# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-375**

## CHEMISTRY REVIEW(S)

# NDA 21-375

## Alavert™ Tablets

## Wyeth Consumer Healthcare

**Chong Ho Kim, Ph.D.**

**Division of Pulmonary and Allergy Drug Products**

# Chemistry Review Data Sheet

1. NDA #: 21-375

2. REVIEW #: 3

3. REVIEW DATE: 06-November-2002

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 23-AUG-01 |
| Amendment[BL] | 21-FEB-02 |
| Amendment[BC] | 08-MAR-02 |
| Amendment[BC] | 13-MAY-02 |
| Amendment[BL] | 24-MAY-02 |
| Amendment[BC] | 31-MAY-02 |
| Amendment[AZ] | 19-JUL-02 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment[AZ] | 14-OCT-02 |
| Amendment[BZ] | 31-OCT-02 |
| Amendment[BC] | 06-NOV-02 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Whitehall-Robins Healthcare |
| Address: | 5 Giralda Farms<br>Madison, NJ 07940 |
| Representative: | Ms. Sharon C. Heddish |
| Telephone: | 973-660-5753; Fax: 973-660-7187 |

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Alavert™ Tablets (OPDRA consult pending)

b) Nonproprietary Name (USAN): Loratadine 10 mg Orally Disintegrating Tablet

c) Code Name/#:

d) Chem. Type/Submission Priority:

- Chem. Type: 3
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Orally Disintegrating Tablet

12. STRENGTH/POTENCY: 10 mg

13. ROUTE OF ADMINISTRATION: Oral

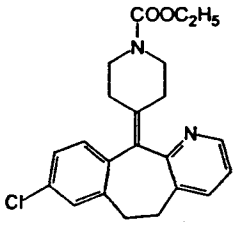
14. Rx/OTC DISPENSED: ___Rx _X_ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note20]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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




Loratadine

Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate

Chemistry Review Data Sheet

Chemical Name: 11-[N-(ethoxycarbonyl)-4-piperidylidene]-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine
1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-ylidene)-ethyl ester

CAS Number: [79794-75-5]

Molecular Formula: $C_{22}H_{23}ClN_2O_2$

Molecular Weight: 382.89

17. RELATED/SUPPORTING DOCUMENTS:

**A. Supporting DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE[1] | STATUS[2] | DATE REVIEW COMPLETED | COMMENTS[3] |
|---|---|---|---|---|---|---|---|
| [redacted] | II | [redacted] | [redacted] | 3 | Adequate@ | 3/28/02 | See below |
| [redacted] | II | [redacted] | [redacted] | 3 | Adequate# | 2/11/02 | See below |
| [redacted] | III | [redacted] | [redacted] | 3 | Adequate* | 2/26/02 | See below |
| [redacted] | III | [redacted] | [redacted] | 3 | Adequate** | 8/24/00 | See below |

[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)
[3] Include reference to location in most recent CMC review

@ Dr. Trimmer reviewed the most recent amendment dated February 22, 2002 with regard to ANDA #75-822 and found it adequate.

# Dr. Klein reviewed the DMF for [redacted] with regard to IND [redacted] and found it adequate.

* Dr. Shaw reviewed the DMF with regard to Prilosec Capsules (NDA 19-810) and found it adequate (review dated 2/26/02).

** Dr. Frankewich reviewed the DMF [redacted] with regard to [redacted] and found it adequate (review dated 8/24/00).

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
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| | | | | | |

**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| ANDA | [redacted] | | |

18. CONSULTS/CMC-RELATED REVIEWS:

| CONSULTS | SUBJECT | DATE FORWARDED | STATUS/ REVIEWER | COMMENTS |
|---|---|---|---|---|
| Biometrics | | | | |
| EES | ds and dp sites | 2/13/02 | acceptable (5/9/02) | |
| Pharm/Tox | | | | |
| Biopharm | dissolution | | Acceptable | applicant's newest proposal met the recommendation. |
| LNC | N/A | | | |
| Methods Validation | | | | * To be requested |
| OPDRA | acceptability of the trade name | | Pending | |
| EA | exclusion requested | | acceptable/5-23-02 | |
| Microbiology | N/A | | | |

***Applicant has provided three copies of method validation package. (Amendment dated November 6, 2002)**

Executive Summary Section

# The Chemistry Review for NDA 21-375

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

This NDA may be approved from a CMC standpoint.

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

None

## II. Summary of Chemistry Assessments

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

1). This application is requesting a switch to OTC status for the allergic rhinitis indication and not the [redacted] indication.

2). Applicant stated that the loratadine orally disintegrating tablet formulation is manufactured and tested as described in ESI Lederle ANDA 75-822, which is under review.

