

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

021951Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: May 21, 2012
TO: Review #3 of NDA 21-951
FROM: Tarun Mehta, M.Sc.
Review Chemist, ONDQA
SUBJECT: **Final Recommendation.**

The CMC Review #3 dated April 18, 2012, indicated the following list of deficiencies:

1. Regarding cGMP inspection:
 - Office Compliance has not made the final recommendation on the facilities involved in this resubmission.

2. Regarding labels:
 - The term, (b) (4) should be removed from the immediate container and carton labels.
 - The established name should be revised to “(isotretinoin) capsules”.
 - The size of the established name should be at least 50% of the trade name.

On May 21, 2012, the Office of Compliance has issued an overall “Acceptable” recommendation for all the facilities involved in this application (see the **Attachment-1**)

All the label issues are resolved satisfactorily (see the **Attachment-2**)

Therefore, from the ONDQA perspective, this application is now recommended for approval with the following statement in the action letter.

The expiration dating of the 40mg capsules should be no more than 24 months at this time until real time stability data beyond 24 months are available.

Attachment-1

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 21951/000	Sponsor:	CIPHER
Org. Code:	540		2200 SANTA MONICA BLVD
Priority:	3S		SANTA MONICA, CA 90404
Stamp Date:	01-JUL-2005	Brand Name:	CIP-ISOTRETINOIN CAPSULES
PDUFA Date:	29-MAY-2012	Estab. Name:	
Action Goal:		Generic Name:	ISOTRETINOIN
District Goal:	30-MAR-2012	Product Number; Dosage Form; Ingredient; Strengths	001; CAPSULE; ISOTRETINOIN; 10MG
FDA Contacts:	J. DAVID	Project Manager	3017964247
	T. MEHTA	Review Chemist	3017961712
	S. DING	Team Leader	3017961349

Overall Recommendation:	ACCEPTABLE	on 21-MAY-2012	by A. INYARD	(HFD-323)	3017965363
	PENDING	on 08-DEC-2011	by EES_PROD		
	ACCEPTABLE	on 26-APR-2006	by DAMBROGIOJ		

Attachment-2

Immediate Container Label (Bottle)

3 PAGES DRAFT LABELING HAVE BEEN
WITHHELD IN FULL AS B4 (CCI/TS)
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/s/

TARUN D MEHTA
05/21/2012

MOO JHONG RHEE
05/21/2012
Chief, Branch IV

NDA 21-951

(b) (4)
(isotretinoin) Capsules
10mg, 20mg, 30mg and 40mg

Cipher Pharmaceuticals, LTD

Tarun Mehta
ONDQA
Division of New Drug Quality Assessment II
Branch IV

For the Division of Dermatology and Dental Products
(HFD-540)

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA # 21-951

2. REVIEW #: 3

3. REVIEW DATE: 4/16/12

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

Original

06/27/05

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Resubmission (Response to the CR letter of April 25, 2007)

11/29/11

Amendment (SEQ 0007)- CMC response

02/23/12

Amendment (SEQ 0009)- CMC response

03/20/12

Amendment (SEQ 0010)- CMC response

03/23/12

Amendment (labeling)

03/16/12

Updated Dissolution data (SEQ 0012)

04/03/12

Amendment (SEQ 0013)- CMC response

04/12/12

Email - Dissolution specification commitment
(need to update with the official submission)

04/12/12

7. NAME & ADDRESS OF APPLICANT:

Name: Cipher Pharmaceuticals Ltd.

Address: 5650 Tomken Road, Uint 16
Mississauga, Ontario L4W 4P1 Canada

Chemistry Review Data Sheet

Representative: Arthur M. Deboeck, VP & Gen Mgr, Galephar PR

Telephone: 787 – 713-0340

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Isotretinoin
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDQA only):
• Chem. Type: 3
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Severe recalcitrant nodular acne

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 10, 20, 30 and 40mg

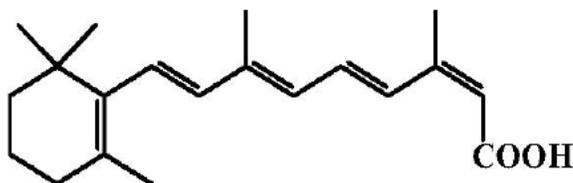
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 300.44

13-cis-retinoic acid

13-Z-retinoic acid



Molecular formula: $C_{20}H_{28}O_2$
CAS#: 4759-48-2

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				4	Adequate	2/16/12	Reviewed by Tarun Mehta
				3	Adequate	4/21/98	reviewed; Actively used as an excipient in the USA in pharmaceutical products.
				3	Adequate	6/23/10	Reviewed by Zimmerman, Stuart E
				3	Adequate	12/15/10	Reviewed by Jao, Edwin
				3	Adequate	11/22/10	Reviewed by Jiang-Baucom, Ping

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")

* (b) (4) send letter on March 20, 2006 confirming “There have been no revision to DMF (b) (4) in the past year. (b) (4) commits that the subject matters of the DMF remains current”. See attached scan copy of letter page 67 of this document.

