

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-250s000

CHEMISTRY REVIEW(S)

**Ampyra (fampridine)
Extended Release Tablets
NDA 22-250**

**Summary Basis for Recommended Action
from Chemistry, Manufacturing, and Controls**

Applicant: Acorda Therapeutics, Inc.
15 Skyline Drive
Hawthorn, NY 10532

Indication: Fampridine is a selective potassium channel blocker intended for improvement of walking ability in patients with Multiple Sclerosis.

Presentation: Fampridine (b) (4) tablets are film-coated, white to off-white, biconvex, oval shaped, non-scored tablets with flat edge, debossed with "A10" on one side and approximately 13 x 8 mm in size. The tablets are packaged in 14-count physician's samples and 60-count HDPE, round bottles with child-resistant (b) (4) closures, foil induction seals, (b) (4) desiccant canister.

EER Status: Acceptable 31-Jul-09

Consults: ONDQA Biopharmaceutics: Acceptable, H. Mahayni, 05-May-09
Methods Validation – Revalidation by Agency not requested
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Pharm/Tox – R. Houghtling (documented in L. Soldatova review 14-Dec-09)

Original Submission: 30-Jan-2009

Resubmission: 22-Apr-2009

Post-Approval Agreements: None

Drug Substance:

The drug substance, fampridine (chemical name: 4-aminopyridine) has the molecular formula C₅H₆N₂ and molecular weight 94.12. The drug substance is non-hygroscopic, only one (b) (4) form has been identified. Fampridine is soluble in water (b) (4) and other polar solvents such as alcohols, acetonitrile, and N,N-dimethylformamide. The bulk drug substance is manufactured by (b) (4) Information regarding the manufacture, characterization, and control of fampridine is incorporated by cross-reference to (b) (4) DMF # (b) (4) This DMF is Adequate as per Review #2 dated 14-Dec-2009 (by Dr. Lyudmila Soldatova).

The proposed drug substance specification, analytical procedures and method validation data, as well as batch analysis data are included in the NDA. Three potentially genotoxic impurities were identified and shown to be controlled at acceptable levels. The proposed retest period of (b) (4) is supported by adequate stability data.

Conclusion: Drug substance is satisfactory.

Drug product:

The drug product is a 10 mg oral extended release tablet with a recommended dose of twice daily (20 mg/day). The release-controlling mechanism is a hydrophilic matrix using hydroxypropyl methylcellulose. All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements, including: microcrystalline cellulose, hydroxypropyl methylcellulose, colloidal silicon dioxide, magnesium stearate, and (b) (4)

Fampridine extended release tablets will be manufactured at two sites - Elan Pharma (Athlone, County Westmeath, Ireland) and (b) (4). The manufacturing process uses (b) (4) steps followed by (b) (4) of a (b) (4) using a (b) (4) Parameters evaluated during manufacturing development include fampridine (b) (4)

Critical formulation attributes and process parameters were determined and suitable in-process controls are in place for the process and intermediates. Standard specifications for solid oral dosage forms have been proposed including appearance, identification (HPLC and UV), dissolution, assay (HPLC), content uniformity, moisture (KF), and impurity content (HPLC). Limits for potentially genotoxic degradation products are found acceptable.

Based on the drug product stability data, a shelf-life of 36 months is recommended for fampridine ER tablets. The drug product is stored at 25°C (77°F) with excursions permitted 15-30°C (59-86°F).

Conclusion: Drug product is satisfactory.

Additional Items:

- The applicant originally proposed a proprietary name of Amaya. The proposed name was changed during the review cycle and a revised name of Ampyra was found acceptable (D. Baugh, 18-Dec-09).
- The established name, fampridine, was found to be unacceptable due to similarity with other products. The revised established name is pending at the time of this memo.
- All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

- The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion: NDA 22-250 for Fampridine ^{(b)(4)} Tablets is recommended for **APPROVAL** from a Chemistry, Manufacturing and Controls standpoint.

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22250

ORIG-1

ACORDA
THERAPEUTICS
INC

FAMPRIDINE TABLETS

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/s/

CHRISTINE M MOORE
12/23/2009

NDA/ 22-250

Fampridine ^{(b) (4)} Tablets

Acorda Therapeutics, Inc.

