CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-130

21-131

21-132

CHEMISTRY REVIEW(S)

HFD-520/Dowrie-Miller

DEC 9 1999

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 21-132 **Chemistry review #1** **Review date 6 December, 1999**

Submission	Document date	CDER date	Completed date
Presubmission			
CMC (vol 2.1-2.6)	11 May, 1999	17 May, 1999	6 December, 1999
CMC (vol 4.1-4.3)	30 July, 1999	30 July, 1999	6 December, 1999
Clinical submission and PDUFA starting time.			
CMC (vol 7.1)	15 October, 1999	18 October, 1999	

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Oral Suspension

Strength
100 mg/ 5 mL

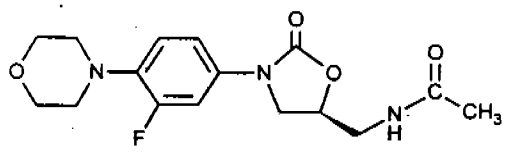
Route of administration
Oral

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Chemical name, structural formula, molecular formula, molecular weight

Chemical Name	(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo- 5-oxazolidinyl]methyl]-acetamide
U.S. Adopted Name (USAN)	Linezolid
International Non-Proprietary Name (INN)	Linezolid
Generic Name	Linezolid
Laboratory Codes	PNU-100766
Chemical Abstract Service (CAS) Name	Acetamide, N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, (S)-
CAS Registry Number	165800-03-3
Other Chemical Names	N-({(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide N-[[(S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide
Trademarked Product Names	ZYVOX™

Supporting documents

[redacted]

Related documents

NDA 21-131 Linezolid injection;
NDA 21-132 Linezolid suspension

Consults

Trade name consult submitted to HFD-400.
CMC micro for sterility controls NDA 21-131 was sent as a consult to HFD-160 on 8/11/99. Completed and found acceptable.
Inspection request was made 5/26/99. Not completed at this time.
Methods for analytic control sent to Puerto Rico and St. Louis FDA laboratories 8/13/99. Not complete at this time.

Summary

This NDA 21-132 is for Linezolid, oral suspension for treatment of gram positive bacterial infection. Linezolid is entirely synthetic. Single enantiomer and identified polymorphic form proposed for the product. Both these physical aspects have controls and no conversion occurs on stability. Stability characteristics are excellent.

Drug product is manufactured in [redacted] The site has an acceptable FDA inspection specific for this product.

An environmental assessment is waved based on amount projected to be introduced to the environment being below levels set in guidelines for limits considered to have a significant impact.

Method validation work is not complete.

The firm will provide a stability data update to provide 18 months of data. In addition, supporting data for clinical trial batches are up to the proposed 24 month expiration date.

Conclusions & recommendations

Recommend approval pertaining to chemistry, manufacturing, and controls.

/S/ 12/6/99

J. Timper, Review chemist
12/6/99

NDA 21-132; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 12/9/99
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

HFD-520

DEC 13 1999

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 21-130 **Chemistry review #1** **Review date 8 December, 1999**

Submission	Document date	CDER date	Completed date
Presubmission			
CMC (vol 2.1-2.6)	11 May, 1999	17 May, 1999	8 December, 1999
CMC (vol 4.1-4.3)	30 July, 1999	30 July, 1999	8 December, 1999
Clinical submission and PDUFA starting time.			
CMC (vol 7.1)	15 October, 1999	18 October, 1999	

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Tablet

Strength
400 mg, 600 mg

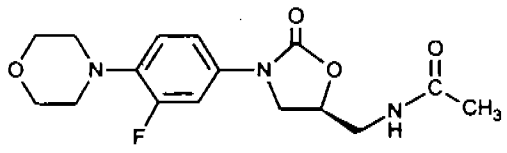
Route of administration
Oral

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Chemical name, structural formula, molecular formula, molecular weight

Chemical Name	(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo- 5-oxazolidinyl]methyl]-acetamide
U.S. Adopted Name (USAN)	Linezolid
International Non-Proprietary Name (INN)	Linezolid
Generic Name	Linezolid
Laboratory Codes	PNU-100766
Chemical Abstract Service (CAS) Name	Acetamide, N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, (S)-
CAS Registry Number	165800-03-3
Other Chemical Names	N-({(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide N-[[(S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide
Trademarked Product Names	ZYVOX™

Supporting documents

[redacted]

Related documents

NDA 21-131 Linezolid injection;
NDA 21-132 Linezolid suspension

Consults

Trade name consult submitted to HFD-400.
CMC micro for sterility controls NDA 21-131 was sent as a consult to HFD-160 on 8/11/99. Completed and found acceptable.
Inspection request was made 5/26/99. Not completed at this time.
Methods for analytic control sent to Puerto Rico and St. Louis FDA laboratories 8/13/99. Not complete at this time.