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	pending		

Executive Summary Section

The Chemistry Review for NDA 21-951

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this resubmission has now submitted sufficient information to assure the identity, strength, purity, and quality of the drug product.

However, the Office of Compliance has *not* made an overall “Acceptable” recommendation for the facilities involved in this resubmission.

Also issues on the labels have *not* been resolved as of this date of review.

Therefore, from the ONDQA perspective, this resubmission is *not* recommended for approval in its present form per 21 CFR 314.125(b)(6), and (13).

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

NA

II. Summary of Chemistry Assessments

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

There are several new CMC information in this resubmission.

An alternative commercial production site has been added, which is an additional manufacturing site of the current supplier. This alternative site has the same process, functionality of the equipment, and the process controls as the original site.

The drug substance specification is revised to include the particle size distribution limits. The drug substance, isotretinoin, USP, is manufactured ^{(b) (4)}. The Chemistry, Manufacturing and Control information of the drug substance is described in ^{(b) (4)} and deemed adequate to support the NDA.

The drug product section has added a new strength, 40mg capsules. The 40mg capsules has true dose proportional formulation compare to 10, 20 ad 30mg strengths. In this resubmission, the applicant has manufactured several batches of 10mg and 20mg capsules for Phase III clinical trials, and 40mg capsules for pK studies. All these new capsules are deemed adequate for assessing the clinical data.

Executive Summary Section

In this resubmission, the applicant did not respond adequately to the request of changing the dissolution test to have multiple time points as delineated in the last CR action letter. After multiple discussion with the applicant, April 12, 2012, the applicant proposed an interim dissolution test method with two time points, which was accepted by Biopharm Reviewer (see Dr. Minerva Hughe's Review, dated April 16, 2012). With the revised dissolution test, the specification for the drug product is now deemed satisfactory.

Satisfactory 36-months real-time stability data were provided for 10mg, 20mg and 30mg batches. Based on the current specification (including the tentative dissolution test), it is concluded that the drug products will remain stable during the proposed expiration dating period. Therefore, 36 month of the expiration dating period is granted for these strengths.

However, single batch of 40mg capsules has only 22 months of the long term stability data and its stability study is ongoing. Based on available data, 24-month of expiration dating period can be given to the 40mg strength capsules.

CIP-Isotretinoin Capsules 10, 20, 30 and 40mg capsules will be packaged in blister sheets of 10 capsules, which will be then packaged in (b) (4) boxes. Capsules were made of (b) (4) hard gelatin (b) (4) in order to protect from light. Stability data on the drug product support the adequacy of this container/closure system.

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

The proposed drug product is provided as 10mg, 20mg, 30mg and 40mg oral immediate release HG capsule. Ten mg capsules (dark yellow) imprinted "G240" on cap and "10" on body, 20mg capsules (red) imprinted "G241" on cap and "20" on body, 30mg capsules (brown) imprinted "G242" on cap and "30" on body, 40mg capsules (brown cap and red body) imprinted "G325" on cap and "40" on body, they are packaged in boxes (b) (4) containing (b) (4) packs of 10 capsules. Product should be stored at room temperature, protected from light. CIP-Isotretinoin should be administered with a meal. The recommended dose range for CIP-Isotretinoin is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. Once daily dosing is NOT recommended.

C. Basis for Not-Approval Recommendation as of this Review

21 CFR 314.125 (13)

- An overall recommendation from the Office of Compliance has *not* been issued.

21 CFR 314.125 (6)

- Issues on container and carton labels have *not* been finalized

(See the **List of Deficiencies** on p. 33)

Executive Summary Section

III. Administrative

A. Reviewer's Signature : Electronically entered in the DFS

B. Endorsement Block

Chemist:	Tarun Mehta, M.Sc.
Branch Chief :	Moo-Jhong Rhee, Ph.D.
Clinical Project Manager:	Matthew White
CMC Project Manager:	Catherine Tran-Zwanetz

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/s/

TARUN D MEHTA
04/17/2012

MOO JHONG RHEE
04/18/2012
Chief, Branch IV

NDA 21-951

CIP-ISOTRETINOIN CAPSULES
10mg, 20mg and 30mg

Cipher Pharmaceuticals LTD

Tarun Mehta
ONDQA Division II Branch III
(HFD-540)

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A. Labeling & Package Insert:.....	62
B. Environmental Assessment or Claim of Categorical Exclusion Acceptable.....	633
List Of Deficiencies To Be Communicated To Applicant:	633

Chemistry Review Data Sheet

1. NDA # 21-951

2. REVIEW #: 2

3. REVIEW DATE: 4/12/07

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

27/06/05

7. NAME & ADDRESS OF APPLICANT:

Name: Cipher Pharmaceuticals Ltd.