Division of Neurology Products

**Lyudmila N. Soldatova, Ph. D.
DPAI/ONDQA**

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 22-250
2. REVIEW #3
3. REVIEW DATE: December 14, 2009
4. REVIEWER: Lyudmila N Soldatova
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-JAN-2009
Amendment	06-FEB-2009
Re-submission	22-APR-2009
Amendment	22-JUN-2009
Amendment	30-JUN-2009
Amendment	04-AUG-2009
Review #1	14-SEP-2009
Amendment	16-SEP-2009
Amendment	18-SEP-2009
Amendment	21-SEP-2009
Review #2	15-OCT-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
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7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Acorda Therapeutics, Inc.
Address: 15 Skyline Drive
Hawthorn, NY 10532
Representative: Brian Walter, Ph.D.
Senior Director, Regulatory Affairs
Telephone: 914-347-4300 x 139

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): fampridine
c) Code Name/# (ONDC only): EL-970
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Multiple sclerosis (MS)

11. DOSAGE FORM: ER Tablets

12. STRENGTH/POTENCY: 10 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

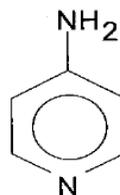
Chemistry Review Data Sheet

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

4-Pyridinamine

Molecular weight: 94.12

Molecular formula: C₅H₆N₂



17. RELATED/SUPPORTING

DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II			(b) (4) 1	Adequate	12-14-2009	Drug substance
	IV			4	Adequate	N/A	Tablet film coating
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			3	Adequate	N/A	Packaging
	III			3	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			4	Adequate	N/A	Packaging
	III			3	Adequate	N/A	Packaging

Chemistry Review Data Sheet

			(b) (4)				
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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 related 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall recommendation Acceptable	31-Jul-2009	Office of Compliance
Pharm/Tox	Pending		Richard Houghtling, Ph.D.
Biopharm/ONDQA	In vitro dissolution method and specification are Acceptable	05-May-2009	Houda Mahayni, Ph.D.
DDMAC	Pending		
DMEPA	Proprietary name is pending Recommendations on Label and Labeling are made	14-Aug-2009	Denise Baugh, Pharm.D., BCPS
Methods Validation	Methods validation is not recommended for FDA labs (as per this review)		Lyudmila N. Soldatova, Ph.D.
EA	Claim for Categorical Exclusion from EA preparation is acceptable		Lyudmila N. Soldatova, Ph.D.



CHEMISTRY REVIEW



Chemistry Review Data Sheet

	as per this Review.		
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The Chemistry Review for NDA 22-250

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-250 for Fampridine (b) (4) Tablets is recommended for APPROVAL from a Chemistry, Manufacturing and Controls standpoint. Based on the drug product stability data, shelf-life of 36 months is recommended for fampridine ER Tablets packaged in 60-count, 60 cc HDPE round bottles, and physician samples packaged in 14-count in 30 cc HDPE round bottles. The overall OC recommendation for drug substance and drug product manufacturing facilities is Acceptable.

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

None as per this review.

II. Summary of Chemistry Assessments

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

The proposed dosage form for Fampridine (b) (4) tablets, 10 mg is an extended release tablet containing 10 mg of fampridine. The tablets are film coated, white to off-white biconvex, oval shaped tablets with a flat edge; tablets are debossed with "A10" on one side, and are approximately 13 x 8 mm in size. All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements; they are: microcrystalline cellulose (b) (4) hydroxypropyl methylcellulose (b) (4) colloidal silicon dioxide (b) (4) magnesium stearate and film coating solution (b) (4). The release-controlling mechanism is (b) (4).

Fampridine extended release tablets are manufactured using a (b) (4) process followed by (b) (4) of a (b) (4). Parameters evaluated during manufacturing development include fampridine (b) (4).

Fampridine extended-release tablets will be packaged in (b) (4) (physician samples) and 60-count (commercial packaging) HDPE round bottles (as per clarification in the Amendment dated September 18, 2009) with child-resistant (b) (4) closures and foil induction seals. Each bottle will contain (b) (4) desiccant canister. Fampridine extended release tablets will be manufactured at two sites, i.e., the Elan Pharma facility in Athlone, County Westmeath, Ireland and the (b) (4) facility in (b) (4). Standard specifications for solid oral dosage forms have been proposed; dissolution method and specification for extended release tablets were found acceptable by ONDQA biopharm reviewer. The NDA stability package includes extensive long

Executive Summary Section

term stability data for Fampridine tablets in round HDPE bottles (i.e., (b) (4) months for (b) (4) primary and supportive batches of drug product).

The drug product is stored at 25°C (77°F). Excursions permitted 15-30°C (59-86°F).

The active ingredient, fampridine (chemical name: 4-aminopyridine) is a small molecule with molecular formula C₅H₆N₂ and molecular weight 94.12. Fampridine is soluble in water (b) (4)

(b) (4) The drug substance is non hygroscopic and no (b) (4) forms are described.

