

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-436

CHEMISTRY REVIEW(S)



Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA 21-436
2. REVIEW # 2
3. REVIEW DATE: 8/28/02
4. REVIEWER: Sherita McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

none

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original Submission

Amendment

Amendment

Amendment

Document Date

10/31/01

2/28/02

6/24/02

6/03/02

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceuticals Company, Ltd

2-9 Kanda Tsukasa-cho

Address: Chiyoda-Ku Tokyo

101-8535, Japan

Representative: Dr. Gary Ingenito

Telephone: 203.677.6674

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Abilitat (not accepted)

b) Non-Proprietary Name / USAN [1997]: Aripiprazole

CRED **CHEMISTRY REVIEW TEMPLATE** **CRED**

Chemistry Assessment Section

- c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Schizophrenia
11. DOSAGE FORM: Immediate Release Tablet
12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet
13. ROUTE OF ADMINISTRATION: oral
14. Rx/OTC DISPENSED: Rx OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

SPOTS product – Form Completed

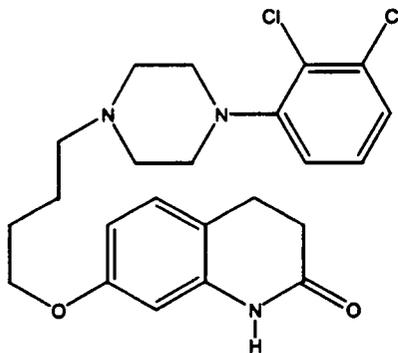
Not a SPOTS product

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

Chemical Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.38



17. RELATED/SUPPORTING DOCUMENTS:

**Number of Pages
Redacted** 1



**Confidential,
Commercial Information**

CDER CHEMISTRY REVIEW TEMPLATE CDER

Chemistry Assessment Section

	1	Adequate	12-06-01	N/A
	1	Adequate	4-24-00 10-25-99 07-28-00	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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Commercial IND Indication: Treatment of Schizophrenia Sponsor: Otsuka America Pharm
IND		Commercial IND Indication: _____ Sponsor: Otsuka Pharm

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Withhold	7/26/02	B. Hartman
Pharm/Tox	N/A	10/17/01	Lois Freed, Ph.D.
Biopharm	N/A	11/20/01	Hong Zhao, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.
OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A

Microbiology	N/A	N/A	N/A
--------------	-----	-----	-----

The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-436 is not approvable because of the cGMP issues with respect to the drug product manufacturing site (withhold recommendation). The applicant will be sent a list of deficiencies in the FDA Action Letter.

Methods validation will be submitted after all CMC issues have been addressed.

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

N/A

II. Summary of Chemistry Assessments

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

Aripiprazole is a member of the quinolinone class of compounds and is indicated for the treatment of patients with schizophrenia. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

Aripiprazole was originally investigated under IND _____ In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15 mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are portionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with "A-006" and "2" debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular shape tablet with "A-007" and "5" debossed on one side and scored on the other. The 10 mg

Chemistry Assessment Section

dosage is a pink, modified rectangular shape tablet with "A-008" and "10" debossed on one side. The 15 mg dosage is a yellow, round tablet with "A-009" and "15" debossed on one side. The 20 mg dosage is a white to pale yellowish white, round tablet with "A-010" and "20" debossed on one side. The 30 mg dosage is a pink, round tablet with "A-011" and "30" debossed on one side. The tablet weights of the 2, 5, 10, and 15 mg tablets are 95.0 mg. The 20 and 30 mg tablets are 189.76 mg and 285.0 mg, respectively. Each of the six strengths are packaged in 95 and 200-cc square, white opaque HDPE bottles, induction heat sealed and capped with a closure. The closures for the 95 and 200 cc bottles are child resistant and non child resistant, respectively. Additionally, each of the six strengths are packaged in aluminum/aluminum cold-form blisters.

The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is $C_{23}H_{27}Cl_2N_3O_2$ and the molecular weight is 448.38. The applicant indicates that the drug substance will be manufactured by Otsuka Pharmaceuticals in Japan.

is

is

The applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available.