Address: 409 Matheson Blvd. East
Mississauga, Ontario L4Z2H2 Canada

Representative: Larry Andrews, President

Telephone: 905-602-5840

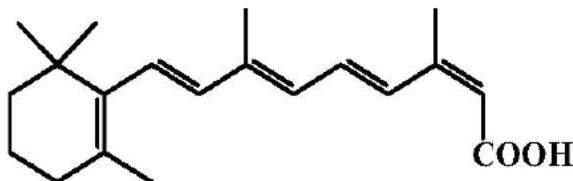
8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Review Data Sheet

- a) Proprietary Name: CIP- Isotretinoin Capsules--
b) Non-Proprietary Name (USAN): Isotretinoin
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDQA only):
• Chem. Type: 3
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)
10. PHARMACOL. CATEGORY: Severe recalcitrant nodular acne
11. DOSAGE FORM: Capsules
12. STRENGTH/POTENCY: 10, 20 and 30mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
 SPOTS product – Form Completed
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1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 300.44
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Molecular formula: $C_{20}H_{28}O_2$
CAS#: 4759-48-2

Chemistry Review Data Sheet

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A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)				3	Adequate	8/21/01*	Reviewed by Nashed Nashed, Ph.D.
				3	Adequate	4/21/98	reviewed; Actively used as an excipient in the USA in pharmaceutical products.
				3	Adequate	1/23/03	Reviewed by George Lunn
				3	Adequate	9/22/05	Reviewed by Shulin Ding
				3	Adequate	9/20/05	Reviewed by Donald Klein

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1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

* (b) (4) send letter on March 20, 2006 confirming “There have been no revision to DMF (b) (4) in the past year. (b) (4) commits that the subject matters of the DMF remains current”. See attached scan copy of letter page 67 of this document.

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Chemistry Review Data Sheet

B. Other Documents: NA

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Adequate	10/22/05	Drug Substance manufacturing site: FDA inspection January of 2004, form 483 was addressed. DP production site: FDA inspection November 2004; No 483 issued.
Pharm/Tox	Approved	4/10/06	Yao, Jaiquin
Biopharm	Approvable	4/10/06	Denis Badshaw

The Chemistry Review for NDA 21-951

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA is recommended as “approvable” pending satisfactory resolution of the CMC-deficiency delineated in the deficiency list.

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

NA

II. Summary of Chemistry Assessments

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

Isotretinoin is a well known therapeutically active drug substance. It has been used for several severe skin disorders like cystic acne, hypertrophic lumps erythematosus and keratinisation disorders. Drug is poorly to almost insoluble in aqueous media but has shown increased solubility in fatty acids. Due to the poor aqueous media solubility, drug has reduced absorption after oral intake when taken in absence of food.

(b) (4)

Drug product was developed with a good understanding of the drug substance’s poor solubility and sensitivity to heat and light.

The manufacturing process is controlled with in-process acceptance criteria. Critical attributes are tested during the manufacturing of the capsules (b) (4)

These in-process control parameters are monitored to assure the reproducibility of the manufacturing process.

Executive Summary Section

Satisfactory 36-months real-time stability data were updated on November 7, 2006 submission for complete response to NDA approvable letter dated May 1, 2006 for long term condition for two lots of 10mg, 3 lots of 20mg and one lot of 30mg for clinical validation batches, along with 6 months of accelerated stability data for all nine lots of the clinical study. Based on current specification (including tentative dissolution), it is concluded that the drug will remain stable during the proposed shelf life. Therefore, 36 month of the expiration date is granted. However, the dissolution specification modification is required.

Applicant has not established final *dissolution* acceptance criteria for commercial batches. Applicant need to provide justification and reference data on which acceptances criteria will be based.

Current immediate release dissolution specification (b) (4) should be revised as having multiple time points (30mins, 60minutes, 120minutes, 180minutes and 240 minutes) with appropriate acceptance criteria.

CIP-Isotretinoin Capsules 10, 20 and 30mg capsules will be packaged in blister sheets of 10 capsules, which will be then packaged in (b) (4) boxes. Capsules were made of (b) (4) hard gelatin (b) (4) in order to protect from light. Stability data on the drug product also support the usage of this container/closure system.

The drug substance is isotretinoin, USP, and is manufactured (b) (4). The Chemistry, Manufacturing and Control information of the drug substance is described in (b) (4) and deemed adequate to support the NDA.