3). Up to 18 months room temperature stability data and 3 months accelerated stability data on two production-scale batches are provided in the original application. However, updated stability data (24 months at room temperature and 6 months at accelerated condition) were provided in the amendment dated March 8, 2002. With this sufficient actual stability data in hand, a biometrics consult on the proposed 24 months expiration dating period was not necessary.

4). The test methods for drug substance and for the drug product are acceptable.

5). The loratadine drug substance is manufactured by [redacted] at their [redacted] facility. The DMF is adequate to support the current NDA.

6). The formulation of loratadine 10 mg orally disintegrating tablet is slightly different from the referenced drug. Most excipients are compendial excipients except the natural and artificial mint flavor [redacted] The drug product will be marketed in blister packaging.

7). All drug product manufacturing, packaging and testing facilities have an acceptable EER status.

Executive Summary Section

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

The drug product is orally disintegrating tablets. It will be used for the treatment of seasonal allergic rhinitis symptoms.

### C. Basis for Approvability or Not-Approval Recommendation

The application may be approved from a CMC standpoint.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

| | |
|---|---|
| ChemistName/Date: | Chong Ho Kim/ 06-NOV-2002 |
| ChemistryTeamLeaderName/Date: | Guirag Poochikian/ |
| ProjectManagerName/Date: | Anthony Zeccola/ |

### C. CC Block

Orig. NDA #21-375
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/AZeccola
R/D Init. by:

Doc: n21-375r3.N06

21 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

/s/

Chong-Ho Kim
11/7/02 03:24:38 PM
CHEMIST

Guiragos Poochikian
11/7/02 04:32:02 PM
CHEMIST

# NDA 21-375

## Alavert™ Tablets

## Wyeth Consumer Healthcare

**Chong Ho Kim, Ph.D.**

**Division of Pulmonary and Allergy Drug Products**

# Chemistry Review Data Sheet

1. NDA #: 21-375

2. REVIEW #: 2

3. REVIEW DATE: 12-SEPTEMBER-2002

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| Original | 23-AUG-01 |
| Amendment[BL] | 21-FEB-02 |
| Amendment[BC] | 08-MAR-02 |
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| Amendment[BL] | 24-MAY-02 |
| Amendment[BC] | 31-MAY-02 |

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| Amendment[AZ] | 19-JUL-02 |

7. NAME & ADDRESS OF APPLICANT:

| | |
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| Name: | Whitehall-Robins Healthcare |
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Chemistry Review Data Sheet

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a) Proprietary Name: Alavert™ Tablets (OPDRA consult pending)

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c) Code Name/#:

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- Chem. Type: 3
- Submission Priority: S

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

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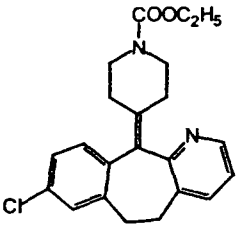


Loratadine

Ethyl 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]-cyclohepta [1,2-b]pyridin-11-ylidene)-1-piperidinecarboxylate

Chemical Name: 11-[N-(ethoxycarbonyl)-4-piperidylidene]-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]-pyridine

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| | II | | | 3 | Adequate@ | 3/28/02 | See below |
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Chemistry Review Data Sheet

** Dr. Frankewich reviewed the DMF ( ) with regard to ( ) and found it adequate (review dated 8/24/00).

**B. Other Supporting Documents:**

| Doc # | OWNER | ITEM REFERENCED | STATUS | DATE REVIEW COMPLETED | COMMENTS |
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**C. Related Documents:**

| DOCUMENT | APPLICATION NUMBER | OWNER | DESCRIPTION/COMMENT |
|---|---|---|---|
| ANDA | ( ) | | |

18. CONSULTS/CMC-RELATED REVIEWS:

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| Pharm/Tox | | | | |
| Biopharm | dissolution | | Acceptable | applicant's newest proposal met the recommendation. |
| LNC | N/A | | | |
| Methods Validation | | | | * |
| OPDRA | acceptability of the trade name | | Pending | |
| EA | exclusion requested | | acceptable/5-23-02 | |
| Microbiology | N/A | | | |

***Applicant should provide three copies of method validation package, once we reach agreement on the specifications.**

Executive Summary Section

# The Chemistry Review for NDA 21-375

## *The Executive Summary*

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None

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4). The test methods for drug substance and for the drug product are acceptable. However, no agreement is reached for specifications. **Applicant should provide new copies of method validation packages, once we reach agreement on the specifications.**

5). The loratadine drug substance is manufactured by ——— at their ——— facility. The DMF is adequate to support the current NDA.

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7). All drug product manufacturing, packaging and testing facilities have an acceptable EER

status.

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

The drug product is orally disintegrating tablets. It will be used for the treatment seasonal allergic rhinitis symptoms.