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

Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.

The applicant has requested a 24 month shelf life for all potencies of Aripiprazole Tablets in bottles and blisters (V 1.5, page 1). As indicated in the stability section of this review, the



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

applicant provided up to 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site and 6 months of data for one batch each of the 20 and 30 mg tablets from the Puerto Rico site. The applicant also included certificates of analyses for the 5, 10, 15, 20 and 30 mg tablets manufactured at the Puerto Rico facility.

In light of the dissolution problems at the Mayaguez, Puerto Rico facility (see page 57 of this review), the limited amount of stability data available from the Mayaguez, Puerto Rico facility and the apparent limited amount of data available for the current formulations of the 20 and 30 mg tablets, we will not set an expiry for the drug product at this time. Moreover, the applicant has not provided adequate data to support the manufacture of the 2 mg tablets at the Mayaguez, Puerto Rico facility.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-436 is Not Approvable from the chemistry, manufacturing and controls (CMC) standpoint. The "Not Approvable" recommendation is based on the following:

- **Withhold** recommendation from the FDA's Office of Compliance regarding cGMP status of Britol's Mayaguez, PR site (CFN #2627673). This site was submitted as a manufacturer, packager, and release tester of the drug product.
- Other CMC concerns related to the drug substance and drug product sections as outlined in Chemistry Review #1 by Dr. Sherita McLamore. These deficiencies outlined in Chemistry Review #1 constitute an APPROVABLE recommendation from the CMC standpoint.

Before NDA 21-436 can be approved for CMC, the proposed site for drug product manufacturing, packaging and release testing (CFN #2627673) should receive an acceptable recommendation from the Office of Compliance and the CMC issues (outlined in Review #1) be properly addressed. Alternatively, because two sites were submitted for the manufacturing, packaging and release testing of the drug product, the applicant can withdraw the BMS Mayaguez, Puerto Rico facility (CFN 2627673) from their application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

SHardeman (PM)/Date

C. CC Block

Orig. NDA 21-436

HFD-120/Division File

HFD-120/SHardeman

HFD-120/SMcLamore

HFD-120/TOliver

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

2 pages



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

27-AUG-2002

FDA CDER BES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 1 of 3

Application : NDA 21436/000	Sponsor: OTSUKA PHARM
Org Code : 120	101
Priority : 18	TOKYO, , JA
Stamp Date : 31-OCT-2001	Brand Name : ABILITAT (ARIPIPRAZOLE)
FDUFA Date : 31-AUG-2002	10MG/15MG/30MG
Action Goal :	Estab. Name:
District Goal: 02-JUL-2002	Generic Name: ARIPIPRAZOLE
	Dosage Form: (TABLET)
	Strength : 2, 5, 10, 15, 20, 30 MG

FDA Contacts:	S. HARDEMAN	Project Manager (HFD-120)	301-594-2850
	S. MCLAMORE	Review Chemist (HFD-810)	301-594-5359
	T. OLIVER	Team Leader (HFD-810)	301-594-2570

Overall Recommendation: WITHHOLD on 23-AUG-2002 by B. HARTMAN (HFD-324) 301-827-0067

Establishment :

DMP No:

Responsibilities:

Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-NOV-01		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

Establishment : CFN : 2627673 FEI : 2627673
BRISTOL LABORATORIES INC DIV BRISTOL MYERS CO
FOREIGN TRADE ZONE 7 RD 114
MAYAGUEZ, PR 00680

DMP No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	23-AUG-02		
Decision :	WITHHOLD		
Reason :	EIR REVIEW-CONCUR W/DISTRICT		

Establishment : CFN : 1819504 FEI : 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD BXPY
EVANSVILLE, IN 477210001

DMP No: AADA:



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

27-AUG-2002

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Page 2 of 3

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1825662 FEI : 1825662
BRISTOL MYERS SQUIBB CO
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

27-ADG-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 3 of 3

OTSUKA PHARMACEUTICAL CO LTD
MATSUTANI ITANO-CHO ITANO-GUN
TOKUSHIMA, , JA

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment : CPN : 9611255 FEI : 3002807834
OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY
KAWAUCHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment :

DMF No:

Responsibilities:

Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-NOV-01		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

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

/s/

Sherita McLamore
8/28/02 09:41:40 AM
CHEMIST

Thomas Oliver
8/28/02 12:35:10 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 21-436

Aripiprazole Tablets

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.

