

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**40301**

**CHEMISTRY REVIEW(S)**

DIVISION REVIEW SUMMARY

ANDA: 40-301

FIRM: Taro Pharmaceutical U.S.A. Inc.  
U.S. Agent for: Taro Pharmaceuticals Inc.  
5 Skyline Drive  
Hawthorne, NY 10532

DOSAGE FORM: Tablet      STRENGTH: 1 mg, 2 mg, 2.5 mg, 3 mg  
4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg

DRUG: Warfarin Sodium

CGMP STATEMENT/EIR UPDATE STATUS: Pending as of 06/22/99.

BIO STUDY INFORMATION: The firm conducted three bio-studies, one each, for the following strengths: 2 mg, 5 mg and 10 mg. A bio-waiver was requested for the following strengths: 1, 2.5, 3, 4, 6, and 7.5 mg. The studies and waivers were found acceptable 07/09/98.

METHODS VALIDATION: N/A; compendial; method verification was performed by \_\_\_\_\_ (5/5/98) and no problems were encountered.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? yes

The containers used in the stability study are of the same size and material as those described in the container section. The firm submitted accelerated stability data for the product packaged in all container sizes.

The firm requests an expiration date of 24 months based on the data submitted.

The stability tests and specifications are indicated in the following table:

TEST	SPECIFICATION
Appearance	See each individual tablet description.*
Assay	‡
Related Compounds	Single      NMT      ‡ Total        NMT      ‡
Dissolution	NLT    ‡ in 30 min
Isopropyl Alcohol	NLT    ‡

Water LOD	NMT %
Hardness	kp

\*

1 mg- Pink, flat beveled tablet, scored on one side, engraved "T31" on the other side.

2 mg- Lavender, flat beveled tablet, scored on one side, engraved "T32" on the other side.

2.5 mg- Green, flat beveled tablet, scored on one side, engraved "T33" on the other side.

3 mg- Tan, flat beveled tablet, scored on one side, engraved "T38" on the other side

4 mg- Blue, flat beveled tablet, scored on one side, engraved "T34" on the other side.

5 mg- Peach, flat beveled tablet, scored on one side, engraved "T35" on the other side.

6 mg- Greenish-yellow, flat beveled tablet, scored on one side, engraved "T39" on the other side.

7.5 mg- Yellow, flat beveled tablet, scored on one side, engraved "T36" on the other side

10 mg- White, flat beveled tablet, scored on one side, engraved "T37" on the other side.

LABELING: AP; 06/15/99

STERILIZATION VALIDATION: N/A

SIZE OF BIO BATCH - The firm compressed tablets for 3 bio-batches; 2 mg(#780100; )tabs); 5 mg(#780049; tabs); 10 mg (#780060; )tabs).

SIZE OF STABILITY BATCHES - The test batch size for each strength was )tablets.

PROPOSED PRODUCTION BATCH -

The drug product is manufactured by

A comparative equipment summary for the ANDA batch versus the scale-up batch is provided on p. 6608. The equipment is of the

same type differing only in capacity.

The blank batch records begin on p. 6609. The intended production size batch is ( ) tablets.

RECOMMENDATION: Approvable pending EER.

SIGNATURE:

/S/

DATE: 7/4/99  
7/7/99

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Chem

1. CHEMISTRY REVIEW NO. 1
2. ANDA # 40-301
3. NAME AND ADDRESS OF APPLICANT  
Taro Pharmaceutical U.S.A. Inc.  
U.S. Agent for: Taro Pharmaceuticals Inc.  
Attention: Lorraine Sachs  
5 Skyline Drive  
Hawthorne, NY 10532
4. LEGAL BASIS FOR SUBMISSION  
The basis is the reference listed drug, Coumadin Tablets,  
manufactured by Dupont Pharmaceuticals.
5. SUPPLEMENT(s)  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Warfarin Sodium
8. SUPPLEMENT(s) PROVIDE(s) FOR:  
N/A
9. AMENDMENTS AND OTHER DATES:  
Orig Submission Mar 02, 1998  
New Correspondence Mar 17, 1998  
Ack. Ltr Mar 19, 1998
10. PHARMACOLOGICAL CATEGORY  
Anti-coagulant
11. Rx or OTC  
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM  
Tablet
14. POTENCY  
1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg
15. CHEMICAL NAME AND STRUCTURE  
3(alpha-acetonilybenzyl)0-4-hydroxycoumarin  
USP drug substance and drug product.
16. RECORDS AND REPORTS  
N/A
17. COMMENTS
18. CONCLUSIONS AND RECOMMENDATIONS  
Not approvable.
19. REVIEWER: Andrew J. Langowski  
DATE COMPLETED: 4/30/98

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Chem Review #1

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-301

APPLICANT: Taro Pharmaceuticals Inc.

DRUG PRODUCT: Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg,  
3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg.

The deficiencies presented below represent MAJOR deficiencies.