The bulk drug substance is manufactured by (b) (4) in one step from (b) (4) Information regarding the manufacture, characterization, and control of fampridine is incorporated by cross-reference to (b) (4) DMF # (b) (4) This DMF is found to be Adequate according to Review #2 by Dr. Soldatova dated 14-Dec-2009. The proposed drug substance specification, analytical procedures and method validation data, as well as batch analysis data are included in the NDA. A second drug substance supplier, i.e., (b) (4) was used as a supplier for clinical trials during the IND phase. Due to commercial reasons this firm will not be used as bulk supplier under the NDA. Per agreement with the Agency, however, stability data generated from drug product batches manufactured using (b) (4) drug substance are submitted to support qualification of an alternate drug product manufacturer, i.e., (b) (4)

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

Fampridine (b) (4) tablets are supplied as a single 10 mg dosage strength. It is packaged for commercial distribution in 60-count, 60 cc HDPE bottles, and physician samples are packaged in 14-count in 30 cc HDPE bottles; each bottle will contain (b) (4) and a (b) (4) desiccant canister. The drug will be administered orally. The recommended dose is 10 mg taken twice daily (20 mg/day).

C. Basis for Approvability or Not-Approval Recommendation

The applicant has addressed all deficiencies satisfactory. The drug substance DMF (b) (4) is adequate as per Review #2 dated 14-Dec-2009 (by Dr. L. Soldatova). The overall recommendation for drug substance and drug product facilities from the Office of Compliance is Acceptable.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS

Executive Summary Section

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Don Henry
Clinical Project Manager Name: James Reese, Ph.D.

C. CC Block

See DARRTS.

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Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22250

ORIG-1

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THERAPEUTICS
INC

FAMPRIDINE TABLETS

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/s/

LYUDMILA N SOLDATOVA
12/14/2009

RAMESH K SOOD
12/14/2009

NDA/ 22-250

Fampridine ^{(b) (4)} Tablets

Acorda Therapeutics, Inc.

Division of Neurology Products

**Lyudmila N. Soldatova, Ph. D.
DPAI/ONDQA**

Review of Chemistry, Manufacturing, and Controls

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List Of Deficiencies To Be Communicated.....	22

Chemistry Review Data Sheet

1. NDA 22-250
2. REVIEW #2
3. REVIEW DATE: October 14, 2009
4. REVIEWER: Lyudmila N Soldatova
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	30-JAN-2009
Amendment	06-FEB-2009
Re-submission	22-APR-2009
Amendment	22-JUN-2009
Amendment	30-JUN-2009
Amendment	04-AUG-2009
Review #1	14-SEP-2009

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	16-SEP-2009
Amendment	18-SEP-2009
Amendment	21-SEP-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Acorda Therapeutics, Inc.

Address: 15 Skyline Drive
Hawthorn, NY 10532

Chemistry Review Data Sheet

Representative: Brian Walter, Ph.D.
Senior Director, Regulatory Affairs
Telephone: 914-347-4300 x 139

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): fampridine
c) Code Name/# (ONDC only): EL-970
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Multiple sclerosis (MS)

11. DOSAGE FORM: ER Tablets

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

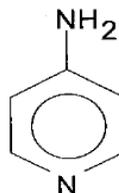
Not a SPOTS product

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

4-Pyridinamine

Molecular weight: 94.12

Molecular formula: C₅H₆N₂



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)	II	[REDACTED]	(b) (4)	1	Inadequate	09-16-2009	Drug substance
	IV		4	Adequate	N/A	Tablet film coating	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	

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 related revision since last review

Chemistry Review Data Sheet

- 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall recommendation Acceptable	31-Jul-2009	Office of Compliance
Pharm/Tox	Pending		Richard Houghtling, Ph.D.
Biopharm/ONDQA	In vitro dissolution method and specification are Acceptable	05-May-2009	Houda Mahayni, Ph.D.
DDMAC	Pending		
DMEPA	Proprietary name Amaya is acceptable Recommendations on Label and Labeling are made	04-Aug-2009 14-Aug-2009	Denise Baugh, Pharm.D., BCPS Denise Baugh, Pharm.D., BCPS
Methods Validation	Methods validation is not recommended for FDA labs (as per this review)		Lyudmila N. Soldatova, Ph.D.
EA	Claim for Categorical Exclusion from EA preparation is acceptable as per this Review.		Lyudmila N. Soldatova, Ph.D.

The Chemistry Review for NDA 22-250

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-250 for Fampridine (b) (4) Tablets cannot be approved in this current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) and drug product deficiencies. The overall OC recommendation for drug substance and drug product manufacturing facilities is Acceptable.

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

None as per this review.

