

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202971Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 19 FEB 2013
FROM: David J. Claffey, PhD
SUBJECT: Approval recommendation for NDA 202-971

A 25 JUL 2012 memo rescinded a previous approval recommendation for this application from a CMC perspective due to a “Withhold” recommendation from CDER OC for the manufacturing site of the drug product’s vial of Sterile Water for Injection (b)(4). In this review cycle the Applicant replaced this manufacturer with (b)(4). This site was found acceptable by CDER OC (b)(4). The cross-referenced DMF was found to be acceptable by prior CMC reviewers and by Microbiology (Dr. Jessica Cole, 19 FEB 2013).

Therefore an approval recommendation can now be made from a CMC perspective for this application.

ATTACHMENT OC Recommendation

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 202971/000	Sponsor:	OTSUKA PHARM
Org. Code:	130		2440 RESEARCH BLVD
Priority:	3		ROCKVILLE, MD 20850
Stamp Date:	26-SEP-2011	Brand Name:	ABILIFY MAINTENA (aripiprazole) for exte
PDUFA Date:	28-FEB-2013	Estab. Name:	
Action Goal:		Generic Name:	aripiprazole extended release suspension
District Goal:	30-DEC-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; INJECTION; ARIPIPRAZOLE; 300MG
			002; INJECTION; ARIPIPRAZOLE; 400MG
FDA Contacts:	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	C. TELE	Team Leader	3017961762

Overall Recommendation:	ACCEPTABLE	(b) (4)	by T. SHARP	()	3017963208
	PENDING		by EES_PROD		
	WITHHOLD		by EES_PROD		
	ACCEPTABLE		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
Profile:	(b) (4)		OAI Status: NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: **CFN:** 3009562680 **FEI:** 3009562680
OTSUKA PHARMACEUTICAL CO LTD
306-2 AZA OTSUBO, KONIU
NAKA-CHO, NAKA-GUN, TOKUSHIMA, JAPAN 771-5209

DMF No: **AADA:**

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

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUL-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9613571 **FEI:** 3003808559
OTSUKA PHARMACEUTICAL CO., LTD.
5006-5 AZA HIGASHIYAMA OMAGARI
YOSHINO GARI-CHO KANZAKI-GUN, SAGA, JAPAN

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAY-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** 9611255 **FEI:** 3002807834
OTSUKA PHARMACEUTICAL CO., LTD. - SECOND TOKUSHIMA FACTORY
224-18 HIRAISHI, EBISUNO
KAWAUCHI, TOKUSHIMA, , JAPAN

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-JUL-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: [REDACTED] FEI: (b) (4)
[REDACTED] (b) (4)

DMF No: [REDACTED] **AADA:** [REDACTED]

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: [REDACTED] (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-JAN-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

DAVID J CLAFFEY
02/19/2013

RAMESH K SOOD
02/19/2013

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 25 JUL 2012

FROM: David J. Claffey, PhD

SUBJECT: **Rescinding** of Approval recommendation for NDA 202-971

A 20 JUL 2012 memo by this reviewer recommended that this application be approved from a CMC perspective. However it has come to light that the manufacturing site for the vial of Sterile Water for Injection (b)(4) which is included in the drug product kit was not entered into EES and was not evaluated by CDER OC in connection with this application. On entering this site into EES on (b)(4), CDER OC found this site to be unacceptable due to observations during a (b)(4) inspection and revised their prior “acceptable” recommendation to “Withhold”.

Therefore this application can **not** be approved from a CMC perspective until CDER OC finds this site to be acceptable.

