CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-431

Chemistry Review(s)

6/4/04

CHEMISTRY REVIEW

NDA 21-431

CAMPRAL (acamprosate calcium) Tablets

Lipha Pharmaceuticals, Inc.

David B. Lewis, Ph.D.

Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-431

2. REVIEW #: 3

3. REVIEW DATE: May 24th, 2004

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL NDA	21/12/01
NDA 21-431 CMC REVIEW # 1	07/06/02
NDA 21-431 NA Letter	27/06/02
NDA 21-431 CMC REVIEW # 2	19/04/04
NDA 21-431 AE Letter	20/04/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
AMENDMENT	29/04/04
AMENDMENT	03/05/04
AMENDMENT	19/05/04

- The amendment of April 29th, 2004 provided updated color copies of each of the product packaging, along with a revised package insert.
- The amendment of May 3rd, 2004 provided responses to the two CMC deficiencies from the April 20th deficiency letter.
- The amendment of May 19th, 2004 provided responses to the CMC telephone request of May 17th, 2004 regarding dissolution acceptance criteria.

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Name:	Lipha Pharmaceuticals, Inc.
Address:	1114 Avenue of the Americas, NY, NY 10036
Representative:	Anita Goodman, M.D.
Telephone:	(212) 398-4602 X 16

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CAMPRAL®
b) Non-Proprietary Name (USAN): acamprosate calcium (acamprosate is INN, BAN)
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P (the original NDA was priority status for the 1st review cycle)

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

10. PHARMACOL. CATEGORY: abstinence from alcohol consumption

11. DOSAGE FORM: Tablet, delayed release

12. STRENGTH/POTENCY: 333 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

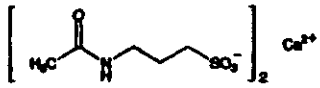
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__x__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: The nomenclature for the drug substance is as follows:

- INN/USAN Name: Acamprosate calcium (USAN). Acamprosate is INN and BAN.
- Inverted IUPAC Name: 3-Propoanesulfonic acid, 3-(acetylamino), calcium salt
- Other chemical names: 3-Acetamido-propanesulfonic acid, calcium acetylaminopropane sulfonate, and calcium acetylhomotaurine
- CAS Registry Number: [77337-76-9] (for the free acid)
- Structural Formula: $C_{10}H_{20}N_2O_8S_2Ca$ (400.48 g/mol, calcium salt); $C_5H_{11}NO_4S$ (181.21 g/mol, free acid).
- Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	II	LIPHA	Calcium acamprosate	1	Adequate	30/03/04	
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		
—	III	—	—	7	N/A		

[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)

The Type III packaging DMF's, which were referenced in the application, were not reviewed due to the current ONDC policy regarding container closure components for solid oral dosage forms. All of the container closure components (and the raw materials from which they were fabricated) meet the current 21 CFR requirements for food storage safety (*information contained within the referenced DMF's*).

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A*		
EES	Pending**		
Pharm/Tox	Not approvable***	10/06/02	K. Haberny
Biopharm	Adequate (approval)	07/06/02	D. Lee
LNC	N/A		
Methods Validation	None at this time****		
ODS_1	Adequate	12/06/02	N. Roselle, Pharm.D.
ODS_2 *****	Adequate	15/03/04	C. Hoppes, R. Ph., M.P.H.
EA	Adequate	07/06/02	D. Lewis, Ph.D.
Microbiology	N/A		

* The stability data submitted in support of this NDA was not submitted to Biometrics for statistical analysis, since all of the quantitative attributes were essentially flatline (*e.g.*, minimal degradation and loss of potency).

** The cGMP status for NDA 21-431 is pending completion of one inspection of a testing facility.

Chemistry Review Data Sheet

*** A second pharmacology & toxicology review is being conducted at this time, but there are no CMC-related issues (*e.g.*, the P. Tox review concerns toxicity and safety of the pure drug substance).

**** Based on the interim criteria for initiating FDA methods Validation (see summary enclosed in the body of this review), Methods Validation is not being requested at this time.

***** A second ODS (DMETS) review concluded that the proprietary name, CAMPRAL remained adequate for the drug product (in the light of the emergence of new proprietary and established names on the U.S. market).

The Chemistry Review for NDA 21-431

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approve pending a satisfactory cGMP status from the Office of Compliance.

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

None; however, the following statement should be communicated to the applicant: "Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified."

I. Summary of Chemistry Assessments

NDA 21-431 provides CMC information for CAMPRAL® (acamprosate calcium) tablets. Acamprosate calcium is a new molecular entity (NME) in the U.S., but has been marketed in Europe for more than 10 years as a pharmaceutical agent for the maintenance of sobriety in recovering alcoholics. NDA 21-431 was submitted on December 21st, 2001, and amended on January 30th, March 13th, April 11th, April 19th, April 24th, and May 22nd, 2002. The 1st review cycle resulted in a NOT APPROVABLE (NA) action, which included four CMC-related deficiencies; these deficiencies included the notification that DMF [ ] was not adequate to support this NDA for the drug substance, acamprosate calcium. A deficiency letter was also submitted to the holder of DMF [ ] CMC Review # 2 addressed the NDA applicant's responses to the CMC deficiencies along with reference to the responses submitted by the DMF [ ] holder regarding the CMC information for the drug substance, acamprosate calcium. A second deficiency letter containing two items was communicated to the applicant on April 20th, 2004 following CMC review # 2. DMF [ ] was reviewed and found adequate to support NDA 21-431 for acamprosate calcium as the active drug substance (see DMF [ ] CMC review dated May 20th, 2004, D. Lewis, Ph.D., reviewer). *This review (CMC # 3) addresses the applicant's responses to the two CMC deficiencies from the April 20th, 2004 letter.* The applicant responded *via* amendment on May 3rd, 2004. A further request was made *via* telephone on May 17th, 2004, to which the applicant responded with an amendment on May 19th, 2004. While the cGMP status was found acceptable for the 1st review cycle, the manufacturing, testing, and packaging facilities were re-submitted to the Office of Compliance (OC) for this resubmission due to the time period between the last inspection and the resubmission. The cGMP status for this NDA is pending completion of inspections and DO/OC evaluation of that status.