Summary

This NDA 21-130 is for Linezolid, tablet for treatment of gram positive bacterial infection. Linezolid is entirely synthetic. Single enantiomer and identified polymorphic form proposed for the product. Both these physical aspects have controls and no conversion occurs on stability. Stability characteristics are excellent.

Drug product is manufactured in [redacted]. The site has an acceptable FDA inspection specific for this product.

An environmental assessment is waved based on amount projected to be introduced to the environment being below levels set in guidelines for limits considered to have a significant impact.

Method validation work is not complete.

The firm will provide a stability data update to provide 18 months of data. In addition, supporting data for clinical trial batches are up to the proposed 24 month expiration date.

Conclusions & recommendations

Recommend approval pertaining to chemistry, manufacturing, and controls.

/S/ 12/8/99

J. Timper, Review chemist
12/8/99

NDA 21-130; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 12/13/99
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

HFD-520/Duvall-Miller

DEC 30 1999

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 21-131 **Chemistry review #1** **Review date 23 December, 1999**

Submission	Document date	CDER date	Completed date
Presubmission			
CMC (vol 2.1-2.6)	11 May, 1999	17 May, 1999	23 December, 1999
CMC (vol 4.1-4.3)	30 July, 1999	30 July, 1999	23 December, 1999
Clinical submission and PDUFA starting time.			
CMC (vol 7.1)	15 October, 1999	18 October, 1999	

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Injection

Strength
2 mg/mL; 100, 200, 300 mL

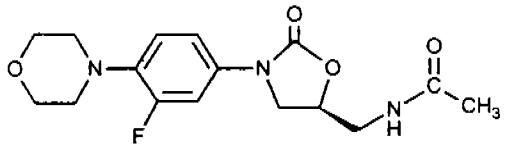
Route of administration
Intravenous Solution

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Summary

This NDA 21-131 is for Linezolid, injection for treatment of gram positive bacterial infection. Linezolid is entirely synthetic. Single enantiomer and identified polymorphic form proposed for the product. Both these physical aspects have controls and no conversion occurs on stability. Stability characteristics are excellent.

Drug product is manufactured by [redacted]
Pharmacia & Upjohn Company, Kalamazoo, MI.

An environmental assessment is waved based on amount projected to be introduced to the environment being below levels set in guidelines for limits considered to have a significant impact.

Method validation work is not complete.

The firm will provide a stability data update to provide 18 months of data. In addition, supporting data for clinical trial batches are up to the proposed 24 month expiration date.

APPEARS THIS WAY
ON ORIGINAL

Conclusions & recommendations

Recommend approval pertaining to chemistry, manufacturing, and controls.

/S/ 12/23/99

J. Timper, Review chemist
12/23/99

NDA 21-131; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 12/30/99
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

HFD 520
DUVALL-MILLER

FEB 3 2000

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 21-130 **Chemistry review #2** **Review date 6 January, 2000**

Submission	Document date	CDER date	Completed date
Amendment	8/11/99	8/16/99	1/20/00
New Corresp.	8/30/99	9/1/99	1/20/00
Amendment	10/14/99	10/18/99	1/20/00
New Corresp.	11/15/00	11/17/99	1/20/00
Amendment BC	11/30/99	12/2/99	1/20/00

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Tablet

Strength
400 mg, 600 mg

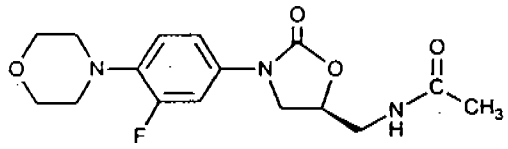
Route of administration
Oral

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Summary

Summary of new submissions to NDA 21-130

Amendment	**8/11/99**	**8/16/99**	**1/20/00**
Draft of Non-Insert Labeling:		**Adequate**	
New Corresp.	**8/30/99**	**9/1/99**	**1/20/00**
Response to chemist's question regarding historical changes in synthetic method of linezolid.		**Adequate**	
Amendment	**10/14/99**	**10/18/99**	**1/20/00**
Typographical error. Specification of impurity to be [redacted] Adequate			
New Corresp.	**11/15/00**	**11/17/99**	**1/20/00**
Reply to chemist's inquiry regards to need to set particle size specification for the drug substance. Adequate			
Amendment BC	**11/30/99**	**12/2/99**	**1/20/00**
Stability update. Adequate			

Conclusions & recommendations

Recommend approval pertaining to chemistry, manufacturing, and controls.