ATTACHMENT OC Recommendation

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 202971/000	Sponsor:	OTSUKA PHARM
Org. Code:	130		2440 RESEARCH BLVD
Priority:	3		ROCKVILLE, MD 20850
Stamp Date:	26-SEP-2011	Brand Name:	ABILIFY MAINTENA (aripiprazole) for exte
PDUFA Date:	26-JUL-2012	Estab. Name:	
Action Goal:		Generic Name:	aripiprazole extended release suspension
District Goal:	27-MAY-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; INJECTION; ARIPIPRAZOLE; 300MG
			002; INJECTION; ARIPIPRAZOLE; 400MG
FDA Contacts:	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	C. TELE	Team Leader	3017961762

Overall Recommendation:	WITHHOLD		(b) (4) by T. GOOEN	(HFD-320)	3017963257
	ACCEPTABLE		by A. INYARD	(HFD-323)	3017965363
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
			(b) (4)
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE MANUFACTURER	OAI Status:	POTENTIAL OAI
Profile:	(b) (4)		
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JUL-2012		
Decision:	WITHHOLD		
Reason:	DISTRICT RECOMMENDATION		

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/s/

DAVID J CLAFFEY
07/25/2012

RAMESH K SOOD
07/25/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 20 JUL 2012
FROM: David J. Claffey, PhD
SUBJECT: Approval recommendation for NDA 202-971

At completion of the CMC review of this application (22 MAY 2012) an approval recommendation could not be made from a CMC perspective as recommendations from CDER OC and the microbiological reviewer had not yet been finalized.

On 19 JUL 2012 the microbiological reviewer, Jessica Cole, PhD, made an approval recommendation from a microbiological review perspective after the Applicant withdrew the alternative drug substance manufacturing site (b) (4)

On 20 JUL 2012 CDER OC provided an overall acceptable recommendation for the manufacturing sites.

An **approval** recommendation from a CMC perspective can now be made for this application.

ATTACHMENT OC Recommendation

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST DETAIL REPORT

Application: NDA 202971/000
Stamp Date: 26-SEP-2011
Regulatory: 26-JUL-2012

Action Goal:
District Goal: 27-MAY-2012

Applicant: OTSUKA PHARM
 2440 RESEARCH BLVD
 ROCKVILLE, MD 20850

Brand Name: ABILIFY MAINTENA (aripiprazole) for exte
Estab. Name:
Generic Name: aripiprazole extended release suspension

Priority: 3
Org. Code: 130

Product Number; Dosage Form; Ingredient; Strengths
 001; INJECTION; ARIPIPIRAZOLE; 300MG
 002; INJECTION; ARIPIPIRAZOLE; 400MG

Application Comment: (b) (4)
 [REDACTED]

(b) (4) by T.
 INTRAMUSCULAR DEPOT EXTENDED-RELEASE INJECTABLE SUSPENSION FOR
 BOUIE () 3017961649)

FDA Contacts:	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	C. TELE	Team Leader	3017961762

Overall Recommendation:	ACCEPTABLE	(b) (4)	by A. INYARD	(HFD-323)	3017965363
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		
	PENDING		by EES_PROD		

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/s/

DAVID J CLAFFEY
07/20/2012

RAMESH K SOOD
07/20/2012

NDA 202-971

**ABILIFY Maintena
aripiprazole for extended release injectable suspension**

Otsuka Pharmaceuticals Inc

**David J. Claffey, PhD
ONDQA**

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A categorical exclusion was claimed as the proposed product is intended as an alternative to daily administration for patients already stabilized on aripiprazole. Additionally, the expected introduction concentration (EIC) of aripiprazole at the point of entry to the aquatic environment is calculated to be (b) (4). This is based on a projection of production (b) (4) per day of water entering publicly owned treatment works in the US.	187
Evaluation: This is adequate as the EIC is less than 1 ppb and the proposed product is a replacement to the daily oral tablets.....	187



III. List Of Deficiencies To Be Communicated.....188

Chemistry Review Data Sheet

1. NDA: 202-971
2. REVIEW #: 1
3. REVIEW DATE: 21 MAY 2012
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 67,380
NDA 21-436