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

The drug product is manufactured as a 333-mg enteric-coated solid oral tablet; which is intended for use in maintaining abstinence from alcohol consumption (in recovering alcoholics). The drug product is packaged in plastic HDPE bottles, and in unit-dose blister packs. The drug product consists of a tablet core containing acamprosate calcium, crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, and magnesium stearate and an enteric coat consisting mainly of *Eudragit L30D* (a compendial [USP] preparation of methacrylic acid and acrylic acid ethyl ester). The active ingredient makes up about — % of the tablet core and — % of the total coated tablet. The enteric coating controls the dissolution of the drug product, with essentially no dissolution in acid media (stomach contents) and practically complete dissolution in buffered (neutral) media (intestinal contents). Some of the clinical trials of acamprosate calcium were carried out using a drug product of different formulation (different enteric coating), but the currently marketed European product utilizes the same formulation as proposed in this NDA. The proposed proprietary name CAMPRAL is the name under which the drug product has been marketed in Europe, and has been found acceptable by ODS (Office of Drug Safety).

The drug substance, *acamprosate calcium* is a 2:1 calcium salt of *N*-acetyl homotaurinic acid, and is manufactured by Lipha in two facilities in France (Calais and Meyzieu). The proposed nomenclature for the drug substance *acamprosate calcium* was adopted by USAN in 2003. CMC information regarding acamprosate calcium is provided in DMF [ ] which was reviewed and found adequate to support this NDA for acamprosate calcium as the drug substance for CAMPRAL (the 2nd CMC review of DMF [ ] addressed the DMF holder's responses to the deficiencies, which were communicated by the Agency in May and June, 2002). Acamprosate calcium is [ ] Particle size is not a critical physico-chemical property, since the substance is highly soluble in most aqueous media [ ] The proposed retest date (shelf life) for acamprosate calcium [ ] which is supported by [ ] of long-term ICH stability data; the substance appears to be highly stable when stored at 25°C and 60% RH, with no detectable impurities and/or degradants [ ] of storage. Only one degradant was produced [ ] impurities were not detected (below Limit of Detection) for over 20 batches.

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

CAMPRAL® (acamprosate calcium) tablets are intended for use in maintaining abstinence from alcohol in recovering (or currently treated) alcoholics. The proposed dose is 2 grams per day (actually, 1998 grams, administered as two 333-mg tablets three times daily). The primary stability lots were packaged in [ ] bottles and in unit-dose blister

packs, and additional stability lots were packaged in [ ] bottles designed to hold 180 and 1080 tablets, respectively. The proposed expiration dating period is 36 months with storage at room temperature. The NDA applicant provided 36 months of acceptable ICH long-term stability data (25°C and 60% RH) accompanied by [ ] of ICH intermediate stability data (30°C and 60% RH) and [ ] of ICH accelerated stability data (40°C and 75% RH) on three full-scale lots ([ ] bottles and blister packs) and 24 months of ICH long-term, [ ] of ICH intermediate, and [ ] of ICH accelerated stability data for product stored in 180-count and 1080-count bottles. In addition, [ ] of stability data was provided for the European product (similar, but different formulation, stored at 20-25°C/30-40% RH, 20-25°C/70-80% RH, 37°C/40% RH, and 45°C/70% RH). The primary stability studies indicate that the drug product is highly stable in the proposed package presentations (essentially no loss of potency, no change in dissolution or disintegration behavior, no generation of degradants, and no change in mean tablet weight). The submitted stability data supports the proposed shelf life of [ ] (full-time data for blister packs and [ ] bottles; [ ] of acceptable stability data for the larger plastic bottles). The partial stability submission for the larger plastic bottles is adequate to support the 36-month expiry in light of the "rock stable" stability profile for the drug product (i.e., practically no degradation, no buildup of impurities, and little variability & change between lots and with time) and in light of the complete stability data for the other package presentations. The recommended storage conditions on the labeling state: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The application may be approved from the standpoint of CMC pending an acceptable cGMP status for all pertinent manufacturing, packaging, and testing facilities. All CMC deficiencies, which were pending following CMC review # 2 were addressed adequately in the amendments dated May 3rd and 19th, 2004. There is a minor CMC-related deficiency in the latest version of the package insert (nomenclature for the drug product), but this seems to be an error of omission, since the correct nomenclature appears elsewhere throughout the labeling. This omission may be cleared up via final labeling request, to be communicated to the applicant prior to the action goal date. The latest revision to the labeling has addressed all other pending CMC-related labeling issues.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: David Lewis, Ph.D.
ChemistryTeamLeaderName/Date: Ravi Harapanhalli, Ph.D.
ProjectManagerName/Date: Lisa Basham-Cruz

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 12

page(s) of trade secret and/or confidential commercial information

(b4)

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

/s/

David Lewis
6/3/04 02:37:54 PM
CHEMIST
May be approved pending an acceptable cGMP status.
Changes to table of contents, Status (p. 6-7), recommendation (p. 8), endorsement block (p. 11), stability protocol (P.8.2, p. 18), and MV package (p. 19).