II. Summary of Chemistry Assessments

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

The proposed dosage form for Fampridine (b) (4) tablets, 10 mg is an extended release tablet containing 10 mg of fampridine. The tablets are film coated, white to off-white biconvex, oval shaped tablets with a flat edge; tablets are debossed with "A10" on one side, and are approximately 13 x 8 mm in size. All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements; they are: microcrystalline cellulose (b) (4) hydroxypropyl methylcellulose (b) (4) colloidal silicon dioxide (b) (4) magnesium stearate and film coating solution (b) (4). The release-controlling mechanism is a (b) (4)

(b) (4) Fampridine extended release tablets are manufactured using a (b) (4) process followed by (b) (4) of a (b) (4)

Parameters evaluated during manufacturing development include fampridine (b) (4)

Fampridine extended-release tablets will be packaged in 14-count (physician samples) and 60-count (commercial packaging) HDPE round bottles (as per clarification in the Amendment dated September 18, 2009) with child-resistant (b) (4) closures and foil induction seals. Each bottle will contain (b) (4) desiccant canister. Fampridine extended release tablets will be manufactured at two sites, i.e., the Elan Pharma facility in Athlone, County Westmeath, Ireland and the (b) (4) facility in (b) (4). Standard specifications for solid oral dosage forms have been proposed; dissolution method and specification for extended release tablets were found acceptable by ONDQA biopharm reviewer. The NDA stability package includes extensive long

Executive Summary Section

(b) (4)

term stability data for Fampridine tablets in round HDPE bottles (i.e. (b) (4) months for (b) (4) primary and supportive batches of drug product). The recommendation (b) (4) the expiration dating period for drug product in all packaging configurations is currently pending upon resolution of the issue on the potential genotoxicity of the drug product degradation products and the issue on the specification limit for (b) (4) impurity (consulted with pharm/tox reviewer). The drug product is stored at 25°C (77°F). Excursions permitted 15-30°C (59-86°F).

The active ingredient, fampridine (chemical name: 4-aminopyridine) is a small molecule with molecular formula C₅H₆N₂ and molecular weight 94.12. Fampridine is soluble in water (b) (4). The drug substance is non hygroscopic and no polymorphic forms are described. The bulk drug substance is manufactured by (b) (4) in one step from (b) (4). Information regarding the manufacture, characterization, and control of fampridine is incorporated by cross-reference to (b) (4) DMF # (b) (4). This DMF is currently Inadequate pending the (b) (4) response to the Deficiency Letter dated 7/10/2009. The proposed drug substance specification, analytical procedures and method validation data, as well as batch analysis data are included in the NDA. A second drug substance supplier, i.e., (b) (4) was used as a supplier for clinical trials during the IND phase. Due to commercial reasons this firm will not be used as bulk supplier under the NDA. Per agreement with the Agency, however, stability data generated from drug product batches manufactured using (b) (4) drug substance are submitted to support qualification of an alternate drug product manufacturer, i.e., (b) (4).

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

Fampridine (b) (4) tablets are supplied as a single 10 mg dosage strength. It is packaged for commercial distribution in 60-count, 60 cc HDPE bottles, and physician samples are packaged in 14-count in 30 cc HDPE bottles; each bottle will contain (b) (4) desiccant canister. The drug will be administered orally. The recommended dose is 10 mg taken twice daily (20 mg/day).

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-250 for Fampridine (b) (4) Tablets cannot be approved in this current form from the CMC standpoint. The outstanding issues that need to be resolved include the control of five potentially genotoxic impurities in the drug substance and/or drug product and Acorda's action on this issue. Acorda should either determine that these impurities are negative when tested directly in in vitro genotoxicity assays, or to demonstrate that the maximum daily intake of each of these impurities is less than 1.5 µg/day, and to provide appropriate validation data for the analytical methods of quantification of these impurities at this safety level. The proposed drug substance and drug product specifications control these impurities at the levels that are much higher than acceptable limit, suggesting the potential exceeding of the safe level for the potentially genotoxic impurities in the drug product batches. Acorda has addressed the issue on the maximum daily intake for two

Executive Summary Section

out of three potentially genotoxic drug substance impurities, [REDACTED] (b) (4) [REDACTED], in the Amendment dated September 18, 2009. The [REDACTED] (b) (4) [REDACTED] impurity was identified as a metabolite; this statement is under evaluation by pharm/tox reviewer. However, the issue with the drug product potentially genotoxic impurities is still pending. In addition, the limit for [REDACTED] (b) (4) [REDACTED] impurity in the drug product specification of NMT [REDACTED] (b) (4) [REDACTED] causes a concern to the pharm/tox reviewer. The number of other non-resolved issues and currently deficient drug substance DMF [REDACTED] (b) (4) [REDACTED] provide a basis for the current recommendation for this NDA.