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original (N-000)
Amendment N-0001
Amendment N-005
Amendment (stability update) N-0017
Amendment N-020 (response to IR)
Amendment N-0023 (kits)

Document Date

26 SEP 2012
14 OCT 2012
10 NOV 2012
22 MAR 2012
10 MAY 2012
15 MAY 2012

7. NAME & ADDRESS OF APPLICANT:

Name:

Otsuka Pharmaceutical Co., Ltd

Chemistry Review Data Sheet

Address: 2-9 Kanda Tsukasa-cho, Chiyado-ku Tokyo, Japan

Representative: Otsuka, Rockville, MD

Telephone:

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN): Aripiprazole Monohydrate
- c) Code Name/# (ONDC only): OPC-14597H2O
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 2
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Maintenance Treatment of Schizophrenia

11. DOSAGE FORM: Extended Release Injectable Suspension

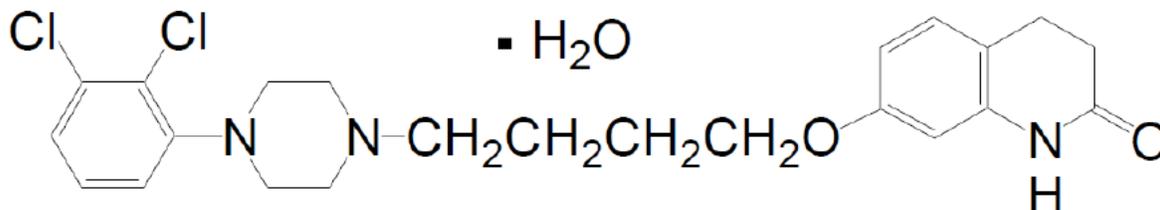
12. STRENGTH/POTENCY: 300 mg/vial and 400 mg/vial (strength expressed in terms of anhydrous aripiprazole).

13. ROUTE OF ADMINISTRATION: Intramuscular

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

Chemistry Review Data Sheet

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

**Molecular Formula**C₂₃H₂₇Cl₂N₃O₂ · H₂O**Molecular Weight**

466.40

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)		Otsuka	(b) (4)	1	Adequate	9 MAR 2012	
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	9 MAR 2012	

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

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Pending		
LNC	N/A		
Methods Validation	N/A		
OPDRA			
EA	N/A		
Microbiology	Pending		

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes ___ No If no, explain reason(s) below:

The Chemistry Review for NDA 202-971

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An approval recommendation can not be made from a CMC perspective at this time as recommendations from CDER OC and the microbiological reviewer have not yet been received. A separate memo will be filed on receipt of these recommendations.

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)

Drug Substance: The drug substance is sterile aripiprazole monohydrate. The equivalent non-sterile anhydrous polymorphic form is marketed in aripiprazole tablets.

(b) (4)

Drug substance for the commercial product will be manufactured at a (b) (4) sites, Otsuka, Japan (b) (4). Details of the process at the Otsuka site were provided in this application. Details of manufacturing at the (b) (4) site are referenced to DMF (b) (4) (found to be adequate). The clinical lots were manufactured at a different site (b) (4); however batch analysis data were comparable. Aripiprazole monohydrate is manufactured from the (b) (4) anhydrous aripiprazole. Details of the manufacture of the latter are cross referenced to NDA for aripiprazole tablets. The ensuing manufacturing steps to sterile aripiprazole monohydrate drug substance involve (b) (4)

(b) (4)

Executive Summary Section

The drug substance specification contains tests and acceptance criteria typical of an injectable suspension. [REDACTED] (b) (4)

Stability studies are underway on three lots of drug substance manufactured at each commercial site. Data through 18 months (30°C/65%RH) was provided from material produced at the [REDACTED] (b) (4) site and through six months from the Otsuka site. Similarly, data through six months under accelerated conditions from each site were provided. Data supported the proposed “expiry periods” of three years and one year, respectively (30°C/65%RH).