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

The proposed drug product is provided as 10mg, 20mg and 30mg oral immediate release HG capsule. Ten mg capsules (dark yellow) imprinted "G240" on cap and "10" on body, 20mg capsules (red) imprinted "G241" on cap and "20" on body, 30mg capsules (brown) imprinted "G242" on cap and "30" on body, they are packaged in boxes (b) (4) packs of 10 capsules. Product should be stored at room temperature, protected from light. CIP-Isotretinoin should be administered with a meal. The recommended dose range for CIP-Isotretinoin is 0.5 to 1.0 mg/kg/day given in two divided doses with food for 15 to 20 weeks. Once daily dosing is NOT recommended.

C. Approvability Recommendation**Approvable**

All deficiencies listed on the previous AE letter were adequately resolved, except for the dissolution issue, in the amendment dated, November 7, 2006. This dissolution issue was conveyed to the sponsor in an IR letter dated, February 17, 2007, and as of this review, this issue has not been resolved.

Executive Summary Section

Therefore, this NDA is approvable pending resolution of the dissolution issue.

III. Administrative

A. Reviewer's Signature : Electronically entered in the DFS

B. Endorsement Block

Chemist: Tarun Mehta, M.Sc.
Branch Chief : Moo-Jhong Rhee, Ph.D.
Project Manager: Melinda, Harris-Bauerlien

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CHEMIST

Moo-Jhong Rhee
4/12/2007 03:17:48 PM
CHEMIST
Chief, Branch III

NDA 21-951

CIP-ISOTRETINOIN CAPSULES
10mg, 20mg and 30mg

Cipher Pharmaceuticals LTD

Tarun Mehta
ONDQA Division II Branch III
(HFD-540)

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Additional Deficiencies To Be Communicated To Applicant:.....	Error! Bookmark not defined.

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Chemistry Review Data Sheet

1. NDA # 21-951

2. REVIEW #: 1

3. REVIEW DATE: 4/10/06

4. REVIEWER: Tarun Mehta

5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

27/06/05

7. NAME & ADDRESS OF APPLICANT:

Name: Cipher Pharmaceuticals Ltd.

Address: 409 Matheson Blvd. East
Mississauga, Ontario L4Z2H2 Canada

Representative: Larry Andrews, President

Telephone: 905-602-5840

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: CIP- Isotretinoin Capsules--
b) Non-Proprietary Name (USAN): Isotretinoin
c) Code Name/#: N/A
d) Chem. Type/Submission Priority (ONDQA only):
• Chem. Type: 3
• Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: Severe recalcitrant nodular acne

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 10, 20 and 30mg

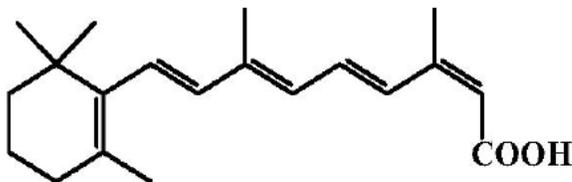
13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

1. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 300.44

13-cis-retinoic acid

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B. Other Documents: NA

Chemistry Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	10/22/05	Drug Substance manufacturing site: FDA inspection January of 2004, form 483 was addressed. DP production site: FDA inspection November 2004; No 483 issued.
Pharm/Tox	Approved	4/10/06	Yao, Jaiquin
Biopharm	Approvable	4/10/06	Denis Badshaw
Methods Validation	Package will be sent to FDA lab for validation		
DMETS	Pending		
EA	Categorical Exclusion	3/1/06	Tarun Mehta

The Chemistry Review for NDA 21-951

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls (CMC) standpoint, the NDA is recommended as approvable pending satisfactory resolution of CMC-related deficiencies listed in section "R Regional Information, part III".

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

NA

II. Summary of Chemistry Assessments

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

Isotretinoin is a well known therapeutically active drug substance. It has been used for several severe skin disorders like cystic acne, hypertrophic lumps erythematosus and keratinisation disorders. Drug is poorly to almost insoluble in aqueous media but has shown increased solubility in fatty acids. Due to the poor aqueous media solubility, drug has reduced absorption after oral intake when taken in absence of food.

(b) (4)

Drug product was developed with a good understanding of the drug substance's poor solubility and sensitivity to heat and light.

The manufacturing process is controlled with in-process acceptance criteria. Critical attributes are tested during the manufacturing of the capsules. (b) (4)

These in-process control parameters are monitored to assure the reproducibility of the manufacturing process.

Executive Summary Section

III. Administrative

A. Reviewer's Signature : Electronically entered in the DFS

B. Endorsement Block

Chemist/Date:	Tarun Mehta, M.Sc. / 06-Feb-2006
Branch Chief /Date:	Moo-Jhong Rhee, Ph.D.
Project Manager/Date	Melinda, Harris-Bauerlien

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/s/

Tarun Mehta
4/13/2006 02:41:20 PM
CHEMIST

Moo-Jhong Rhee
4/13/2006 02:53:11 PM
CHEMIST
Chief, Branch III