Ravi Harapanhalli
6/4/04 11:29:15 AM
CHEMIST
AP pending recommendation from the Office of Compliance

4/20/04

CHEMISTRY REVIEW

NDA/ANDA 21-431

CAMPRAL (acamprosate calcium) Tablets

Lipha Pharmaceuticals, Inc.

David B. Lewis, Ph.D.

Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-431

2. REVIEW #: 2

3. REVIEW DATE: April 19th, 2004

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
ORIGINAL NDA	21/12/01
NDA 21-431 CMC REVIEW # 1	07/06/02
NDA 21-431 NA Letter	27/06/02

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
AMENDMENT	23/10/03
AMENDMENT	19/12/03

7. NAME & ADDRESS OF APPLICANT:

Name:	Lipha Pharmaceuticals, Inc.
Address:	1114 Avenue of the Americas, NY, NY 10036
Representative:	Anita Goodman, M.D.
Telephone:	(212) 398-4602 X 16

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CAMPRAL
b) Non-Proprietary Name (USAN): acamprosate calcium (INN and BAN, pending USAN)
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P (the original NDA was priority status for the 1st review cycle)

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

10. PHARMACOL. CATEGORY: abstinence from alcohol consumption

11. DOSAGE FORM: Tablet, delayed release

12. STRENGTH/POTENCY: 333 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

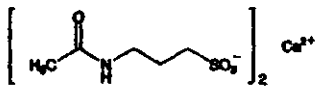
14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: The nomenclature for the drug substance is as follows:

- INN/USAN Name: Acamprosate calcium (INN and BAN, pending USAN adoption)
- Inverted IUPAC Name: 3-Propoanesulfonic acid, 3-(acetylamino), calcium salt
- Other chemical names: 3-Acetamido-propanesulfonic acid, calcium acetylaminopropane sulfonate, and calcium acetylhomotaurine
- CAS Registry Number: [77337-76-9] (for the free acid)
- Structural Formula: $C_{10}H_{20}N_2O_8S_2Ca$ (400.48 g/mol, calcium salt); $C_5H_{11}NO_4S$ (181.21 g/mol, free acid).
- Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	LIPHA	Calcium acamprosate	1	Adequate	30/03/04	
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		
	III			7	N/A		

[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)

The Type III packaging DMF's, which were referenced in the application, were not reviewed due to the current ONDC policy regarding container closure components for solid oral dosage forms. All of the container closure components (and the raw materials from which they were fabricated) meet the current 21 CFR requirements for food storage safety (*information contained within the referenced DMF's*).

B. Other Documents: None

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A*		
EES	Pending**		
Pharm/Tox	Not approvable***	10/06/02	K. Haberny
Biopharm	Adequate (approval)	07/06/02	D. Lee
LNC	N/A		
Methods Validation	Pending		
ODS_1	Adequate	12/06/02	N. Roselle, Pharm.D.
ODS_2 ****	Adequate	15/03/04	C. Hoppes, R. Ph., M.P.H.
EA	Adequate	07/06/02	D. Lewis, Ph.D.
Microbiology	N/A		

* The stability data submitted in support of this NDA was not submitted to Biometrics for statistical analysis, since all of the quantitative attributes were essentially flatline (*e.g.*, minimal degradation and loss of potency).

** The cGMP status for NDA 21-431 is pending completion of one inspection of a testing facility.

*** A second pharmacology & toxicology review is being conducted at this time, but there are no CMC-related issues (*e.g.*, the P. Tox review concerns toxicity and safety of the pure drug substance).

**** A second ODS (DMETS) review concluded that the proprietary name, CAMPRAL remained adequate for the drug product (in the light of the emergence of new proprietary and established names on the U.S. market).

The Chemistry Review for NDA 21-431

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable pending an adequate response to the CMC deficiency letter (2 items), the submission of adequate labeling for the drug product, and a satisfactory cGMP status from the Office of Compliance.

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

N/A

I. Summary of Chemistry Assessments

NDA 21-431 provides CMC information for CAMPRAL™ (acamprosate calcium) tablets. Acamprosate calcium is a new molecular entity (NME) in the U.S., but has been marketed in Europe for more than 10 years as a pharmaceutical agent for the maintenance of sobriety in recovering alcoholics. NDA 21-431 was submitted on December 21st, 2001, and amended on January 30th, March 13th, April 11th, April 19th, April 24th, and May 22nd, 2002. The 1st review cycle resulted in a NOT APPROVABLE (NA) action, which included four CMC-related deficiencies; these deficiencies included the notification that DMF [ ] was not adequate to support this NDA for the drug substance, acamprosate calcium. A deficiency letter was also submitted to the holder of DMF [ ] This review (CMC Review # 2) addresses the NDA applicant's responses to the CMC deficiencies along with reference to the responses submitted by the DMF[ ] holder regarding the CMC information for the drug substance, acamprosate calcium. The NDA applicant and the DMF holder are the same company. While the cGMP status was found acceptable for the 1st review cycle, the manufacturing, testing, and packaging facilities were re-submitted to the Office of Compliance (OC) for this resubmission due to the time period between the last inspection and the resubmission. The cGMP status for this NDA is pending completion of inspections and DO/OC evaluation of that status.