DRUG PRODUCT: It is proposed to market the drug product as part of a kit containing either 300 mg/vial or 400 mg/vial of aripiprazole [REDACTED] (b) (4) of drug substance together with CMC [REDACTED] (b) (4). (Note that the strength is expressed in terms of anhydrous aripiprazole.)

The drug product is intended to be administered [REDACTED] (b) (4) *via* gluteal injection. Its extended-release characteristics depend most critically on the drug product [REDACTED] (b) (4)

[REDACTED] (b) (4)

Product labeling also includes instructions on achieving a 200 mg strength by administering 1.0 ml rather than 1.5 ml of the suspension from the 300 mg/vial product.

The excess volume of [REDACTED] (b) (4) is stated to be for vial, vial adapter, needle and syringe loss to deliver 1.5 ml (300 mg/vial strength) or 2.0 ml (400 mg/vial strength). The drug product kit will include the diluent in a vial containing 2 ml of Water for Injection along with two needles (1.5” and 2.0”), two syringes (one for reconstitution and one for administration) and a vial adapter.

The drug product vial [REDACTED] (b) (4) is manufactured at Otsuka Pharmaceuticals, Tokushima Wajiki site, Japan. [REDACTED] (b) (4)

Executive Summary Section

(b) (4)

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

As is stated above, the drug product will be marketed in two strengths (300 and 400 mg/vial) as a kit which includes a vial (b) (4) drug substance and excipients, a vial of diluent, two needles (1.5" and 2.0"), two syringes (one for reconstitution and one for administration) and a vial adapter. It requires reconstitution in a specified volume of the provided diluent (SWFI) and is intended to be administered (b) (4) *via* gluteal injection. It is intended to be administered 'immediately' after reconstitution. Drug product expiry period is 36 months while being stored below 30°C while avoiding freezing.

C. Basis for Approvability or Not-Approval Recommendation

On receipt of an acceptable recommendation from CDER OC and an approval recommendation from the microbiological reviewer, an approval recommendation from a CMC perspective can be made based on the CMC data provided in this application and the adequate response to the (b) (4) information request. DMF (b) (4) for Sterile Aripiprazole Monohydrate and DMF (b) (4) for the SWFI vial were found to adequately support this application.

III. Administrative

Executive Summary Section

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

David Claffey: Same date as draft review
Ramesh Sood
Kimberly Updegraff

C. CC Block

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/s/

DAVID J CLAFFEY
05/22/2012

RAMESH K SOOD
05/22/2012

Initial Quality Assessment

Office of New Drug Quality Assessment Division of New Drug Quality Assessment I

OND Division: Division of Psychiatry Products
NDA: **202-971**
Applicant: Otsuka Pharmaceutical Company, Ltd.
NDA Filing Category: 505(b)(1)
Letter Date: 26-SEP-11
Stamp Date: 26-SEP-11
PDUFA Date: 26-JUL-12
Proposed Trade Name: Abilify[®] Sociell[™]
Established Name: aripiprazole
Dosage Form: Suspension for Injection (Extended-release)
Strengths: 300 mg/Vial and 400 mg/Vial
Route of Administration: Intramuscular Depot
Indication: Maintenance treatment of schizophrenia
Assessor: **Chhagan G. Tele, Ph.D.**
ONDQA Fileability: Yes

SUMMARY AND CRITICAL ISSUES:

Summary

The applicant submitted this NDA under section 505(b)(1) in an e-CTD format seeking approval for Aripiprazole monohydrate Extended-release Suspension for Injection (Intramuscular Depot). Aripiprazole is a dopamine-serotonin system stabilizer discovered by Otsuka Pharmaceutical Company and co-developed with Bristol-Myers Squibb. Aripiprazole is a second generation antipsychotic, currently available in tablet (Otsuka NDA 21-436, approved November 15, 2002 for the treatment of schizophrenia), oral solution (Otsuka NDA 21-713, approved December 10, 2004 for the treatment of schizophrenia), orally disintegrating tablet (Otsuka NDA 21-729, approved June 7, 2006 for the treatment of schizophrenia), and injectable formulation (NDA 21-866, approved September 20, 2006 for the treatment of agitation associated with schizophrenia or bipolar I disorder). Clinical rationale provided by the applicant for the development of an aripiprazole IM depot formulation is its proven efficacy and established safety/tolerability profile of a once-monthly treatment. Aripiprazole monohydrate Extended-release Suspension for Injection (300 mg/Vial and 400 mg/Vial) was developed for the maintenance treatment of schizophrenia under IND 67,380 (13-MAY-2003). Two CMC specific meetings have been held with the sponsor prior to submission of the NDA. The first was an End of Phase 2 meeting held on 09-SEP-2009 to discuss the designation of sterile aripiprazole monohydrate as part of the drug product manufacturing process, particle size distribution, (b) (4) dissolution profiles between the (b) (4) drug substance and drug product specifications, and stability protocols and dissolution testing methodology. The second was Pre-NDA CMC specific meeting held on 09-MAY-2011 to discuss the proposed dissolution method, quantitation of amorphous material in the drug product, proposal of not including the maximum injection force, the suspension viscosity, particle morphology, delivery volume of drug product, and the amorphous limit test in the drug product release. Discussion relevant to product packaging (kit) was also held with DMEPA and CDRH for the device information requirements. Pre-NDA meeting with the clinical division (07-JUN-2011) was held to discuss the development of Aripiprazole monohydrate Extended-release Suspension for Injection for the maintenance treatment of schizophrenia. Minutes of these meetings can be found in DARRTS and should be read by the reviewer. The reviewer needs to bridge the agreements evolved from these meetings in the application. The applicant provided Quality Overall Summary in the submission.

Drug Substance

Aripiprazole monohydrate is a white to off-white (b) (4) Its structure has been confirmed by (b) (4) structure analysis. (b) (4). The commercial sterile aripiprazole monohydrate drug substance will be manufactured, quality tested, released, and packaged by Otsuka Pharmaceutical Co (Tokushima, Japan) (b) (4). Otsuka, Tokushima factory is the same facility that has been used to manufacture aripiprazole (b) (4) drug substance in NDA 21-436 for Abilify® tablets (approved 15-NOV-02). The applicant referred DMF (b) (4) submitted by drug substance manufacturing facility (b) (4). Letter of Authorization is provided in the submission, DMF (b) (4) will need to be reviewed and found adequate to support NDA. Sterile aripiprazole monohydrate is manufactured (b) (4) drug substance of which manufacturing process is referenced to NDA 21-436 for Abilify tablets. The (b) (4) process for sterile aripiprazole monohydrate is essentially similar to (b) (4) of anhydrous aripiprazole (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Product

Aripiprazole Intramuscular (IM) Depot is a sterile, single-dose, lyophilized cake for reconstitution, extended-release injectable suspension to deliver 300 mg of aripiprazole in 300-mg/vial strength and 400 mg of aripiprazole in 400-mg/vial strength. The commercial formulation is comprised of Sterile Aripiprazole Monohydrate (active, in-house), Carboxymethylcellulose Sodium USP, Mannitol USP, Sodium Phosphate, Monobasic, Monohydrate, USP, Sodium Hydroxide NF, (b) (4) and Water for Injection, USP. No novel excipients are commonly used in the formulation. None of the excipients are of human or animal origin. The applicant provided pharmaceutical and manufacturing process development studies to achieve required scale up, dissolution profile, and content uniformity. The assigned reviewer needs to review in detail about these studies for the compatibility and robust manufacturability of the drug product.