### C. Basis for Approvability or Not-Approval Recommendation

The application is approvable. However, the pending deficiencies listed at the end of this review should be addressed to gain approval.

## III. Administrative

### A. Reviewer's Signature

### B. Endorsement Block

| | |
|---|---|
| ChemistName/Date: | Chong Ho Kim/ 12-SEP-2002 |
| ChemistryTeamLeaderName/Date: | Guirag Poochikian/ |
| ProjectManagerName/Date: | Anthony Zeccola/ |

### C. CC Block

Orig. NDA #21-375
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/AZeccola
R/D Init. by:

Doc: n21-375r2.913

15 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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

/s/

Chong-Ho Kim
9/16/02 09:09:37 AM
CHEMIST

Guiragos Poochikian
9/16/02 09:21:19 AM
CHEMIST

# NDA 21-375

## Alavert™ Tablets

## White-Robins Healthcare

Chong Ho Kim, Ph.D.
Division of Pulmonary and Allergy Drug Products

# Table of Contents

# Chemistry Review Data Sheet

1. NDA #: 21-375

2. REVIEW #: 1

3. REVIEW DATE: 30-MAY-2002

4. REVIEWER: Chong Ho Kim, Ph.D.

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
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| Original | 23-AUG-01 |
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Chemistry Review Data Sheet

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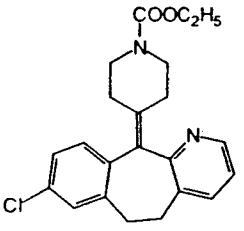


Loratadine

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Chemistry Review Data Sheet

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| Biopharm | dissolution | | acceptable | applicant's newest proposal met the recommendation. |
| LNC | N/A | | | |
| Methods Validation | | | | * |
| OPDRA | acceptability of the trade name | | pending | |
| EA | exclusion requested | | acceptable/ 5-23-02 | |
| Microbiology | N/A | | | |

***Submission of three copies of method validation package was requested (5/28/02).**

Executive Summary Section

# The Chemistry Review for NDA 21-375

## *The Executive Summary*

## I. Recommendations

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Approvable from a CMC standpoint.

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### A. Reviewer's Signature

### B. Endorsement Block

ChemistName/Date: Chong Ho Kim/ 06-JUN-2002
ChemistryTeamLeaderName/Date: Guirag Poochikian/
ProjectManagerName/Date: Anthony Zeccola/

### C. CC Block

Orig. NDA #21-375
HFD-570/Division File
HFD-570/CHKim
HFD-570/GPoochikian
HFD-570/AZeccola
R/D Init. by:

Doc: n21-375r1f.606

37 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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/s/

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Chong-Ho Kim
6/10/02 10:35:21 AM
CHEMIST

Guiragos Poochikian
6/10/02 10:41:35 AM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

| | | | |
|---|---|---|---|
| Application: | NDA 21375/000 | Action Goal: | |
| Stamp: | 04-SEP-2001 | District Goal: | 05-MAY-2002 |
| Regulatory Due: | 04-JUL-2002 | Brand Name: | ALAVERT (LORATADINE HCL) |
| Applicant: | WYETH CONS | Estab. Name: | 10MG TABLETS |
| | 5 GIRALDA FARMS | Generic Name: | LORATADINE HCL |
| | MADISON, NJ 079400871 | | |
| Priority: | 3S | Dosage Form: | (TABLET) |
| Org Code: | 570 | Strength: | 10 MG |

Application Comment:

| | | | | |
|---|---|---|---|---|
| FDA Contacts: | A. ZECCOLA | (HFD-550) | 301-827-2147 | , Project Manager |
| | C. KIM | (HFD-570) | 301-827-1050 | , Review Chemist |
| | G. POOCHIKIAN | (HFD-570) | 301-827-1050 | , Team Leader |

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Overall Recommendation: ACCEPTABLE on 09-MAY-2002by S. FERGUSON(HFD-324)301-827-0062
ACCEPTABLE on 23-APR-2002by J. D AMBROGIO(HFD-324)301-827-0062

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Establishment: [redacted] FEI [redacted]

[redacted]

DMF No: AADA:
Responsibilities: [redacted]

Profile: TCM OAI Status: NONE

Estab. Comment: [redacted]

[redacted]

| Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 13-FEB-2002 | | | | KIMCH |
| SUBMITTED TO DO | 13-FEB-2002 | 10D | | | DAMBROGIOJ |
| DO RECOMMENDATION | 23-APR-2002 | | | ACCEPTABLE BASED ON FILE REVIEW | STHOMA |

A PRE-APPROVAL AND CGMP INSPECTION WAS CONDUCTED AT THE ABOVE NAMED ESTABLISHMENTS TO EVALUATE THE FIRM'S CAPABILITY AS A [redacted] SITE FOR LORATADINE TABLETS. THE INSPECTIONS WERE CONDUCTED FROM 07/11 - 08/09/2000 AND COVERED THE "TCM" AND "CTL" PROFILE CLASSES. A 5-ITEM FDA-483, INSPECTIONAL OBSERVATIONS, WAS ISSUED DURING THE AUGUST 2000 INSPECTION AND CORRECTIVE ACTION WAS IMPLEMENTED PROMPTLY BY THE FIRM.