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

See electronic signatures in DFS

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Don Henry
Clinical Project Manager Name: James Reese, Ph.D.

C. CC Block

See DARRTS.

15 pp withheld immediately after this page as (b)4) CCI/TS.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22250

ORIG-1

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THERAPEUTICS
INC

FAMPRIDINE TABLETS

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/s/

LYUDMILA N SOLDATOVA
10/14/2009

RAMESH K SOOD
10/15/2009

NDA/ 22-250

AMAYA (fampridine)

Acorda Therapeutics, Inc.

Division of Neurology Products

**Lyudmila N. Soldatova, Ph. D.
DPAI/ONDQA**

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA 22-250
2. REVIEW #1
3. REVIEW DATE: September 10, 2009
4. REVIEWER: Lyudmila N Soldatova
5. PREVIOUS DOCUMENTS:

Previous Documents

IND 17,627

Document Date

01-MAR-1983

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment

Re-submission

Amendment

Amendment

Amendment

Document Date

30-JAN-2009

06-FEB-2009

22-APR-2009

22-JUN-2009

30-JUN-2009

04-AUG-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Acorda Therapeutics, Inc.

Address: 15 Skyline Drive
Hawthorn, NY 10532Representative: Brian Walter, Ph.D.
Senior Director, Regulatory Affairs

Telephone: 914-347-4300 x 139

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Fampridine ^{(b) (4)} Tablets
b) Non-Proprietary Name (USAN): fampridine
c) Code Name/# (ONDC only): EL-970
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Multiple sclerosis (MS)

11. DOSAGE FORM: ER Tablets

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\)](#):

SPOTS product – Form Completed

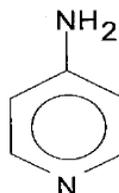
Not a SPOTS product

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

4-Pyridinamine

Molecular weight: 94.12

Molecular formula: C₅H₆N₂



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)	II		(b) (4)	1	Inadequate	09-XX-2009	Drug substance
	IV		4	Adequate	N/A	Tablet film coating	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		4	Adequate	N/A	Packaging	
	III		3	Adequate	N/A	Packaging	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

Chemistry Review Data Sheet

- 2 – Type 1 DMF
- 3 – Reviewed previously and no related 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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Overall recommendation Acceptable	31-Jul-2009	Office of Compliance
Pharm/Tox	Pending		Richard Houghtling, Ph.D.
Biopharm/ONDQA	In vitro dissolution method and specification are Acceptable	05-May-2009	Houda Mahayni, Ph.D.
DDMAC	Pending		
DMEPA	Proprietary name Amaya is acceptable Recommendations on Label and Labeling are made	04-Aug-2009 14-Aug-2009	Denise Baugh, Pharm.D., BCPS Denise Baugh, Pharm.D., BCPS
Methods Validation	Methods validation is not recommended for FDA labs (as per this review)		Lyudmila N. Soldatova, Ph.D.
EA	Claim for Categorical Exclusion from EA preparation is acceptable as per this Review.		Lyudmila N. Soldatova, Ph.D.

The Chemistry Review for NDA 22-250

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 22-250 for Amaya (fampridine) ER Tablets cannot be approved in this current form from the CMC standpoint. The approval is contingent upon satisfactory resolution of the drug substance DMF (b) (4) and drug product deficiencies. The overall OC recommendation for drug substance and drug product manufacturing facilities is Acceptable.

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

None as per this review.

II. Summary of Chemistry Assessments

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

The proposed dosage form for Amaya (fampridine) ER tablets, 10 mg is an extended release tablet containing 10 mg of fampridine. The tablets are film coated, white to off-white biconvex, oval shaped tablets with a flat edge; tablets are debossed with "A10" on one side, and are approximately 13 x 8 mm in size. All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements; they are: microcrystalline cellulose (b) (4) hydroxypropyl methylcellulose (b) (4) colloidal silicon dioxide (b) (4), magnesium stearate and film coating solution (b) (4). The release-controlling mechanism is a (b) (4)

Fampridine extended release tablets are manufactured using a (b) (4) process followed by (b) (4) of a (b) (4). Parameters evaluated during manufacturing development include fampridine (b) (4)

Fampridine extended-release tablets will be packaged in (b) (4) and 14-count (physician samples) and 60-count (commercial packaging) HDPE round (b) (4) bottles with child-resistant (b) (4) closures and foil induction seals. Each bottle will contain (b) (4) desiccant canister. Fampridine extended release tablets will be manufactured at two sites, i.e., the Elan Pharma facility in Athlone, County Westmeath, Ireland and the (b) (4) facility in (b) (4)