Aripiprazole IM Depot (300 mg/vial and 400 mg/vial) will be manufactured and bulk packaged at the Otsuka Pharmaceutical Co., Ltd., Tokushima Wajiki Factory, Naka-gun, Tokushima 771-5209, Japan facility (b) (4) for the final packaging operation of Aripiprazole IM Depot vial and convenience kit. Convenience kits for both

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Critical Issues for Review

- The NDA applicant references DMF (b) (4) for the manufacturing information on sterile aripiprazole monohydrate. DMF (b) (4) will need to be evaluated and found acceptable to support this NDA.
- (b) (4)
- The reviewer needs to evaluate the provided information whether desired (b) (4) is controlled and assured by the established manufacturing process.
- The compatibility of the excipients used in the drug product will need to be evaluated.
- The adequacy of the dissolution method and specification limits will need to be determined in conjunction with the ONDQA biopharm reviewer.
- Need to evaluate data of the agglomeration of aripiprazole hydrate as a function of time and how such agglomeration could impact drug product dissolution and in vivo performance.
- Stability data (i.e., 18 months accelerated and 6 months long-term data) is provided in the NDA submission for three production batches of the drug product manufactured at Otsuka packaged in commercial configuration and commercial packaging. The reviewer needs to request updated stability data by mid-cycle before the PDUFA date to confirm the expiry period of 3 years.
- The reviewer need to evaluate the acceptability of the data of maximum injection force required for administering the dose, suspension viscosity, morphology of the aripiprazole (b) (4), and deliverable volume included in the Pharmaceutical Development section.
- Need to evaluate the rationale of the applicant for not controlling the amorphous content of the drug product at release and on stability.
- In the proposed labeling, the reviewer needs to confirm consistency in chemical structure, chemical name, molecular formula, and molecular weight of the drug substance with the current USP dictionary and USAN in the Description section of the labeling. Additionally, reviewer need to confirm that all the excipients used in the drug product formulation are included.

Comments and Recommendation:

The NDA is fileable from a CMC perspective. NDA submission does not have QbD elements (no design space, PAT, RTRT, reduced end-product testing etc.). However, it does contain an extensive pharmaceutical development section. NDA submission contains no nanoscale materials.

A claim for categorical exclusion under 21 CFR §25.31 (b) is provided in Module 1. In accordance with 21 CFR §25.31, Otsuka Pharmaceutical claims a categorical exclusion [25.31(a)] from the requirement for an Environmental Assessment or Environmental Impact Statement as approval of the drug product will not increase the use of the active moiety. In addition, the applicant states that to the best of their knowledge, no extraordinary circumstances exist that would preclude this claim for categorical exclusion.

The list of manufacturing, testing, and packaging sites for drug substance and drug product is provided to enter into EES. The PM submitted all testing, packaging, and manufacturing sites into EES. The reviewer will need to confirm that these sites are correct and that there are no additional sites that need to be entered. Assignment of the CMC portion of the NDA to a single reviewer is recommended. The ONDQA Biopharmaceutics team has been consulted for review of the dissolution method and specification (Biopharm reviewer: Dr. Zedong Dong). It is recommended that the microbiology staff be consulted for evaluation of the microbiological controls. Clinical PM was requested to request consult for the device (KIT) reviewer from CDRH.

**CHEMISTRY, MANUFACTURING, AND CONTROLS
FILING CHECKLIST FOR A NEW NDA**

NDA Number: 202-971	Applicant: Otsuka Pharmaceutical Company, Ltd.	Stamp Date: 26-SEP-11
Drug Name: Aripiprazole monohydrate Extended-release Suspension for Injection (IM Depot)	NDA Type: Standard	Filing Meeting:

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

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

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __ Yes__

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

Chhagan G. Tele, Ph.D.
CMC Lead, DNDQA I, ONDQA

28-OCT-11
Date

Ramesh Sood, Ph.D.
Branch Chief, DNDQA I, ONDQA

Date

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

/s/

CHHAGAN G TELE
10/28/2011
IQA

RAMESH K SOOD
10/28/2011