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

The drug product is manufactured as a 333-mg enteric-coated solid oral tablet; which is intended for use in maintaining abstinence from alcohol consumption (in recovering alcoholics). The drug product is packaged in plastic HDPE bottles, and in unit-dose blister packs. The drug product consists of a tablet core containing acamprosate calcium, crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, and magnesium stearate and an enteric coat consisting mainly of

Eudragit L30D (a compendial [USP] preparation of methacrylic acid and acrylic acid ethyl ester). The active ingredient makes up about —% of the tablet core and —% of the total coated tablet. The enteric coating controls the dissolution of the drug product, with essentially no dissolution in acid media (stomach contents) and practically complete dissolution in buffered (neutral) media (intestinal contents). Some of the clinical trials of acamprosate calcium were carried out using a drug product of different formulation (different enteric coating), but the currently marketed European product utilizes the same formulation as proposed in this NDA. The proposed proprietary name CAMPRAL is the name under which the drug product has been marketed in Europe, and has been found acceptable by ODS (Office of Drug Safety).

The drug substance, *acamprosate calcium* is a 2:1 calcium salt of *N*-acetyl homotaurinic acid, and is manufactured by Lipha in two facilities in France (Calais and Meyzieu). The proposed nomenclature for the drug substance *acamprosate calcium* was submitted to the USAN committee for approval; the ONDC staff colocated with HFD-170 found the name acceptable, but final USAN approval is pending (acamprosate calcium is a INN and BAN). CMC information regarding acamprosate calcium is provided in DMF [ ] which was reviewed and found adequate to support this NDA for acamprosate calcium as the drug substance for CAMPRAL (the 2nd CMC review of DMF [ ] addressed the DMF holder's responses to the deficiencies, which were communicated by the Agency in May and June, 2002). Acamprosate calcium is : [ ] Particle size is not a critical physico-chemical property, since the substance is highly soluble in most aqueous media [ ] The proposed retest date (shelf life) for acamprosate calcium [ ] which is supported by [ ] of long-term ICH stability data; the substance appears to be highly stable when stored at 25°C and 60% RH, with no detectable impurities and/or degradants after [ ] of storage. Only one degradant was produced [ ] impurities were not detected (below Limit of Detection) for over 20 batches.

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

Acamprosate calcium is intended for use in maintaining abstinence from alcohol in recovering (or currently treated) alcoholics. The proposed dose is 2 grams per day (administered as two 333-mg tablets three times daily). The primary stability lots were packaged in [ ] bottles and in unit-dose blister packs, and additional stability lots were packaged in [ ] bottles designed to hold 180 and 1080 tablets, respectively. The proposed expiration dating period is 36 months with storage at room temperature. The NDA applicant provided [ ] of acceptable ICH long-term stability data (25°C and 60% RH) accompanied by [ ] of ICH intermediate stability data (30°C and 60% RH) and of ICH accelerated stability data (40°C and 75% RH) on three full-scale lots ([ ] bottles and blister packs) and [ ] long-term and accelerated ICH stability data for product stored in 180-count and 1080-count bottles. In addition, [ ] of stability data was provided for the European product

(similar, but different formulation, stored at 20-25°C/30-40% RH, 20-25°C/70-80% RH, 37°C/40% RH, and 45°C/70% RH). The primary stability studies indicate that the drug product is highly stable in the proposed package presentations (essentially no loss of potency, no change in dissolution or disintegration behavior, no generation of degradants, and no change in mean tablet weight). The maximum expiry which can be assigned on the basis of this data is [ ] based on the quality of the primary stability data (long-term and accelerated storage conditions). The recommended storage conditions on the labeling state: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The application may be considered approvable pending adequate responses to the following deficiencies:

- The proposed acceptance criterion for acamprosate calcium dissolution [ ] medium is not adequate, and needs to be revised.
- Updated ICH stability data for the NDA exhibit batches to support the proposed 36-month expiry.
- The labeling for the drug product needs to be revised (see draft letter of deficiencies attached to the end of this review).

All other CMC information regarding the drug substance and drug product are acceptable, following the review of the DMF holder/NDA applicant's responses to the deficiencies contained in the NA letter (June 27th, 2002), and the DMF deficiency letter (May 13th, 2002).

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

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

C. CC Block

Redacted 15

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

David Lewis
4/19/04 09:49:39 AM
CHEMIST

The application is approvable from the standpoint of CMC pending adequate responses to the deficiency letter, an acceptable GMP status, and submission of acceptable labeling for the drug product.

[illegible] made the other suggested editorial, style, and content changes.

Ravi Harapanhalli
4/20/04 04:19:46 PM
CHEMIST

Newly designed labels are being submitted by Lipha and they have to be reviewed separately.

6/11/02

CHEMISTRY REVIEW

NDA 21-431

(acamprosate calcium)

Lipha Pharmaceuticals, Inc.

David B. Lewis, Ph.D.

Division of Anesthetic and Critical Care Drug Products
(HFD-170)

Table of Contents

Chemistry Review Data Sheet

1. NDA **21-431**

2. REVIEW #: 1

3. REVIEW DATE: 07/06/02

4. REVIEWER: David B. Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 51,809	01/11/96

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ORIGINAL NDA	21/12/01
AMENDMENT	30/01/02
AMENDMENT	13/03/02
AMENDMENT	11/04/02
AMENDMENT	19/04/02
AMENDMENT	24/04/02
AMENDMENT	22/05/02

- The facsimile transmission of January 30th, 2001 provided the address of a new testing facility for the drug product.
- The amendment dated March 13th, 2002 contained the entire (reprinted) NDA with several revisions: additional site addresses, new pagination, and a revised Table of Contents.

- The amendment dated April 11th, 2002 contained a correction regarding the packaging facility for the drug product.
- The amendment dated April 19th, 2002 contained stability data for the 180-count and 1080-count bottles and supportive stability data for the European product ([ ] studies).
- The amendment dated April 24th, 2002 provided draft labeling.
- The Amendment dated May 22nd, 2002 provided Letters of authorization to refer to DMF's [ ] and [ ] (Lipha).