Standard specifications for solid oral dosage forms have been proposed; dissolution method and specification for extended release tablets were found acceptable by ONDQA biopharm reviewer. The NDA stability package includes extensive long term stability data for Amaya tablets in

Executive Summary Section

(b) (4)
round HDPE bottles (i.e., (b) (4) months for (b) (4) primary and supportive batches of drug product). Up to 18-month stability data is provided for drug product in 14-count and 60-count (b) (4) HDPE bottles, and up to (b) (4) data is provided for drug product in (b) (4) (b) (4) HDPE bottles. The additional stability data provided by the firm in the Amendment dated 30-Jun-2009 applies only to the drug product batches packaged in (b) (4) 14-count, and 60-count oblong bottles. The recommendation on the expiration dating period for drug product in all packaging configurations is currently pending upon resolution of the issue on the potential genotoxicity of the drug product degradation products and the issue on the specification limit for (b) (4) (b) (4) (consulted with pharm/tox reviewer).

The drug product is stored at 25°C (77°F). Excursions permitted 15-30°C (59-86°F).

The active ingredient, fampridine (chemical name: 4-aminopyridine) is a small molecule with molecular formula C₅H₆N₂ and molecular weight 94.12. Fampridine is soluble in water (b) (4). The drug substance is non hygroscopic and no polymorphic forms are described. The bulk drug substance is manufactured by (b) (4) in one step from (b) (4). Information regarding the manufacture, characterization, and control of fampridine is incorporated by cross-reference to (b) (4) DMF # (b) (4). This DMF is currently Inadequate pending the (b) (4) response to the Deficiency Letter dated 7/10/2009. The proposed drug substance specification, analytical procedures and method validation data, as well as batch analysis data are included in the NDA. A second drug substance supplier, i.e., (b) (4) was used as a supplier for clinical trials during the IND phase. Due to commercial reasons this firm will not be used as bulk supplier under the NDA. Per agreement with the Agency, however, stability data generated from drug product batches manufactured using (b) (4) drug substance are submitted to support qualification of an alternate drug product manufacturer, i.e., (b) (4).

A categorical exclusion from the preparation of an environmental assessment is claimed by the firm, as provided under 21 CFR 25.31(b).

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

Amaya (fampridine) ER tablets are supplied as a single 10 mg dosage strength. It is packaged for commercial distribution in 60-count, 60 cc HDPE bottles, and physician samples are packaged in either (b) (4) or 14-count in 30 cc HDPE bottles; each bottle will contain (b) (4) desiccant canister. The drug will be administered orally. The recommended dose is 10 mg taken twice daily (20 mg/day).

C. Basis for Approvability or Not-Approval Recommendation

NDA 22-250 for Amaya (fampridine) ER Tablets cannot be approved in this current form from the CMC standpoint. The outstanding issues that need to be resolved include the identification of seven potentially genotoxic impurities in the drug substance and/or drug product and Acorda's action on this issue. Acorda should either determine that these impurities are negative when tested directly in *in vitro* genotoxicity assays, or to demonstrate that the maximum daily intake of each of these impurities is less than 1.5 µg/day, and to provide appropriate validation data for the

Executive Summary Section

analytical methods of quantification of these impurities at this safety level. The proposed drug substance and drug product specifications control these impurities at the levels that are much higher than acceptable limit, suggesting the potential exceeding of the safe level for the potentially genotoxic impurities in the drug product batches. In addition, the limit for (b) (4) impurity in the drug product specification of NMT (b) (4) causes a concern of the pharm/tox reviewer. The number of other non-resolved issues and currently deficient drug substance DMF (b) (4) provide a basis for the current recommendation for this NDA.

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

See electronic signatures in DFS

B. Endorsement Block

Chemist Name: Lyudmila N. Soldatova, Ph.D.
Chemistry Branch Chief: Ramesh K. Sood, Ph.D.
Chemistry Project Manager Name: Don Henry
Clinical Project Manager Name: James Reese, Ph.D.

C. CC Block

See DARRTS.

77 pp withheld immediately after this page as (b)(4) CCI/TS.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS
NDA-22250	ORIG-1	ACORDA THERAPEUTICS INC	FAMPRIDINE TABLETS

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

/s/

LYUDMILA N SOLDATOVA
09/11/2009

RAMESH K SOOD
09/14/2009

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division: Division of Neurology Products/

NDA: 22-250

Applicant: Acorda Therapeutics, Inc.