HFD-120



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary.....	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment	11
I. DRUG SUBSTANCE.....	11
1. Description & Characterization.....	11
a. Description.....	11
b. Characterization / Proof Of Structure.....	11
2. Manufacturer.....	13
3. Synthesis / Method Of Manufacture.....	13
a. Starting Materials - Specs & Tests.....	13
b. Solvents, Reagents, etc.	15
c. Flow Chart.....	17
d. Detailed Description.....	18
4. Process Controls	18
a. Reaction Completion / Other In-Process Tests	18
b. Intermediate Specs & Tests.....	19
5. Reference Standard.....	19



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

a. Preparation.....	19
b. Specifications.....	20
6. Regulatory Specifications / Analytical Methods.....	21
a. Drug Substance Specifications & Tests.....	21
b. Purity Profile.....	21
c. Microbiology.....	25
7. Container/Closure System For Drug Substance Storage.....	26
8. Drug Substance Stability	27
II. DRUG PRODUCT.....	31
1. Components/Composition.....	31
2. Specifications & Methods For Drug Product Ingredients.....	33
a. Active Ingredient(s).....	33
b. Inactive Ingredients.....	33
3. Manufacturer.....	34
4. Methods Of Manufacturing And Packaging.....	36
a. Production Operations.....	39
b. In-Process Controls & Tests.....	39
c. Reprocessing Operations.....	39
5. Regulatory Specifications And Methods For Drug Product.....	40
a. Sampling Procedures.....	40
b. Regulatory Specifications And Methods.....	40
6. Container/Closure System.....	46
7. Microbiology.....	50
8. Drug Product Stability.....	51
III. INVESTIGATIONAL FORMULATIONS	57
IV. ENVIRONMENTAL ASSESSMENT.....	58
V. METHODS VALIDATION.....	58
VI. LABELING.....	59
VII. ESTABLISHMENT INSPECTION.....	61
VIII. DRAFT DEFICIENCY LETTER	62



Chemistry Review Data Sheet

1. NDA 21-436
2. REVIEW # 1
3. REVIEW DATE: 8/1/02
4. REVIEWER: Sherita McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

none

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Original Submission

10/31/01

Amendment

2/28/02

Amendment

6/24/02

Amendment

6/03/02

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceuticals Company, Ltd

2-9 Kanda Tsukasa-cho

Address: Chiyoda-Ku Tokyo

101-8535, Japan

Representative: Dr. Gary Ingenito

Telephone: 203.677.6674

8. DRUG PRODUCT NAME/CODE/TYPE:

Chemistry Assessment Section

- a) Proprietary Name: Abilitat (not accepted)
b) Non-Proprietary Name / USAN [1997]: Aripiprazole
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Schizophrenia

11. DOSAGE FORM: Immediate Release Tablet

12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

SPOTS product – Form Completed

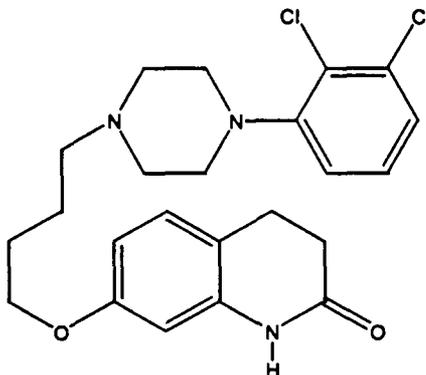
Not a SPOTS product

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

Chemical Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.38



**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

1 page



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

 	1	Adequate	09-23-99	N/A
	1	Adequate	12-06-01	N/A
	1	Adequate	4-24-00 10-25-99 07-28-00	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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Commercial IND Indication: Treatment of Schizophrenia Sponsor: Otsuka America Pharm
IND		Commercial IND Indication:  Sponsor: Otsuka Pharm

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending	7/29/02	N/A
Pharm/Tox	N/A	10/17/01	Lois Freed Ph.D.
Biopharm	N/A	11/20/01	Hong Zhao, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

OPDRA	N/A	N/A	N/A
EA	N/A	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-436 is approvable. The applicant will be sent a list of deficiencies.