/S/ 1/20/00

J. Timper, Review chemist
1/20/00

NDA 21-130; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 1/23/00
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

HFD 520
Duvall-Miller

FEB 3 2000

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

NDA 21-132 **Chemistry review #2** **Review date 3 Feburary, 2000**

Submission	Document date	CDER date	Completed date
M-004	8/11/99	8/16/99	2/3/00
BC	11/30/99	12/2/99	2/3/00

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Oral Suspension

Strength
100 mg/ 5 mL

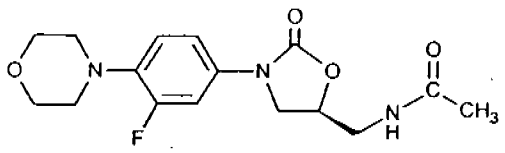
Route of administration
Oral

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Chemical name, structural formula, molecular formula, molecular weight

Chemical Name	(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo- 5-oxazolidinyl]methyl]-acetamide
U.S. Adopted Name (USAN)	Linezolid
International Non-Proprietary Name (INN)	Linezolid
Generic Name	Linezolid
Laboratory Codes	PNU-100766
Chemical Abstract Service (CAS) Name	Acetamide, N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, (S)-
CAS Registry Number	165800-03-3
Other Chemical Names	N-({(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide N-[[(S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide
Trademarked Product Names	ZYVOX™

Supporting documents

[redacted]

Related documents

NDA 21-131 Linezolid injection;
NDA 21-132 Linezolid suspension

Consults

Trade name consult submitted to HFD-400.
CMC micro for sterility controls NDA 21-131: acceptable
Inspections: Acceptable
Methods for analytic control sent to Puerto Rico and St. Louis FDA laboratories 8/13/99. Not complete at this time.

Summary

	letter	CDER	reviewed
Amendment	**8/11/99**	**8/16/99**	**1/21/00**
Draft of Non-Insert Labeling:		**Adequate**	
Amendment BC	**11/30/99**	**12/2/99**	**1/21/00**
Stability update.		**Adequate**	

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Conclusions & recommendations
Recommend approval pertaining to chemistry, manufacturing, and controls.

/S/ 2/3/00

J. Timper, Review chemist
2/3/00

NDA 21-132; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 2/3/00
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

HFD 520
Doubli-Miller

FEB 3 2000

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA 21-131 **Chemistry review #2** **Review date 21 January, 2000**

Submission	Document date	CDER date	Completed date
M-004	8/11/99	8/16/99	1/21/00
NC	10/26/99	10/26/99	1/21/00
BC	11/30/99	12/2/99	1/21/00

Applicant address
Pharmacia & Upjohn Company
7000 Portage Road
Kalamazoo, Michigan 49001

Contact
Peter J. Diroma, Regulatory Manager
(616) 833-8070

Drug product name
Linezolid

Pharmacological indication
Gram Positive Bacterial Infection

Dosage form
Injection

Strength
2 mg/mL; 100, 200, 300 mL

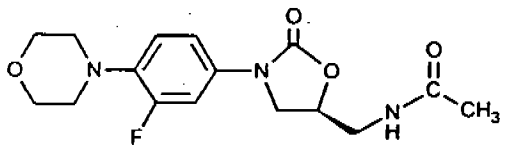
Route of administration
Intravenous Solution

Rx/OTC
Rx

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

PNU-100766



Chemical name, structural formula, molecular formula, molecular weight

Chemical Name	(S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo- 5-oxazolidinyl]methyl]-acetamide
U.S. Adopted Name (USAN)	Linezolid
International Non-Proprietary Name (INN)	Linezolid
Generic Name	Linezolid
Laboratory Codes	PNU-100766
Chemical Abstract Service (CAS) Name	Acetamide, N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]-, (S)-
CAS Registry Number	165800-03-3
Other Chemical Names	N-({(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-1,3-oxazolidin-5-yl}methyl)acetamide N-[[(S)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl]acetamide
Trademarked Product Names	ZYVOX™

Supporting documents

[redacted]

Related documents

NDA 21-130 Linezolid tablet;
NDA 21-132 Linezolid suspension

Consults

Trade name consult submitted to HFD-400.
CMC micro for sterility controls NDA 21-131 Adequate
Inspection request was made 5/26/99. Not completed at this time.
Methods for analytic control sent to Puerto Rico and St. Louis FDA laboratories 8/13/99. Not complete at this time.

