

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-946

CHEMISTRY REVIEW(S)

NDA 21-946

Xolegel (ketoconazole USP) Gel, 2%

Barrier Therapeutics, Inc.

Division of Dermatological and Dental Drug Products

Ernest G. Pappas

**Branch III, Premarketing Assessment Division II
Office of New Drug Quality**

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Chemistry Review Data Sheet

Addendum

1. NDA 21-946
2. REVIEW #: 2
3. REVIEW DATE: 7/24/06
4. REVIEWER: Ernest G. Pappas

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
N.A.	
Original	9/28/05
Amendment	3/1/06
Amendment	5/5/06

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	7/24/06

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Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name: Barrier Therapeutics, Inc.
600 College Road East
Address: Suite 3200
Princeton, NJ 08540
Representative: Isabel Drzewiecki,
Global Head, Regulatory Operations
Telephone: (609) 945-1247

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Xolegel
- b) Non-Proprietary Name (USAN): Ketoconazole (USAN, INN)
- c) Code Name/# : R041400
- d) CAS Number: 65277-42-1
- e) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of seborrheic dermatitis

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 20 mg/g

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: Rx OTC

CHEMISTRY REVIEW

Chemistry Review Data Sheet

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

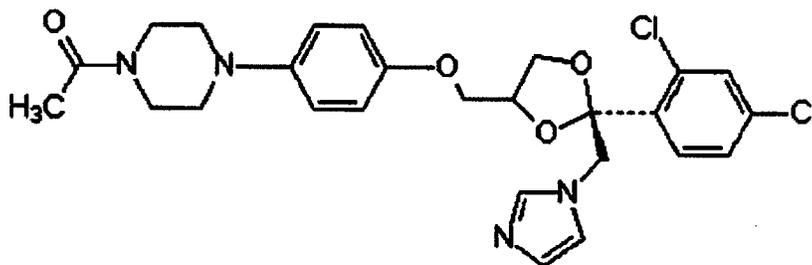
_____ SPOTS product – Form Completed

 x Not a SPOTS product

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

The chemical name is (+)-cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(1Himidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-piperazine.

The structural formula is shown:



Molecular Formula: C₂₆H₂₈Cl₂N₄O₄

Molecular Weight: 531.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	Adequate	3/29/00	*See note below
	II			1	Adequate	2/8/06	
	III			4	Adequate	5/6/03	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

CHEMISTRY REVIEW

Chemistry Review Data Sheet

- 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")

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

* Note: Please note that the review of DMF _____ is current, and there has been no changes in CMCs since the last chemistry review dated 3/29/00.

*Appears This Way
On Original*

CHEMISTRY REVIEW

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	12/14/05	Ambrogio
DMETS	Acceptable for Tradename*	7/21/06	Pedersen
DDMAC	Labeling Revision	5/4/06	Skaiah

* The tradename, "Xolegel" was found acceptable by DMETS as of 7/21/06.

*Appears This Way
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The Chemistry Review for NDA 21-946

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved from a Chemistry standpoint.

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 Product:

The drug product, Xolegel™ (ketoconazole USP) Gel, 2% is a topical anhydrous gel packaged in 2-g and 15-g epoxy-lined, _____ aluminum tubes.

Xolegel™ (ketoconazole, USP) Gel, 2% was developed for the topical treatment of seborrheic dermatitis. This product is manufactured with components that have a history in the pharmaceutical and cosmetic applications. These components have been shown to be compatible through appropriate testing with each other and primary packages. Chemical testing of the product during stability has demonstrated that there are no adverse interactions between Ketoconazole and the excipients. Sebazole™ (ketoconazole, USP) Gel, 2% contains the excipients, Polyethylene Glycol 400, Propylene Glycol, glycerin, PPG-15 Stearyl Ether, Hydroxypropyl Cellulose, Ascorbic Acid, Butylated Hydroxytoluene, Citric Acid, Monohydrate, Citric Acid, Monohydrate, FD&C Yellow No.6, D&C Yellow No.10, and Dehydrated Alcohol .