Deficiencies:

1. We request that you revise the raw material specifications for Warfarin to include USP test <467> for Organic volatile Impurities in accordance with the USP monograph.
2. Please revise the bulk drug specifications for total impurities to % to incorporate the significant figure which is integral to rounding off procedures.
3. We request that you revise the bulk drug specifications to include a specification for particle size distribution.
4. We request that you revise the raw material specifications for Warfarin to include a specification for bulk and/or tap density.
5. Regarding the inactive ingredient Lactose Anhydrous NF, please update the tests and specifications in accordance with the changes indicated in USP 23/NF 18 Supplement 8.
6. Regarding the inactive ingredient Magnesium Stearate NF, please provide a certification statement from the manufacturer regarding compliance with the OVI testing requirements listed under USP <467>.
7. According to the batch records, no routine in-process controls are performed on the final blend. We request that you establish tests and specifications for content uniformity, tap and/or bulk density and particle size. These tests are essential since this is a low dose drug.
8. We request that you specify a range for tablet accountability yield on a revised report form and indicate the yield for each tablet strength.
9. Please provide justification of the significant material loss in the tableting of the 10 mg strength product.
10. Please revise the final product specification for content uniformity to include the decimal place as specified in the USP because of its significance to "rounding off" procedures.
11. We request comparative bulk drug assay data for the in-house method versus the regulatory method. In addition, you should also provide a commitment acknowledging that the USP monograph methods are the official regulatory methods and that in the case of a dispute over results of non-compliant samples, the USP methodology and test results will take precedence.
12. We request that you conduct a forced degradation study on the placebo and finished product in order to validate that your

analytical method is stability indicating. Samples should be exposed to acid, base, peroxide, heat and UV light. Peak purity of the active ingredient should be demonstrated. A reasonable attempt should be made to identify the major degradants. *lu* *3*

13. Please revise the stability specification for assay to include the decimal place as indicated in the monograph because of its significance to rounding off procedures.
14. We request that you include a stability test and specification for isopropyl alcohol. The range should be based on the lower limit of NLT % specified in the USP monograph.
15. Regarding the stability protocol, the stability sample storage temperatures for room temperature and accelerated testing should be revised to allow for excursions from the target temperature. The OGD recommended storage temperature is 25-30° C and the ICH proposed range is 25 ± 2° C. Accelerated studies are performed at 40 ± 2° C/75% RH. Please revise the protocol and submit for review.
16. We request that you analyze the stability samples for ~~(IPA)~~ content and submit the results for review.
17. The stability limit for moisture should be tightened based on the submitted results.
18. It was noted that the potency in some stability samples significantly deviated from the target of % (i.e., as low as %) after 3 months at room temperature. Please provide comment.

Sincerely yours,

*( ' ' /S/ ' )* *Fr.* *7/10/98*  
Frank O. Holcombe, Jr., Ph.D.  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research





1. CHEMISTRY REVIEW NO. 2
- ✓ 2. ANDA # 40-301
3. NAME AND ADDRESS OF APPLICANT  
Taro Pharmaceutical U.S.A. Inc.  
U.S. Agent for: Taro Pharmaceuticals Inc.  
Attention: Lorraine Sachs  
5 Skyline Drive  
Hawthorne, NY 10532
4. LEGAL BASIS FOR SUBMISSION  
The basis is the reference listed drug, Coumadin Tablets,  
manufactured by Dupont Pharmaceuticals.
5. SUPPLEMENT(s)  
N/A
6. PROPRIETARY NAME  
N/A
7. NONPROPRIETARY NAME  
Warfarin Sodium
8. SUPPLEMENT(s) PROVIDE(s) FOR:  
N/A
9. AMENDMENTS AND OTHER DATES:

Orig Submission	Mar 02, 1998
New Correspondence	Mar 17, 1998
Ack. Ltr	Mar 19, 1998
NA Ltr	Jul 14, 1998
Amendment	Sep 22, 1998
Amendment	Oct 21, 1998
10. PHARMACOLOGICAL CATEGORY  
Anti-coagulant
11. Rx or OTC  
Rx
12. RELATED IND/NDA/DMF(s)
13. DOSAGE FORM  
Tablet
14. POTENCY  
1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg
15. CHEMICAL NAME AND STRUCTURE  
3(alpha-acetonybenzyl)-4-hydroxycoumarin  
USP drug substance and drug product.
16. RECORDS AND REPORTS  
N/A
17. COMMENTS  
See item 38,
18. CONCLUSIONS AND RECOMMENDATIONS  
Not Approvable; Fax
19. REVIEWER:  
Andrew J. Langowski
- DATE COMPLETED:  
03/03/99

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Chem Review #2

APR 13 1999

38. Chemistry Comments to be Provided to the Applicant

ANDA: 40-301 . . . . . APPLICANT: Taro Pharmaceuticals USA, Inc.

DRUG PRODUCT: Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg,  
3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg

The deficiency presented below represents a FACSIMILE deficiency.

Deficiency:

Regarding  we request that you expand  
your specification to state that the mean of individual sample  
results should lie within % with a standard relative  
deviation (RSD) of %.

Sincerely yours,

/s/

for

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Florence S. Fang  
Director  
Division of Chemistry II  
Office of Generic Drugs  
Center for Drug Evaluation and Research



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Chem Review #3