOSTAT

**Dosage Form:** (TABLET)

**Strength:** 80 MG & 120 MG

**Application Comment:**

---

**Contacts:**

<table>
<thead>
<tr>
<th>Name</th>
<th>Phone</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. DEAN</td>
<td>301-827-2536</td>
<td>Project Manager</td>
</tr>
<tr>
<td>S. LIN</td>
<td>(HFD-550)</td>
<td>Review Chemist</td>
</tr>
<tr>
<td>J. SMITH</td>
<td>(HFD-550)</td>
<td>Team Leader</td>
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**Overall Recommendation:** ACCEPTABLE on 01-AUG-2005 by J. D AMBROGIO (HFD-322) 301-827-9049

---

**Establishment:**

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</table>

**ABBOTT LABORATORIES**

1401 14TH AND SHERIDAN RD

NORTH CHICAGO, IL 60064

**DMF No:**

**Responsibilities:**

- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE RELEASE TESTER
- DRUG SUBSTANCE STABILITY TESTER
- FINISHED DOSAGE OTHER TESTER

**AADA:**
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CSN  OAI Status: NONE


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<th>Date</th>
<th>Type</th>
<th>Insp. Date</th>
<th>Decision &amp; Reason</th>
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PREVIOUS INSPECTION OF THIS SITE FOR PROFILE CLASS CSN WAS CONDUCTED ON 2/17/04 AND WAS FOUND ACCEPTABLE.

| RECOMMENDATION            | 01-AUG-2005|      |            | ACCEPTABLE                   | DAMBROGIOJ |
|                           |            |      |            | DISTRICT RECOMMENDATION      |           |
Establishment: CPN 1415939 PEI 1415939
ABBOTT LABORATORIES
100/200 ABBOTT PARK RD
ABBOTT PARK, IL 60064

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE PACKAGGR

Profile: TCM OAI Status: NONE

Establishment Comment: THIS SITE WILL DO DRUG PRODUCT MANUFACTURING, PACKAGING, AND TESTING OF COMPONENTS AND CONTAINER CLOSURE SYSTEMS. (on 18-JAN-2005 by S. LIN (HPD-550) 301-827-2525)

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NO DEFICIENCIES WERE FOUND WITH RESPECT TO THIS APPLICATION AT THIS SITE AND THE FD-483 ITEM WAS NOT SYSTEMIC ENOUGH TO MAKE THE INSPECTION VIOLATIVE. IT WILL BE CLASSIFIED VAI.

DO RECOMMENDATION 29-JUL-2005 ACCEPTABLE LJARRELL

INSPECTION CONDUCTED 7/13-29/05.

CC RECOMMENDATION 01-AUG-2005

ACCEPTABLE DAMBROGIOJ

DISTRICT RECOMMENDATION