Methods validation will be submitted after all CMC deficiencies have been addressed.

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

N/A

II. Summary of Chemistry Assessments

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

Aripiprazole is a member of the quinolinone class of compounds and is indicated for the treatment of patients with schizophrenia. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

Aripiprazole was originally investigated under _____ in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15-mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are portionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with "A-006" and "2" debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular

Chemistry Assessment Section

shape tablet with "A-007" and "5" debossed on one side and scored on the other. The 10 mg dosage is a pink, modified rectangular shape tablet with "A-008" and "10" debossed on one side. The 15 mg dosage is a yellow, round tablet with "A-009" and "15" debossed on one side. The 20 mg dosage is a white to pale yellowish white, round tablet with "A-010" and "20" debossed on one side. The 30 mg dosage is a pink, round tablet with "A-011" and "30" debossed on one side. The tablet weights of the 2, 5, 10, and 15 mg tablets are 95.0 mg. The 20 and 30 mg tablets are 189.76 mg and 285.0 mg, respectively. Each of the six strengths are packaged in 95 and 200-cc square, white opaque HDPE bottles, induction heat sealed and capped with a closure. The closures for the 95 and 200 cc bottles are child resistant and non child resistant, respectively. Additionally, each of the six strengths are packaged in aluminum/aluminum cold-form blisters.

The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is $C_{23}H_{27}Cl_2N_3O_2$ and the molecular weight is 448.38. The applicant indicates that the drug substance will be manufactured by Otsuka Pharmaceuticals in Japan.

The applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available.

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

Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.

Chemistry Assessment Section

The applicant has requested a 24 month shelf life for all potencies of Aripiprazole Tablets in bottles and blisters (V 1.5, page 1). As indicated in the stability section of this review, the applicant provided up to 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site and 6 months of data for one batch each of the 20 and 30 mg tablets from the Puerto Rico site. The applicant also included certificates of analyses for the 5, 10, 15, 20 and 30 mg tablets manufactured at the Puerto Rico facility.

In light of the dissolution problems at the Mayaguez, Puerto Rico facility (see page 57 of this review), the limited amount of stability data available from the Mayaguez, Puerto Rico facility and the apparent limited amount of data available for the current formulations of the 20 and 30 mg tablets, we will not set an expiry for the drug product at this time. Moreover, the applicant has not provide adequate data to support the manufacture of the 2 mg tablets at the Mayaguez, Puerto Rico facility.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-436 is Approvable from a Chemistry standpoint due to chemistry, manufacturing and controls concerns related to the drug substance and the drug product as outlined in this review.

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

SMcLamore/Date

TOliver (TL)/Date

SHardeman (PM)/Date

C. CC Block

Orig. NDA 21-436

HFD-120/Division File

HFD-120/SHardeman

HFD-120/SMcLamore

HFD-120/TOliver

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

53 pages



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

30-JUL-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 2 of 3

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1825662 FBI : 1825662
BRISTOL MYERS SQUIBB CO
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620

DMP No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMP No:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN :

DMP No:

Responsibilities

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FBI :



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

APPEARS THIS WAY
ON ORIGINAL



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

30-JUL-2002

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 3 of 3

OTSUKA PHARMACEUTICAL CO LTD
MATSUTANI ITANO-CHO ITANO-GUN
TOKUSHIMA, , JA

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	19-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment : CPN : 9611255 FEI : 3002807834
OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY
KAWAUCHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile :	CSN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	09-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment :

DMF No: --

Responsibilities:

Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	26-NOV-01		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

**APPEARS THIS WAY
ON ORIGINAL**

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

2 pages

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

/s/

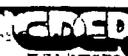
Sherita McLamore
8/13/02 01:04:19 PM
CHEMIST

Thomas Oliver
8/13/02 01:45:12 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

NDA 21-436

Aripiprazole Tablets

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.
HFD-120



Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary.....	8
I. Recommendations.....	8
A. Recommendation and Conclusion on Approvability.....	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments	8
A. Description of the Drug Product(s) and Drug Substance(s).....	9
B. Description of How the Drug Product is Intended to be Used.....	9
C. Basis for Approvability or Not-Approval Recommendation.....	10
III. Administrative.....	10
A. Reviewer's Signature.....	10
B. Endorsement Block.....	10
C. CC Block.....	10
Chemistry Assessment	11
I. DRUG SUBSTANCE.....	11
1. Description & Characterization.....	11
a. Description.....	11
b. Characterization / Proof Of Structure.....	11
2. Manufacturer.....	13
3. Synthesis / Method Of Manufacture.....	13
a. Starting Materials - Specs & Tests.....	13
b. Solvents, Reagents, etc.	15
c. Flow Chart.....	17
d. Detailed Description.....	18
4. Process Controls	18
a. Reaction Completion / Other In-Process Tests	18
b. Intermediate Specs & Tests.....	19
5. Reference Standard.....	19

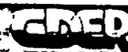


CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

a. Preparation.....	19
b. Specifications.....	20
6. Regulatory Specifications / Analytical Methods.....	21
a. Drug Substance Specifications & Tests.....	21
b. Purity Profile.....	21
c. Microbiology.....	25
7. Container/Closure System For Drug Substance Storage.....	26
8. Drug Substance Stability	27
II. DRUG PRODUCT.....	31
1. Components/Composition.....	31
2. Specifications & Methods For Drug Product Ingredients.....	33
a. Active Ingredient(s).....	33
b. Inactive Ingredients.....	33
3. Manufacturer.....	34
4. Methods Of Manufacturing And Packagingg.....	36
a. Production Operations.....	39
b. In-Process Controls & Tests.....	39
c. Reprocessing Operations.....	39
5. Regulatory Specifications And Methods For Drug Product.....	40
a. Sampling Procedures.....	40
b. Regulatory Specifications And Methods.....	40
6. Container/Closure System.....	46
7. Microbiology.....	50
8. Drug Product Stability.....	51
III. INVESTIGATIONAL FORMULATIONS	57
IV. ENVIRONMENTAL ASSESSMENT.....	58
V. METHODS VALIDATION.....	58
VI. LABELING.....	59
VII. ESTABLISHMENT INSPECTION.....	61
VIII. DRAFT DEFICIENCY LETTER.....	62



Chemistry Review Data Sheet

1. NDA 21-436
2. REVIEW # 2
3. REVIEW DATE: 10/11/02
4. REVIEWER: Sherita McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original Submission	10/31/01
Amendment	2/28/02
Amendment	6/24/02
Amendment	6/03/02

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment (Response to approvable letter)	9/18/02
Amendment	9/18/02
Amendment	10/03/02

7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceuticals Company, Ltd
2-9 Kanda Tsukasa-cho
Address: Chiyoda-Ku Tokyo
101-8535, Japan
Representative: Dr. Gary Ingenito
Telephone: 203.677.6674

8. DRUG PRODUCT NAME/CODE/TYPE:



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

- a) Proprietary Name: Abilitat (not accepted)
- b) Non-Proprietary Name / USAN [1997]: Aripiprazole
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Schizophrenia