7. NAME & ADDRESS OF APPLICANT:

Name:	Lipha Pharmaceuticals, Inc.
Address:	10 Derby Square, Salem, Massachusetts 01970
Representative:	Anita Goodman
Telephone:	(978) 542-1904 (Phone) (978) 542-1950 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CAMPRAL (pending ODS consult review)
b) Non-Proprietary Name (USAN): acamprosate calcium (USAN approval pending)
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: P

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

10. PHARMACOL. CATEGORY: abstinence from alcohol consumption

11. DOSAGE FORM: Tablet, delayed release

12. STRENGTH/POTENCY: 333 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

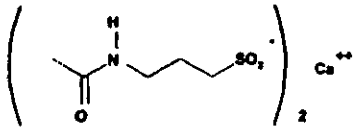
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

- Proposed USAN name: acamprosate calcium (USAN decision is pending)
- INN name: acamprosate calcium
- Inverted IUPAC name: 3-Propanesulfonic acid, 3-(acetylamino), calcium salt
- Alternate chemical names: 3-acetamido-propane sulfonic acid, calcium acetylaminopropane sulfonate, and calcium acetylhomotaurinate.
- CAS Number: [77337-76-9]; for the free sulfonic acid
- Molecular formula: $C_{10}H_{20}N_2O_8S_2Ca$ (400.48 g/mol)
- Chemical structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Lipha	Calcium acamprosate	1	Inadequate	08/05/02	Deficiency letter sent out.
	II	Lipha		7	Pending		Division was notified of this DMF too late.
	III			5, 7	Pending		No LOA *

[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)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Pending as of 07/06/02		
LNC	N/A		
Methods Validation	To be submitted after review		
ODS (formerly OPDRA)	Pending as of 07/06/02		
EA	Waiver granted per 21 CFR 25.31(b)	10/05/02	D. Lewis, Ph.D.
Microbiology	N/A		

The Chemistry Review for NDA 21-431

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable (AE) pending adequate responses to the items outlined in the Draft Letter of Deficiencies. *However, the cGMP inspection of the manufacturing facilities (drug substance and drug product) is ongoing as of this date (June 7th, 2002).*

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

None

II. Summary of Chemistry Assessments

NDA 21-431 provides chemistry, manufacturing and controls (CMC) information regarding CAMPRAL (calcium acamprosate) tablets. Calcium acamprosate is a new molecular entity (NME) in the United States, but has been marketed in Europe for the maintenance of sobriety in recovering alcoholics for more than 10 years.

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

The drug product is manufactured as a 333-mg enteric-coated solid oral tablet; which is intended for use in maintaining abstinence from alcohol consumption (in recovering alcoholics). The drug product is packaged in plastic HDPE bottles, and in unit-dose blister packs. *CMC information regarding the packaging components is incomplete as of this date.* The drug product consists of a tablet core containing acamprosate calcium, crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, and magnesium stearate and an enteric coat consisting mainly of *Eudragit L30D* (a compendial [USP] preparation of methacrylic acid and acrylic acid ethyl ester). The active ingredient makes up about [redacted] of the tablet core and [redacted] of the total coated tablet. The enteric coating controls the dissolution of the drug product, with essentially no dissolution in acid media (stomach contents) and practically complete dissolution in buffered (neutral) media (intestinal contents). Some of the clinical trials of acamprosate calcium were carried out using a drug product of different formulation (different enteric coating), but the currently marketed European product utilizes the same formulation as proposed in this NDA. The proposed proprietary name CAMPRAL is the name under which the drug product has been marketed in Europe.

The drug substance, *acamprosate calcium* is a 2:1 calcium salt of *N*-acetyl homotaurinic acid, and is manufactured by Lipha in two facilities in France (Calais and Meyzieu). The proposed nomenclature for the drug substance *acamprosate calcium* was submitted to the USAN committee for approval; the ONDC staff colocated with HFD-170 found the name acceptable, but final USAN approval is pending. CMC information regarding acamprosate calcium is provided in DMF [ ], which has been reviewed in support of this NDA (outcome pending response to a deficiency letter). [ ] Particle size is not a critical physico-chemical property, since the substance is highly soluble in most aqueous media [ ]. The proposed retest date (shelf life) for acamprosate calcium is [ ] which is supported by [ ] of long-term ICH stability data; the substance appears to be highly stable when stored at 25°C and 60% RH, with no detectable impurities and/or degradants after [ ] of storage. Only one degradant was produced [ ] impurities were not detected (below Limit of Detection) for over 20 batches.

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

Acamprosate calcium is intended for use in maintaining abstinence from alcohol in recovering (or currently treated) alcoholics. The proposed dose is 2 grams per day (administered as two 333-mg tablets three times daily). The primary stability lots were packaged in [ ] bottles and in unit-dose blister packs, and additional stability lots were packaged in [ ] bottles designed to hold 180 and 1080 tablets, respectively. The proposed expiration dating period is 36 months with storage at room temperature; this tentative expiry is supported by [ ] of acceptable ICH long-term stability data (25°C and 60% RH) accompanied by [ ] of ICH intermediate stability data (30°C and 60% RH) and [ ] of ICH accelerated stability data (40°C and 75% RH) on three full-scale lots ([ ] bottles and blister packs) and [ ] long-term and accelerated ICH stability data for product stored in 180-count and 1080-coutn bottles. In addition, [ ] of stability data was provided for the European product (similar, but different formulation, stored at 20-25°C/30-40% RH, 20-25°C/70-80% RH, 37°C/40% RH, and 45°C/70% RH). The primary stability studies indicate that the drug product is highly stable in the proposed package presentations (essentially no loss of potency, no change in dissolution or disintegration behavior, no generation of degradants, and no change in mean tablet weight). The supportive stability studies (European drug product, cited above) contain some inconsistencies, which need to be resolved. The maximum expiry which can be assigned at this date (June 7th, 2002) is [ ] months, based on the quality of the primary stability data (long-term and accelerated storage conditions). The recommended storage conditions on the labeling state: Store at 25°C (77°F); excursions permitted between 15-30°C (59-86°F).