Summary

	letter	CDER	reviewed
Amendment	**8/11/99**	**8/16/99**	**1/21/00**
Draft of Non-Insert Labeling:		**Adequate**	
New Corresp.	**10/26/00**	**10/26/99**	**1/21/00**
Clarification to sites' responsibilities for drug product manufacture. Adequate			
Amendment BC	**11/30/99**	**12/2/99**	**1/21/00**
Stability update. Adequate			

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Conclusions & recommendations

Recommend approvable (pending inspection) pertaining to chemistry, manufacturing, and controls.

/S/ 1/21/00

J. Timper, Review chemist
1/21/00

NDA 21-131; HFD-520/Division file;
HFD-830/Chen/DD
HFD-520/Katague/Chem-teamleader; /S/ 2/3/00
HFD-520/Timper/Chem;
HFD-520/Ross/MO;
HFD-520/Seethaler/Pharm;
HFD-520/Duvall-Miller/Project Manager;

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21130/000
Stamp: 18-OCT-1999
Regulatory Due: 18-APR-2000
Applicant: PHARMACIA AND UPJOHN
7000 PORTAGE RD
KALAMAZOO, MI 490010199
Priority: 1P
Org Code: 520

Action Goal:
District Goal: 18-FEB-2000
Brand Name: ZYVOX (LINEZOLID) 400MG/600MG TABLETS
Estab. Name:
Generic Name: LINEZOLID

Dosage Form: (TABLET)
Strength: 400, 600 MG

Application Comment:
FDA Contacts: E. DUVALL MILLER (HFD-520) 301-827-2125 , Project Manager
J. TIMPER JR (HFD-520) 301-827-2193 , Review Chemist
D. KATAGUE (HFD-520) 301-827-2174 , Team Leader

Overall Recommendation: ACCEPTABLE on 25-OCT-1999 by S. ADAMS (HFD-320) 301-594-0095

Establishment: 2650013
PHARMACIA AND UPJOHN CARIBE INC
HIGHWAY 2 KM 60.0
BARCELONETA/ARECIBO, PR 00617
DMF No: [redacted] AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-MAY-1999				DAMBROGIOJ
SUBMITTED TO DO	26-MAY-1999	PS			DAMBROGIOJ
ASSIGNED INSPECTION	01-JUN-1999	PS			MTORRES
INSPECTION SCHEDULED	11-AUG-1999		30-OCT-1999		MTORRES
INSPECTION PERFORMED	25-OCT-1999		07-OCT-1999		MTORRES
DEVIATIONS NOTED DO NOT WARRANT WITHHOLDING APPROVAL.					
DO RECOMMENDATION	25-OCT-1999			ACCEPTABLE INSPECTION	MTORRES
OC RECOMMENDATION	25-OCT-1999			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	26-MAY-1999				DAMBROGIOJ
SUBMITTED TO DO	26-MAY-1999	PS			DAMBROGIOJ
ASSIGNED INSPECTION	01-JUN-1999	PS			MTORRES
INSPECTION SCHEDULED	11-AUG-1999		30-OCT-1999		MTORRES
INSPECTION PERFORMED	22-OCT-1999		07-OCT-1999		MTORRES
DEVIATIONS NOTED DO NOT WARRANT WITHHOLDING APPROVAL					
DO RECOMMENDATION	25-OCT-1999			ACCEPTABLE INSPECTION	MTORRES
OC RECOMMENDATION	25-OCT-1999			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: 1810189
PHARMACIA AND UPJOHN CO
7000 PORTAGE ROAD
KALAMAZOO, MI 49001
DMF No: AADA:

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Responsibilities: FINISHED DOSAGE PACKAGER
INTERMEDIATE MANUFACTURER

Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-AUG-1999				TIMPERJ
OC RECOMMENDATION	19-AUG-1999			ACCEPTABLE BASED ON PROFILE	ADAMSS

Profile: TCM OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-AUG-1999				TIMPERJ
OC RECOMMENDATION	19-AUG-1999			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: INTERMEDIATE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-AUG-1999				TIMPERJ
OC RECOMMENDATION	19-AUG-1999			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment: [redacted]

DMF No: AADA:
Responsibilities: INTERMEDIATE MANUFACTURER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	19-AUG-1999				TIMPERJ
OC RECOMMENDATION	19-AUG-1999			ACCEPTABLE BASED ON PROFILE	ADAMSS