The solubility of ketoconazole drug substance in Ketoconazole USP 2% Topical Gel Placebo is 5.5 % w/w. Thus, precipitation of ketoconazole is not an issue in Ketoconazole USP 2% Topical Gel. To assure that ketoconazole is fully dissolved during manufacture of the gel, an in-process control for _____

Chemistry Assessment Section

The particle size distribution is controlled by a tight acceptance specification (particle size: _____ Ketoconazole is a _____ drug substance as obtained from the vendor.

Stability data were submitted on three production batches of Ketoconazole USP 2% Topical Gel as packaged in the container/closure system proposed for the marketplace. Up to 24 months of room temperature data were submitted in support of the proposed _____ expiration date. Justification for the 24 months expiration date is based on the Registration Batch Data supporting 24 months on _____ batches and _____ batch. The stability data were found acceptable to support an expiration date of 24 months. The firm commits to a 24 month expiration date per amendment dated 5/5/05.

The Tradename, Xolegel TM, has been reviewed by DMETS and DDMAC, and found acceptable on 7/21/06.

The drug product name, Xolegel TM (ketoconazole, USP) Gel, 0.2% and other portion of the package insert and patient information leaflet, including the carton and tube labels was found acceptable from a chemistry standpoint. The storage condition of Store at 25 ° C (77 ° F) ; excursions permitted to 15°- 30 ° (59-86 ° F).

Establishment Inspections: All facilities as indicated in the NDA are found acceptable for CGMPs. An overall recommendation of “ acceptable” was received from the Office of Compliance on 12/14/05.

Environmental Assessment: The applicant’s claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable since the EIC projection was found to be at a level well below 1ppb.

Chemistry Assessment Section

(2) Drug Substance:

The drug substance, ketoconazole, is manufactured and supplied to Barrier Therapeutics Inc. by _____ Ketoconazole is the subject of approved marketed products, e.g., Ketoconazole Topical 2% Cream (ANDA 076294 and others), Nizoral (ketoconazole) Cream (NDA 19-084), Nizoral (ketoconazole) 2% Topical Shampoo (NDA 19-927) and Ketoconazole 2% Topical Shampoo (ANDA 076294 and others), and Nizoral (ketoconazole) Tablets (NDA 18-533), and (ketoconazole) Tablets (ANDA 075-314 & others). The details of the method of manufacture, controls, and packaging of the drug substance have been described in these NDAs and ANDAs. A letter of authorization was given by _____ to allow FDA reference to DMF _____ and DMF _____ in behalf of Barrier Therapeutics, Inc.

The NDA contained the HPLC method and Validation for the determination of Ketoconazole and related substances. The acceptance criteria and results were reported in the NDA.

The impurity profile was established for ketoconazole and is consistent throughout its manufacturing. The following known related impurities have been determined as follows: _____

_____ The specifications specify these limits for the related impurities in order to assure consistent quality from batch to batch. These impurities were found to fall within the acceptance criteria.

Based on the evaluation of the primary stability data, the proposed retest date of _____ was deemed acceptable.

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

Treatment of seborrheic dermatitis. Apply Sebazole Gel once daily to the affected area for 2 weeks.

C. Basis for Approvability or Not-Approval Recommendation – The NDA is recommended for approval because the information submitted in this NDA ensures the Agency's Quality Standards; i.e., identity, strength, quality and purity. In addition, the establishment inspections for all of the facilities in the NDA are found acceptable. The labeling was found acceptable from a technical standpoint.

III. Administrative**A. Reviewer's Signature**

Chemistry Assessment Section

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

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3 Page(s) Withheld

~~_____~~ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-1/2

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ernest G. Pappas
7/26/2006 03:17:32 PM
CHEMIST

This chemistry review is an addendum to the original
chemistry review. Recommend approval of the NDA.