C. Basis for Approvability or Not-Approval Recommendation

The NDA is approvable (AE), because the deficiencies are relatively minor, and do not pose a significant risk, regarding safety of the drug product.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block: **N/A (signed off in DFS)**

C. CC Block: **N/A (appropriate CC list included in DFS signoff)**

Redacted 56

page(s) of trade secret and/or confidential commercial information (b4)

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

/s/

David Lewis
6/11/02 10:15:40 AM
CHEMIST
Approvable pending adequate response to deficiency letter.
I removed the word "facsimile". The amendments dated January
30th and April 11th are still coming up
in DFS as "C", and the amendment dated
May 22nd is now coming up as "BC".

Dale Koble
6/11/02 10:40:52 AM
CHEMIST

Statistics Review: Dissolution and Stability

Not Applicable

4.5 ENVIRONMENTAL ASSESSMENT

In accordance with FDA's "Guidance for Industry: Environmental Assessment of Human Drug and Biologic Applications", dated July 1998, and under 21 CFR 25.31(b), for NDA 21-431, Lipha Pharmaceuticals, Inc. hereby requests a categorical exclusion from the filing of an environmental assessment. The request for exclusion is based on the estimation of the concentration of acamprosate at the point of entry into the aquatic environment will be below 1 part per billion, and based on Lipha Pharmaceuticals, Inc. knowledge, no extraordinary circumstances exist.

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

A ation:	NDA 21431/000	Action Goal:	
Stamp:	27-DEC-2001	District Goal:	05-JUN-2004
Regulatory Due:	04-AUG-2004	Brand Name:	ACAMPROSATE(CALCIUM
Applicant:	LIPHA	Estab. Name:	ACETYLHOMOTAURINATE
	10 DERBY SQUARE	Generic Name:	CALCIUM
	SALEM, MA 01970		ACETYLHOMOTAURINATE TABS
Priority:	1P		333MG
Org Code:	170	Dosage Form:	(DELAYED RELEASE TABLET
		Strength:	333-MG

Application Comment: ACAMPROSATE IS ENTERIC COATED TABLET FOR THE DELAYED RELEASE. APPLICANT STATED IN A TELEPHONE CONVERSATION DATED 01/28/02 THAT THERE ARE NO NO OTHER FACILITIES SUCH AS CONTRACT LABS IN THE TESTING OF THE DS AND DP. THE NDA WILL RECEIVE A 1P STATUS AND THEREFORE THE FACILITES WILL HAVE TO BE INSPECTED EXPEDITIOUSLY. (on 28-JAN-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)
ACCORDING TO THE AMENDMENT DATED APRIL 11, 2002, THE FOREST FACILITY LOCATED IN COMMACK, NY (CFN 2436283) IS NOT USED FOR RELEASE TESTING OF THE FINISHED DRUG PRODUCT. THE COMMACK SITE IS USED ONLY FOR PACKAGING. (on 15-APR-2002 by D. LEWIS (HFD-510) 301-827-6420)
ANOTHER FACILITY IS BEING SUBMITTED TO THE OFFICE OF COMPLIANCE (FOREST LABORATORIES, COMMACK, NY). THIS FACILITY IS USED FOR PACKAGING AND RELEASE TESTING OF THE DRUG PRODUCT, AND WAS SUBMITTED TO THE AGENCY BY THE FIRM 3 MONTHS POST-SUBMISSION (MARCH 5TH, 2002). (on 15-MAR-2002 by D. LEWIS (HFD-510) 301-827-6420)
THE 1ST REVIEW CYCLE FOR NDA 21-431 RESULTED IN A "NOT APPROVABLE" ACTION. THE EES REQUEST IS BEING RE-SUBMITTED SINCE THE LAST ACTUAL INSPECTION WAS MORE THAN 2 YEARS AGO. ACCORDING TO THE NDA APPLICANT, THERE HAVE BEEN NO CHANGES TO THE MANUFACTURING OR TESTING PROCESSES FOR THE DRUG SUBSTANCE OR THE DRUG PRODUCT WITH THE EXCEPTION THAT THE MEYZIEU FACILITY IS NO LONGER USED TO
t 1 (on 04-MAR-2004 by D. LEWIS (HFD-510) 301-827-6420)
THE APPLICATION WAS FILED AS A PRIORITY REVIEW. THE USER FEE DATE FOR NDA 21-431 IS JUNE 27TH, 2002. THE ACTION GOAL DATE NEEDS TO

BE REVISED, IN ORDER THE GET THE INSPECTIONS DONE IN TIME. (on 11-FEB-2002 by D. LEWIS (HFD-510) 301-827-6420)

FDA Contacts:	L. BASHAM CRUZ	(HFD-170)	301-827-7410	, Project Manager
	D. LEWIS	(HFD-510)	301-827-6420	, Review Chemist
	R. HARAPANHALLI	(HFD-170)	301-827-7410	, Team Leader