Stamp Date: 30-Jan-2009

PDUFA Date: TBD

Trademark: TBD

Established Name: fampridine

Dosage Form: Extended Release Tablets

Route of Administration: Oral

Indication: Multiple sclerosis (MS)

PAL: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

Summary

Fampridine was initially developed during the 1980's at Rush-Presbyterian-St. Luke's Medical Center for treatment of MS under IND 17,627. Elan Pharmaceuticals acquired the IND in 1990 and initiated clinical trials for treatment of stroke in 1996 under IND 51,333. Elan subsequently transferred both INDs to Acorda Therapeutics in 1997. Acorda continued development of fampridine for MS under IND 17,627; but the firm eventually discontinued studies for the stroke indication. In NDA 22-250, Acorda proposes marketing of fampridine as extended-release tablets containing 10 mg fampridine. The recommended dose is 10 mg taken twice daily (20 mg/day).

Drug Substance

The active ingredient, fampridine [Chemical Name: 4-aminopyridine] is a small molecule with molecular formula $C_5H_6N_2$ and molecular weight 94.12. The structural formula for fampridine is:



Fampridine is soluble in water

(b) (4)

The drug substance is non hygroscopic and no polymorphic forms are described.

The bulk drug substance is manufactured by (b) (4) in one step from (b) (4). Information pertaining to manufacture, characterization, and control of fampridine is incorporated by cross-reference to (b) (4) DMF # (b) (4). It is noted that during the IND phase Acorda qualified a second drug substance supplier, i.e., (b) (4) as a supplier for clinical trials. Due to commercial reasons this firm will not be used as bulk supplier under the NDA. Per agreement with the Agency, however, stability data generated from drug product batches manufactured using (b) (4) sourced drug substance are submitted to support qualification of an alternate drug product manufacturer, i.e., (b) (4). [Agency preliminary responses dated 04-Mar-2008 for Type CMC meeting scheduled for 10-Mar-2008; the meeting was subsequently cancelled.]

The proposed drug substance specification is reproduced below. Analytical procedures and method validation data are included in the NDA. The proposed analytical procedures for fampridine are straight-forward. Assay/identification and related substances are determined using a single (b) (4) HPLC method.

Table 1: Proposed Specification for Fampridine

(b) (4)



Drug Product

The proposed dosage form is an extended release tablet containing 10 mg of fampridine. The tablets are film coated, white to off-white biconvex, oval shaped tablets with a flat edge. The tablets are debossed with “A10” on one side, and are approximately 13 x 8 mm in size. The release-controlling mechanism is (b) (4). The quantitative formulation is summarized in Table 1.o

Table 1: Fampridine-SR Tablets, 10 mg Target Composition

Component	Reference to Quality Standard	Function	Mg per Tablet
fampridine (4-aminopyridine)	In House	Drug Substance	10
microcrystalline cellulose (b) (4)	USP	(b) (4)	(b) (4)
hydroxypropyl methylcellulose (b) (4)	USP		
colloidal silicon dioxide (b) (4)	NF		
magnesium stearate	NF		
(b) (4)	(b) (4)		
purified water ²	USP		
Target Tablet Weight			410

1 The composition of (b) (4) is provided in Table 4, Section 3.2.P.4.1.

2 (b) (4)

All tablet excipients are commonly used for manufacture of solid oral dosage forms and comply with compendial requirements. The proposed commercial tablet formulation is identical to the tablets used for Phase 2 and Phase 3 clinical trials.

Fampridine extended-release tablets will be packaged in (b) (4) 14- and 60-count HDPE bottles with child-resistant closures (b) (4) closures and foil induction seals. Each bottle will contain (b) (4) desiccant canister.

Fampridine extended release tablets will be manufactured at two sites, i.e., the Elan Pharma facility in Athlone, County Westmeath, Ireland and the (b) (4) facility in (b) (4). The Elan Athlone facility was used to manufacture all clinical supplies and the primary drug product stability batches.

Fampridine extended release tablets are manufactured using a (b) (4) process followed by (b) (4) of a (b) (4). Parameters evaluated during manufacturing development include fampridine (b) (4).

The proposed regulatory specification for Fampridine Tablets is shown in the following page. Test parameters are typical for an extended release tablet and the analytical methods are straightforward.

Table 1: Proposed Regulatory Release Specifications for Fampridine-SR Tablets, 10mg

Test	Method Description	Acceptance Criteria
(b) (4)		

The NDA stability package includes extensive long term stability data for fampridine (i.e., (b) (4) months for (b) (4) primary and supportive batches of drug product. It is noted that the packaging configurations (e.g., bottle size, shape and tablet count) for some of the primary stability batches differ slightly from the proposed commercial image presentations. As an example, stability batches manufactured in (b) (4) were packaged in (b) (4) and (b) (4) bottles versus the 14- and 60-count commercial configurations. Per agreements made with the firm during end of phase 2 and pre-NDA negotiations (under IND 51,333 and 17,627, respectively), these differences are considered acceptable for the primary stability batches.