Moo-Jhong Rhee
7/26/2006 03:48:12 PM
CHEMIST
Chief, Branch III

NDA 21-946

Trademark (ketoconazole USP) Gel, 2%

Barrier Therapeutics, Inc.

Division of Dermatological and Dental Drug Products

Ernest G. Pappas

**Branch III, Premarketing Assessment Division II
Office of New Drug Quality**

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Chemistry Review Data Sheet

1. NDA 21-946
2. REVIEW #: 1
3. REVIEW DATE: 7/14/06
4. REVIEWER: Ernest G. Pappas

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

N.A.

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

Original

9/28/05

Amendment

3/1/06

Amendment

5/5/06

7. NAME & ADDRESS OF APPLICANT:

Name: Barrier Therapeutics, Inc.
600 College Road East
Address: Suite 3200
Princeton, NJ 08540
Representative: Isabel Drzewiecki,
Global Head, Regulatory Operations

CHEMISTRY REVIEW

Chemistry Review Data Sheet

Telephone: (609) 945-1247

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Ketoconazole (USAN, INN)
- c) Code Name/# : R041400
- d) CAS Number: 65277-42-1
- e) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 3
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of seborrheic dermatitis

11. DOSAGE FORM: Gel

12. STRENGTH/POTENCY: 20 mg/g

13. ROUTE OF ADMINISTRATION: Topical

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:

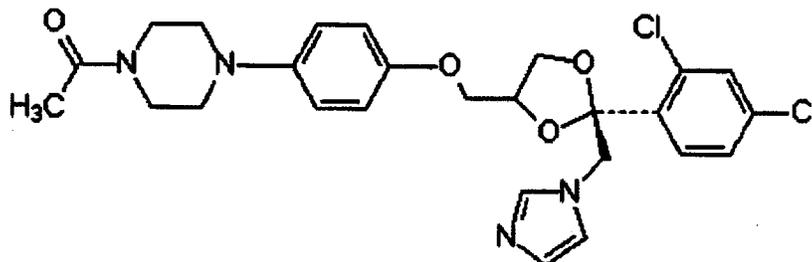
The chemical name is (+)-cis-1-Acetyl-4-[p-[[2-(2,4-dichlorophenyl)-2-(1Himidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-

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piperazine.

The structural formula is shown:



Molecular Formula: $C_{26}H_{28}Cl_2N_4O_4$

Molecular Weight: 531.43

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
/	II	/	/	3	Adequate	3/29/00	*See note below
	II			1	Adequate	2/8/06	
	III			4	Adequate	5/6/03	

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")

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

* Note: Please note that the review of DMF _____ is current, and there has been no changes in CMCs since the last chemistry review dated 3/29/00.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EER	Acceptable	12/14/05	Ambrogio
DMETS	Unacceptable for Tradename*	5/16/06	Hoppes
DDMAC	Labeling Revision	5/4/06	Skaiah

* The tradename, "Sebazole" remains unacceptable by DMETS as of 7/14/06.

Appears This Way
On Original

The Chemistry Review for NDA 21-946

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved from a Chemistry standpoint.

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 Product:

The drug product, **Sebazole™** (ketoconazole USP) Gel, 2% is a topical anhydrous gel packaged in 2-g and 15-g _____ blind-end, aluminum tubes.

Sebazole™ (ketoconazole, USP) Gel, 2% was developed for the topical treatment of seborrheic dermatitis. This product is manufactured with components that have a history in the pharmaceutical and cosmetic applications. These components have been shown to be compatible through appropriate testing with each other and primary packages. Chemical testing of the product during stability has demonstrated that there are no adverse interactions between **Ketoconazole and the excipients. Sebazole™** (ketoconazole, USP) Gel, 2% contains the excipients, Polyethylene Glycol 400, Propylene Glycol, glycerin, PPG-15 Stearyl Ether, Hydroxypropyl Cellulose, Ascorbic Acid, Butylated Hydroxytoluene, Citric Acid, Monohydrate, Citric Acid, Monohydrate, FD&C Yellow No.6, D&C Yellow No.10, and Dehydrated Alcohol .