Overall Recommendation: ACCEPTABLE on 24-JUN-2004by S. ADAMS (HFD-322)301-827-9051

ACCEPTABLE on 16-AUG-2002by S. ADAMS (HFD-322)301-827-9051

ACCEPTABLE on 25-JUN-2002by J. D AMBROGIO(HFD-322)301-827-9049

Establishment: CFN [ ] FEI

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THE FOREST, FACILITY AT NY IS USED FOR RELEASE TESTING OF THE DRUG PRODUCT AND FOR ACCEPTANCE TESTING OF THE PACKAING COMPONENTS. (on 15-APR-2002 by D. LEWIS (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-APR-2002				LEWISD
OC RECOMMENDATION	15-APR-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	04-MAR-2004				LEWISD
OC RECOMMENDATION	04-MAR-2004			ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN FEI

[redacted]

DMF No: AADA:

Responsibilities:

Profile: TCT OAI Status: NONE

Estab. Comment: THE FOREST, FACILITY IN COMMACK, NY IS NOT USED FOR RELEASE TESTING OF THE FINISHED DRUG PRODUCT (SEE AMENDMENT DATED APRIL 11TH, 2002 FROM LIPHA). THIS FACILITY IS USED ONLY FOR PACKAGING OF THE DRUG

PRODUCT. (on 15-APR-2002 by D. LEWIS (HFD-510) 301-827-6420)

THE FORREST FACILITY IS USED FOR DRUG PRODUCT PACKAGING AND RELEASE TESTING OF THE DRUG PRODUCT. THIS FACILITY WAS COMMUNICATED TO THE AGENCY ON MARCH 5TH, 2002. (on 15-MAR-2002 by D. LEWIS (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	15-MAR-2002				LEWISD
SUBMITTED TO DO	15-MAR-2002	GMP			FERGUSONS
DO RECOMMENDATION	04-APR-2002			WITHHOLD	LFARINA
				DRUG NOT MADE HERE	

NO TESTING IS CONDUCTED AT THE FIRM'S COMMACK,NY SITE. RECENT CONTACT WITH FOREST MANAGEMENT DETERMINED THAT THE APPLICATION FOR THIS PRODUCT ERRONEOUSLY STATES THAT TESING IS PERFORMED IN COMMACK. QA DIRECTOR OF FOREST, STATED THAT THE APPLICATION WILL BE AMMENDED TO CORRECT THIS ERROR.

OC RECOMMENDATION	08-APR-2002			WITHHOLD	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

FACILITY NOT DOING FUNCTION

NO TESTING IS CONDUCTED AT THE FIRM'S COMMACK,NY SITE. RECENT CONTACT WITH FOREST MANAGEMENT DETERMINED THAT THE APPLICATION FOR THIS PRODUCT ERRONEOUSLY STATES THAT TESING IS PERFORMED IN COMMACK. QA DIRECTOR OF FOREST, STATED THAT THE APPLICATION WILL BE AMMENDED TO CORRECT THIS ERROR.

SUBMITTED TO OC	15-APR-2002			LEWISD
SUBMITTED TO DO	15-APR-2002	GMP		DAMBROGIOJ
DO RECOMMENDATION	29-APR-2002		ACCEPTABLE	LFARINA
			BASED ON FILE REVIEW	
OC RECOMMENDATION	29-APR-2002		ACCEPTABLE	DAMBROGIOJ
			DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-MAR-2004			LEWISD
ITED TO DO	04-MAR-2004	GMP		FERGUSONS
ASSIGNED INSPECTION T	29-MAR-2004	GMP		LFARINA
INSPECTION PERFORMED	29-MAR-2004			FACTS_EES

AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, DUE TO FIRM BEING OUT OF BUSINESS OR MERGED

DO RECOMMENDATION	17-MAY-2004	ACCEPTABLE	LFARINA
		INSPECTION	

PRE-APPROVAL INSPECTION OF THIS DRUG REPACKING FACILITY CONDUCTED 5/10-12/04 DISCLOSED NO SIGNIFICANT DEFICIENCIES.

OC RECOMMENDATION	17-MAY-2004	ACCEPTABLE	FERGUSONS
		DISTRICT RECOMMENDATION	

Establishment: CFN FEI

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THIS FACILITY IS A CONTRACT WHICH WILL
THIS FACILITY WAS ADDED TO THE NDA
VIA FAX COMMUNICATION DATED JANUARY 30, 2002. (on 05-FEB-2002 by D.
LEWIS (HFD-510) 301-827-6420)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-FEB-2002				LEWISD
OC RECOMMENDATION	05-FEB-2002			ACCEPTABLE BASED ON PROFILE	GARCIAM
SUBMITTED TO OC	04-MAR-2004				LEWISD
SUBMITTED TO DO	04-MAR-2004	GMP			FERGUSONS
ASSIGNED INSPECTION T	08-MAR-2004	GMP			ADAMSS
INSPECTION PERFORMED	14-MAY-2004		14-MAY-2004		ADAMSS
INSPECTION SCHEDULED	21-MAY-2004		14-MAY-2004		ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DO RECOMMENDATION	24-JUN-2004	ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	24-JUN-2004	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9612653 FEI 3002807474
MERCK SANTE S.A.S
5 - 7 RUE CLEMENT ADER
CALAIS, , FR

DMF No: AADA:

R sibilities: INTERMEDIATE MANUFACTURER

Profile: CRU OAI Status: NONE

Estab. Comment: THIS IS AN ALTERNATE SITE FOR THE PRODUCTION THE FINAL INTERMEDIATE FOR THE SYNTHESIS OF THE DRUG SUBSTANCE. APPLICANT STATES THAT THERE IS A SEPARATE DMF FOR THIS FACILITY BUT THEY DO NOT HAVE THE DMF NUMBER YET. (on 28-JAN-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-2002				HARAPANHALL
SUBMITTED TO DO	29-JAN-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	31-JAN-2002	PS			GARCIAM
INSPECTION SCHEDULED	01-MAY-2002		05-JUN-2002		IRIVERA
INSPECTION SCHEDULED	07-MAY-2002		05-JUN-2002		GARCIAM
I CTION PERFORMED	05-JUN-2002		05-JUN-2002		IRIVERA
. CTION PERFORMED	05-JUN-2002		05-JUN-2002		GARCIAM

This inspection revealed that the firm did not always conduct adequate investigations

[redacted] observed in finished API product, and that

were not always met/documented

There were no refusals. No samples were collected. Appendix B of CP 7356.002F was provided to the firm to request information/samples to be provided to the Agency.

Correspondence should be sent to:

Site Director

Merck Lipha, S.A.S.

Centre de Production de Calais

5,7 rue Clement-Ader

France 62100 Calais

DO RECOMMENDATION	25-JUN-2002	ACCEPTABLE	DAMBROGIOJ
		INSPECTION	

ACCEPTABLE RECOMMENDATION MADE BASED ON REVIEW OF FD-483

OC RECOMMENDATION	25-JUN-2002	ACCEPTABLE	DAMBROGIOJ

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

		DISTRICT RECOMMENDATION	
DO RECOMMENDATION	16-AUG-2002	ACCEPTABLE	ADAMSS
		INSPECTION	
OC RECOMMENDATION	16-AUG-2002	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-MAR-2004		LEWISD
OC RECOMMENDATION	04-MAR-2004	ACCEPTABLE	ADAMSS
		BASED ON PROFILE	

Establishment: CFN 9615692 FEI 3002807502
MERCK SANTE S.A.S
MEYZIEU, , FR

DMF No: [redacted] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: CSN OAI Status: NONE

Estab. Comment: THE MEYZIEU FACILITY IS NO LONGER UTILIZED FOR THE MANUFACTURE OF THE DRUG SUBSTANCE INTERMEDIATE, (CHANGE NOTED FOR THE SECOND REVIEW CYCLE). HOWEVER, THE MEYZIEU FACILITY STILL MANUFACTURES THE DRUG SUBSTANCE, (on 04-MAR-2004 by D. LEWIS (HFD-510) 301-827-6420)
THIS FACILITY MANUFACTURES THE DS, THE FINAL INTERMEDIATE, RELEASE-TESTS, PACKAGES (on 28-JAN-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

M stone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-JAN-2002				HARAPANHALL
SUBMITTED TO DO	29-JAN-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	31-JAN-2002	PS			GARCIAM

INSPECTION SCHEDULED	01-MAY-2002	11-JUN-2002	IRIVERA
INSPECTION SCHEDULED	07-MAY-2002	11-JUN-2002	GARCIAM
INSPECTION PERFORMED	11-JUN-2002	11-JUN-2002	IRIVERA

IS ACCEPTABLE.

INSPECTION PERFORMED	11-JUN-2002	11-JUN-2002	GARCIAM

The previous inspection was conducted in April 1998 classified VAI with an FDA 483 issued for failure to validate the [ ] [ ] and to have written procedures to perform this operation; inadequate investigation into the causes of the possible contamination of two lots [ ] the sampling plan for the finished drug bulk is different from that described in the DMF; and, failure to include samples of labels used as part of the bulk drug history records.

This inspection revealed that the firm has not effectively demonstrated [ ] during the performance qualification [ ]

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

samples were composited for analyses.

DO RECOMMENDATION	25-JUN-2002	ACCEPTABLE INSPECTION	DAMBROGIOJ
ACCEPTABLE RECOMMENDATION MADE BASED ON REVIEW OF FD-483			
OC RECOMMENDATION	25-JUN-2002	ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ
DO RECOMMENDATION	16-AUG-2002	ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	16-AUG-2002	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
ITTED TO OC	04-MAR-2004		LEWISD
OC RECOMMENDATION	04-MAR-2004	ACCEPTABLE BASED ON PROFILE	FERGUSONS

Establishment: CFN FEI

MERCK SANTE S.A.S

115 AVENUE LACASSAGNE

LYON, , FR 69003

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: TCT OAI Status: NONE

E. Comment: THIS SITE MANUFACTURES, PACKAGES, RELEASE-TESTS AND STABILITY-TESTS THE DRUG PRODUCT (on 28-JAN-2002 by R. HARAPANHALLI (HFD-170) 301-827-7410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator

SUBMITTED TO OC	28-JAN-2002				HARAPANHALL
SUBMITTED TO DO	29-JAN-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	30-JAN-2002	PS			GARCIAM
INSPECTION SCHEDULED	01-MAY-2002		18-JUN-2002		IRIVERA
CTION PERFORMED	18-JUN-2002		18-JUN-2002		IRIVERA
DO RECOMMENDATION	25-JUN-2002			ACCEPTABLE	DAMBROGIOJ
				INSPECTION	

ACCEPTABLE RECOMMENDATION MADE BASED ON REVIEW OF FD-483

FEI 3008672212

OC RECOMMENDATION	25-JUN-2002			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	04-MAR-2004				LEWISD
SUBMITTED TO DO	04-MAR-2004	PS			FERGUSONS
DO RECOMMENDATION	08-MAR-2004			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	

6/2002 AC EI

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION	08-MAR-2004	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

Methods Validation:

Not Completed