11. DOSAGE FORM: Immediate Release Tablet

12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

SPOTS product – Form Completed

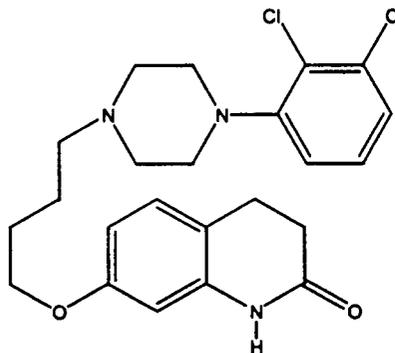
Not a SPOTS product

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

Chemical Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone

Molecular Formula: $C_{23}H_{27}Cl_2N_3O_2$

Molecular Weight: 448.39



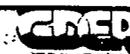
**Number of Pages
Redacted** 1



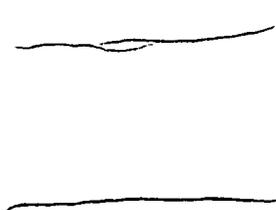
**Confidential,
Commercial Information**



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

	1	Adequate	09-23-99	N/A
	1	Adequate	12-06-01	N/A
	1	Adequate	4-24-00 10-25-99 07-28-00	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)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND		Commercial IND Indication: Treatment of Schizophrenia Sponsor: Otsuka America Pharm
IND		Commercial IND Indication:  Sponsor: Otsuka Pharm

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	10/8/02	N/A
Pharm/Tox	N/A	10/17/01	Lois Freed Ph.D.
Biopharm	N/A	11/20/01	Hong Zhao, Ph.D.
LNC	N/A	N/A	N/A
Methods Validation	Pending	Pending	Sherita McLamore, Ph.D.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

OPDRA	Acceptable (Abilify™)	8/25/02	Charlie Hoppes
EA	N/A	N/A	N/A
Microbiology	N/A	N/A	N/A

The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) perspective, it is recommended that NDA 21-436 be approved.

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

N/A

II. Summary of Chemistry Assessments

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

Aripiprazole is a member of the quinolinone class of compounds and is indicated for the treatment of patients with schizophrenia. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

Aripiprazole was originally investigated under _____ in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15 mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are proportionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with "A-006" and "2" debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular shape tablet with "A-007" and "5" debossed on one side and scored on the other. The 10 mg dosage is a pink, modified rectangular shape tablet with "A-008" and "10" debossed on one



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

side. The 15 mg dosage is a yellow, round tablet with "A-009" and "15" debossed on one side. The 20 mg dosage is a white to pale yellowish white, round tablet with "A-010" and "20" debossed on one side. The 30 mg dosage is a pink, round tablet with "A-011" and "30" debossed on one side. The tablet weights of the 2, 5, 10, and 15 mg tablets are 95.0 mg. The 20 and 30 mg tablets are 189.76 mg and 285.0 mg, respectively. Each of the six strengths are packaged in 95 and 200-cc square, white opaque HDPE bottles, induction heat sealed and capped with a closure. The closures for the 95 and 200 cc bottles are child resistant and non child resistant, respectively. Additionally, each of the six strengths are packaged in aluminum/aluminum cold-form blisters.

The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is $C_{23}H_{27}Cl_2N_3O_2$ and the molecular weight is 448.38. The applicant indicates that the drug substance will be manufactured by Otsuka Pharmaceuticals in Japan.

f

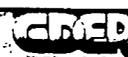
Initially, the applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available. The applicant later proposed the name Abilify. The Division of Medication Errors and Technical Support (DMETS) indicated that there were no objections to the use of Abilify as the proprietary name for Aripiprazole Tablets.

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

Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

The applicant included 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site. In addition to the data submitted from the Japanese site, the applicant included a limited amount of data from the site in Mayaguez, Puerto Rico (CFN 2627673). Upon inspection, the site in Puerto Rico was found unacceptable by the Office of Compliance. As a result, the overall recommendation from OC of withhold was issued for the application. To circumvent this problem, the applicant withdrew the site from the application.