The solubility of ketoconazole drug substance in Ketoconazole USP 2% Topical Gel Placebo is 5.5 % w/w. Thus, precipitation of ketoconazole is not an issue in Ketoconazole USP 2% Topical Gel. To assure that ketoconazole is fully dissolved during manufacture of the gel, an in-process control for _____

Chemistry Assessment Section

The particle size distribution is controlled by a tight acceptance specification (particle size: _____). Ketoconazole is a _____ drug substance as obtained from the vendor.

Stability data were submitted on three production batches of Ketoconazole USP 2% Topical Gel as packaged in the container/closure system proposed for the marketplace. Up to 24 months of room temperature data were submitted in support of the proposed _____ expiration date. Justification for the 24 months expiration date is based on the Registration Batch Data supporting 24 months on _____ batches and _____ batch. The stability data were found acceptable to support an expiration date of 24 months. The firm commits to a 24 month expiration date per amendment dated 5/5/05.

The Tradename, **Sebazole™**, is currently under review by DMETS and DDMAC, and it is to be determined later by the OND Division. The labeling was reviewed and found acceptable from a technical standpoint. The storage condition of Store at 25 ° C (77 ° F) ; excursions permitted to 15°- 30 ° (59-86 ° F).

Establishment Inspections: All facilities as indicated in the NDA are found acceptable for CGMPs. An overall recommendation of "acceptable" was received from the Office of Compliance on 12/14/05.

Environmental Assessment: The applicant's claim of categorical exclusion under regulation 21 CFR 25.31 (b) is acceptable since the EIC projection was found to be at a level well below 1ppb.

(2) Drug Substance:

The drug substance, ketoconazole, is manufactured and supplied to Barrier Therapeutics Inc. by _____. Ketoconazole is the subject of approved marketed products, e.g., Ketoconazole Topical 2% Cream (ANDA 076294 and others), Nizoral

Chemistry Assessment Section

(ketoconazole) Cream (NDA 19-084), Nizoral (ketoconazole) 2% Topical Shampoo (NDA 19-927) and Ketoconazole 2% Topical Shampoo (ANDA 076294 and others), and Nizoral (ketoconazole) Tablets (NDA 18-533), and (ketoconazole) Tablets (ANDA 075-314 & others). The details of the method of manufacture, controls, and packaging of the drug substance have been described in these NDAs and ANDAs. A letter of authorization was given by _____ to allow FDA reference to DMF _____ and DMF _____ in behalf of Barrier Therapeutics, Inc.

The NDA contained the HPLC method and Validation for the determination of Ketoconazole and related substances. The acceptance criteria and results were reported in the NDA.

The impurity profile was established for ketoconazole and is consistent throughout its manufacturing. The following known related impurities have been determined as follows: _____

_____ The specifications specify these limits for the related impurities in order to assure consistent quality from batch to batch. These impurities were found to fall within the acceptance criteria.

Based on the evaluation of the primary stability data, the proposed retest date of _____ was deemed acceptable.

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

Treatment of seborrheic dermatitis. Apply Sebazole Gel once daily to the affected area for 2 weeks.

- C. Basis for Approvability or Not-Approval Recommendation** – The NDA is recommended for approval because the information submitted in this NDA ensures the **Agency's Quality Standards; i.e., identity, strength, quality and purity. In addition, the establishment inspections for all of the facilities in the NDA are found acceptable. The labeling was found acceptable from a technical standpoint.**