Critical issues for review

Drug Substance

As drug substance information has been submitted in the (b) (4) DMF (b) (4) critical issues are not included in this initial quality assessment.

Drug Product

(b) (4)

Additional issues

Administrative: The applicant's claim for categorical exclusion from environmental assessment under 21 CFR 25.31(b) is included in Module 1 of the application.

Establishment Evaluation: Manufacturing facilities are identified within the application but the information provided on the original Form 356h was incomplete. The ONDQA Project Manager contacted the firm and requested that the 356h be revised to include all required facility information. A revised 356h was received on 06-Feb-2009. Refer to attached facility information.

Labeling/Established Name: The active ingredient, fampridine, is free base. Thus, there are no issues related to consistency between the established name "fampridine extended-release tablets" and labeled potency. The applicant, however, consistently refers to the product as "sustained release tablets in the application and will be advised to correct the established name.

Organization—The application is submitted in e-CTD format. Within individual modules, the headings are disordered when viewed in Global Submit. As a example, the normal organization of the Pharmaceutical Development section is compared to the actual order in the application below. The sponsor has been advised to correct this.

P.2 Pharmaceutical Development

- P.2.1 Components of the Drug Product
- P.2.2 Drug Product
- P.2.3 Manufacturing Process Development
- P.2.4 Container Closure System
- P.2.5 Microbiological Attributes
- P.2.6 Compatibility

3.2.P.2. Pharmaceutical Development

- Container Closure System
- Drug Product
- Components of the Drug Product
- Container Closure USP Testing Report: 30 c
- Compatibility
- Container Closure USP Testing Report: 30 c
- Manufacturing Process Development
- Microbiological Attributes
- Container Closure USP Testing Report: 60 c

Comments for 74-Day Letter

You refer to the drug product within the NDA, and in draft labeling, as “fampridine sustained release tablets.” The established name for the product should be “fampridine extended release tablets.” Please submit revised labeling that reflects the correct established name.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective pending correction of the e-CTD format. The drug substance is a well-characterized small molecule and the dosage form is relatively simple. No novel manufacturing processes are involved and the submission does not appear to require a review by the Manufacturing Sciences Branch.

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead

09-Feb-2009
Date

Ramesh Sood, Ph.D.
Branch Chief

09-Feb-2009
Date

**CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA**

NDA Number: 22-250

Applicant: Acorda Therapeutics, Inc.

Stamp Date: 30-Jan-2009

Drug Name: fampridine tablets

NDA Type: TBD

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

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?		X	Sponsor was asked to correct order of e-CTD CMC section
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		DMF (b) (4) is referenced.
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes__

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

09-Feb-2009

Pharmaceutical Assessment Lead, DPA 1, ONDQA

Date

Ramesh Sood, Ph.D.

09-Feb-2009

Branch Chief, DPA 1, ONDQA

Date

Attachment B

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Drug Substance

Company Name / Address	Contact Details	Processing / Testing Step
(b) (4)	(b) (4)	Manufacturing, packaging, analytical testing and release of fampridine (4AP) drug substance Drug Substance stability testing

Drug Product

Company Name / Address	Contact Details	Processing / Testing Step
Elan Pharma International Ltd Monksland Industrial Estate, Athlone, Co. Westmeath Ireland <u>Establishment Registration Number:</u> 3002806875	Phil Shanahan V.P. Quality Tel: 353-90-649-5398 email: phil.shanahan@elan.com <u>US Agent</u> Wayne Wiley Director, Regulatory Affairs Elan Holdings Inc 1300 Gould Drive Gainesville GA 30504 Tel.: 770-538-6360 Fax: 770-534-8247 email: wayne.wiley@elan.com	Tablet manufacturing, bulk packaging and labeling. Analytical testing and release of bulk Drug Product. Drug Product stability testing

Company Name / Address	Contact Details	Processing / Testing Step
Elan Holdings Inc 1300 Gould Drive Gainesville GA 30504 <u>Establishment Registration Number:</u> 1035761	Sherida Burks QA Director Tel.: 770-538-6344 Fax: 770-534 8247 email: sherida.burks@elan.com	Finished Drug Product Packaging and labeling, release of finished Drug Product
(b) (4)		
(b) (4)		Finished Drug Product analytical testing and release Drug Product stability testing
(b) (4)		Drug Product stability testing

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

/s/

Martha Heimann
2/9/2009 10:51:10 AM
CHEMIST

Ramesh Sood
2/9/2009 12:04:35 PM
CHEMIST