The applicant has requested expiration dating for all potencies of Aripiprazole Tablets in bottles and blisters (amendment dated 5/31/02). The applicant has not provided adequate stability data to . Based on the stability data included in this application, the applicant will be granted a 24 month shelf life for all potencies of the drug product.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-436 is Approved from the Chemistry standpoint. There are no outstanding chemistry, manufacturing and controls issues related to this application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMcLamore/Date
TOliver (TL)/Date
SHardeman (PM)/Date

C. CC Block

Orig. NDA 21-436
HFD-120/Division File
HFD-120/SHardeman
HFD-120/SMcLamore
HFD-120/TOliver

**THIS SECTION
WAS
DETERMINED
NOT
TO BE
RELEASABLE**

7 pages



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

Bristol-Myers Squibb Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5000 Wallingford, CT 06492-7660

October 3, 2002

ABILIFY™ (aripiprazole) Tablets
OPC-14597 (BMS-337039)

Amendment to NDA 21-436

Russell Katz, M.D., Director
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Control Room 4008
HFD-120
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to NDA No. 21-436 for ABILIFY™ (aripiprazole) tablets, which was submitted on October 31, 2001. Additional reference is made to the Agency's approvable letter for this NDA dated August 29, 2002 and our September 18, 2002 response to the approvable letter.

As noted in the Agency's approvable letter, the Bristol drug product manufacturing, packaging, and release testing facility located in Mayaguez, PR (CFN #2627673) was found to be unacceptable by the FDA's Office of Compliance and a satisfactory inspection will be needed if we plan to use this facility for production of Abilify. The purpose of this submission is to notify the Agency of our decision to withdraw the Mayaguez, PR facility from the NDA at this time, without prejudice to refiling the site at a later date, post NDA approval. As noted in the approvable letter, the NDA contains an accepted alternate site of manufacturing, Otsuka, Japan's Iiano manufacturing site, which will supply tablets for the US market.

If there are any additional questions or concerns regarding this submission, please call me at 203-677-6674.

Sincerely,

Charles D. Wolleben, Ph.D.
Director, Regulatory Science



A Bristol-Myers Squibb Company



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

08-OCT-2002

FDA CDER BES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 1 of 3

Application : NDA 21436/000
Org Code : 120
Priority : 1S

Sponsor: OTSUKA PHARM
101
TOKYO, , JA

Stamp Date : 31-OCT-2001
PDUFA Date : 19-NOV-2002
Action Goal :
District Goal: 02-JUL-2002

Brand Name : ABILITAT (ARIPIPRAZOLE)
10MG/15MG/30MG
Etab. Name:
Generic Name: ARIPIPRAZOLE
Dosage Form: (TABLET)
Strength : 2, 5, 10, 15, 20, 30 MG

FDA Contacts: S. HARDEMAN
S. MCLAMORE
T. OLIVER

Project Manager (HPD-120) 301-594-2850
Review Chemist (HPD-810) 301-594-5359
Team Leader (HPD-810) 301-594-2570

Overall Recommendation: ACCEPTABLE on 07-OCT-2002 by J. D AMBROGIO (HPD-324) 301-827-0062
WITHHOLD on 23-AUG-2002 by B. HARTMAN (HPD-324) 301-827-0062

Establishment :

DMF No: _____

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment CFN : 1819504 FEI : 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXPY
EVANSVILLE, IN 477210001

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : 1825662 FEI : 1825662
BRISTOL MYERS SQUIBB CO
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

08-OCT-2002

FDA CDER BES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Page 2 of 3

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No:

Responsibilities: -----

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment :

DMF No:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-01
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI
CTSUKA PHARMACEUTICAL CO LTD
MATSUTANI ITANO-CHO ITANO-GUN
TOKUSHIMA, JA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-JUL-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION



CHEMISTRY REVIEW TEMPLATE



Chemistry Assessment Section

08-OCT-2002

FDA CDER EES

Page 3 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-JUL-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9611255 FEI : 3002807834
OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY
KAWAUCHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-JUL-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment :

DMF No:

Responsibilities:

Profile : TCM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Sherita McLamore
10/22/02 12:51:51 PM
CHEMIST

Thomas Oliver
10/22/02 12:59:06 PM
CHEMIST

**APPEARS THIS WAY
ON ORIGINAL**

Number of Pages
Redacted 3



Draft Labeling
(not releasable)