BASED ON THE AUGUST 2000 INSPECTIONAL FINDINGS, THE FIRM'S PROMPT CORRECTIVE ACTION OF INSPECTIONAL OBSERVATIONS, AND BECAUSE THE PREVIOUS INSPECTION IS WITHIN THE TWO-YEAR STATUTORY OBLIGATION OF THE FOOD, DRUG & COSMETIC ACT FOR INSPECTION OF DRUG ABLISHMENTS, I AM RECOMMENDING APPROVAL OF NDA 21375 FOR ALAVERT (LORATADINE HCL) 10 MG TABLETS AT THE DISTRICT LEVEL. PROFILE SAMPLES WILL BE COLLECTED DURING THE NEXT

SCHEDULED ROUTINE INSPECTION OF THE FIRM AND FORWARDED TO [redacted] ANALYSIS.

OC RECOMMENDATION 23-APR-2002 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

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Establishment: [redacted] FEI

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: [redacted] (on 13-FEB-2002 by C. KIM (HFD-570) 301-827-1050)

| estone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 13-FEB-2002 | | | | KIMCH |
| SUBMITTED TO DO | 13-FEB-2002 | GMP | | | DAMBROGIOJ |
| DO RECOMMENDATION | 23-APR-2002 | | | ACCEPTABLE BASED ON FILE REVIEW | STHOMA |

A PRE-APPROVAL AND CGMP INSPECTION WAS CONDUCTED AT THE ABOVE NAMED ESTABLISHMENTS TO EVALUATE THE FIRM'S CAPABILITY AS A [redacted] SITE FOR LORATADINE TABLETS. THE INSPECTIONS WERE CONDUCTED FROM 07/11 - 08/09/2000 AND COVERED THE "TCM" AND "CTL" PROFILE CLASSES. A 5-ITEM FDA-483, INSPECTIONAL OBSERVATIONS, WAS ISSUED DURING THE AUGUST 2000 INSPECTION AND CORRECTIVE ACTION WAS IMPLEMENTED PROMPTLY BY THE FIRM.

BASED ON THE AUGUST 2000 INSPECTIONAL FINDINGS, THE FIRM'S PROMPT CORRECTIVE ACTION OF INSPECTIONAL OBSERVATIONS, AND BECAUSE THE PREVIOUS INSPECTION IS WITHIN THE TWO-YEAR STATUTORY OBLIGATION OF THE FOOD, DRUG & COSMETIC ACT FOR INSPECTION OF DRUG ESTABLISHMENTS, I AM RECOMMENDING APPROVAL OF NDA 21375 FOR ALAVERT (LORATADINE HCL) 10 MG TABLETS AT THE DISTRICT LEVEL. PROFILE SAMPLES WILL BE COLLECTED DURING THE NEXT SCHEDULED ROUTINE INSPECTION OF THE FIRM AND FORWARDED TO [redacted] ANALYSIS.

OC RECOMMENDATION 23-APR-2002 ACCEPTABLE DAMBROGIOJ
DISTRICT RECOMMENDATION

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Establishment: [redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THE SITE HAS BEEN DESIGNATED FOR (on 09-MAY-2002 by C. KIM (HFD-570) 301-827-1050)

| Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 09-MAY-2002 | | | | KIMCH |
| OC RECOMMENDATION | 09-MAY-2002 | | | ACCEPTABLE BASED ON PROFILE | FERGUSONS |

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Establishment:

DMF No: AADA:
Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment: THE SITE IS DESIGNATED FOR (on 09-MAY-2002 by C. KIM (HFD-570) 301-827-1050)

| Milestone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| SUBMITTED TO OC | 09-MAY-2002 | | | | KIMCH |
| OC RECOMMENDATION | 09-MAY-2002 | | | ACCEPTABLE BASED ON PROFILE | FERGUSONS |

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Establishment:

DMF No: AADA:
Responsibilities:

Profile: CSN OAI Status: NONE

| EMilestone Name | Date | Type | Insp. Date | Decision & Reason | Creator |
|---|---|---|---|---|---|
| BMITTED TO OC | 13-FEB-2002 | | | | KIMCH |
| RECOMMENDATION | 13-FEB-2002 | | | ACCEPTABLE BASED ON PROFILE | DAMBROGIOJ |

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