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

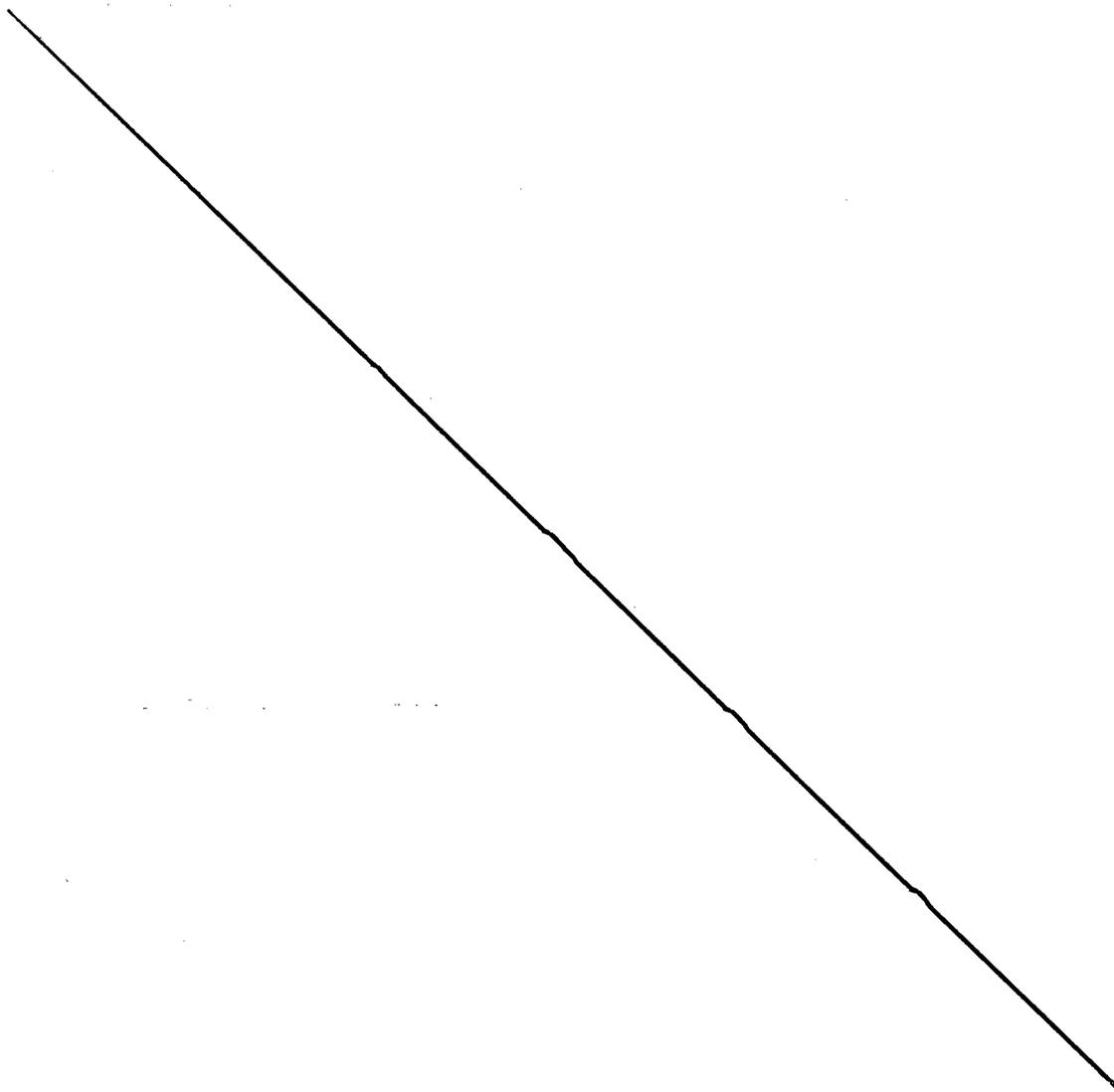


Chemistry Assessment Section

C. CC Block

Chemistry Assessment

**I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2:
Body Of Data**



71 Page(s) Withheld

~~_____~~ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-2/2

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ernest G. Pappas
7/14/2006 03:22:44 PM
CHEMIST

My chemistry review for this NDA is ready for
your signature. Recommend approval of the NDA.

Moo-Jhong Rhee
7/14/2006 04:41:25 PM
CHEMIST
Chief, Branch III