

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207533Orig1s000

CHEMISTRY REVIEW(S)

NDA 207533
Review #1 Addendum

ARISTADA
Aripiprazole Lauroxil Injectable Suspension, Extended-Release

Alkermes, Inc.

Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Products
for
Division of Psychiatry Products

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Chemistry Review Data Sheet

1. NDA: 207533
2. REVIEW: 01 Addendum
3. REVIEW DATE: 01-OCT-2015
4. REVIEWER: Wendy Wilson-Lee, Ph.D. (Drug Product)
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Review #1	22-APR-2015

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	02-JUL-2015
Amendment	26-JUN-2015
Amendment	12-JUN-2015
Amendment	15-MAY-2015

7. NAME & ADDRESS OF APPLICANT:

Name:	Alkermes, Inc.
Address:	852 Winter Street Waltham, MA 02451-1420
Representative:	Georgianna Harris
Telephone:	781-609-6336

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	ARISTADA
b) Non-Proprietary Name (USAN):	Aripiprazole Lauroxil
c) Code Name/# (ONDQA only):	ALKS 9072; RDC-3317
d) Chem. Type/Submission Priority (ONDQA only):	
• Chem. Type:	1
• Submission Priority:	Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2)¹
10. PHARMACOL. CATEGORY: Quinolinone-derived atypical anti-psychotic
11. DOSAGE FORM: Injectable Suspension, Extended-Release
12. STRENGTH/POTENCY: 441 mg, 662 mg, 882 mg

¹ The OPQ primary review filed on April 22, 2015 erroneously listed the legal basis for this submission as 505(b)(1).

Executive Summary Section

13. ROUTE OF ADMINISTRATION: Intramuscular

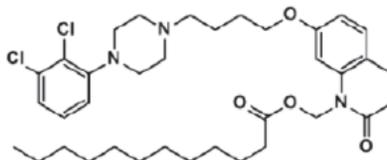
14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

Chemical Name: 7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl)methyl dodecanoate

Molecular Formula: C₃₆H₅₁Cl₂N₃O₄

Molecular Weight: 660.71



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	REVIEW DATE	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	02-MAR-2015	
	III			4	N/A		
	III			4	N/A		
	IV			4	N/A		
	III			1	Adequate	21-APR-2015	
	V			1	Adequate	27-MAR-2015	
	V			1	Adequate	15-APR-2015	

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)

Executive Summary Section

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107249	Aripiprazole lauroxil
Site Master File	Sharp Corporation	Labeling, (b) (4) Packaging
510(k)	(b) (4)	(b) (4)
510(k)	(b) (4)	(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
Facilities	Approval	7-JUL-2015	Rose Xu
Pharm/Tox	N/A	-	-
Biopharm	Approval	18-JUN-2015	Elsbeth Chikale
LNC	N/A	-	-
Methods Validation	Pending		Michael Trehy
DMEPA	N/A	-	-
Environmental Assessment	Categorical exclusion granted	20-APR-2015	Wendy Wilson-Lee
CDRH	Approval	9-JUL-2015	Ryan McGowan
Microbiology	Approval	7-AUG-2015	Vinayak Pawar

Chemistry Review Addendum for NDA 207533

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

The OPQ recommended action for NDA 207533 is approval.

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

None

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

ARISTADA (aripiprazole lauroxil) is a (b) (4) white to off-white, (b) (4), extended-release suspension provided as a single-use, 5 mL pre-filled syringe combination product in dosage strengths of 441 mg, 662 mg, and 882 mg. In vivo, aripiprazole lauroxil undergoes a two-step bioconversion to aripiprazole, through N-hydroxymethyl aripiprazole. The first step is de-esterification. Both in vitro and in vivo, aripiprazole lauroxil is known to be de-esterified via hydrolysis (likely enzymatic in nature) to N-hydroxymethyl aripiprazole, its alcohol component, and lauric acid (dodecanoic acid), its carboxylic acid component. In step two, the N-hydroxymethyl aripiprazole metabolite is likely non-enzymatically cleaved through water-mediated hydrolysis to aripiprazole and formaldehyde.² The (b) (4) vehicle (b) (4) contains sorbitan monolaurate (b) (4), polysorbate 20 (b) (4), sodium chloride (b) (4) and Water for Injection, USP (WFI). **Based on the stability data and in accordance with ICH Q1E, we grant a 27 month shelf-life for ARISTADA when stored at the recommend storage condition in the commercial container closure.**

Aripiprazole lauroxil is a new molecular entity. Aripiprazole lauroxil is an ester of N-hydroxymethyl aripiprazole. N-hydroxymethyl aripiprazole is the active moiety in the drug product³. It is an (b) (4) white to off-white solid. (b) (4)

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

Aripiprazole lauroxil is indicated for the treatment of schizophrenia. ARISTADA will be administered every 4 – 6 weeks⁴ by a health care professional in a clinical setting as an intramuscular injection by either the deltoid (441 mg) or gluteal route (442 mg, 662 mg, and 882 mg). The drug product is supplied as a kit containing the pre-filled syringe and safety needles. The single-use syringe consists of a (b) (4) syringe fitted with a (b) (4) cap and plunger. The 441 mg strength kit contains a 1-inch 21 gauge needle, a 1½-inch 20 gauge needle, and a 2-inch 20 gauge needle. The 662 mg and 882 mg strength kits each contain a 1½-inch 20 gauge needle and 2-inch 20 gauge

² Description of in vivo conversion updated based on final review of information in submission.

³ The OPQ primary review filed on April 22, 2015 erroneously identified aripiprazole as the active moiety. The active moiety in Aristada is N-hydroxymethyl aripiprazole, consistent with the definition provided in 21 CFR 314.108(a). See Dr. Norman Schmuff's memo regarding the active moiety determination for aripiprazole lauroxil (NDA 207533).

⁴ Dosing schedule updated from previous review based on final determination of recommended dosing by DPP.

Executive Summary Section

needle. ARISTADA should be stored at USP controlled room temperature. The product requires resuspension via tapping and shaking prior to administration.

C. Basis for Approvability or Not-Approval Recommendation

The OPQ recommended action is approval based on adequate responses to the deficiencies noted in the product quality discipline review letter, an overall acceptable facilities recommendation, and approval recommendations from the OPQ review team members (See Section 18 of the Chemistry Review Data Sheet). A pending methods validation report does not impact the OPQ approval recommendation because the results only serve as confirmation that the proposed analytical procedures are appropriate for their intended use. Our review of the submitted descriptions of the analytical procedures and accompanying method validation information serves as the basis for our approval recommendation. Any suggested revisions to the proposed regulatory analytical procedures will be communicated to the applicant post-approval, if noted by the FDA Labs.

Wendy I.
Wilson -S

Digitally signed by Wendy I.
Wilson -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
396790, cn=Wendy I. Wilson -S
Date: 2015.10.01 11:49:43 -04'00'

Wendy I. Wilson-Lee, Ph.D.
Drug Product Primary Reviewer
Branch Chief (Acting), Branch 1
DNDP1/ONDP/OPQ

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=200055
8826
Date: 2015.10.01 11:58:54 -04'00'

Olen Stephens, Ph.D.
Secondary Reviewer
Branch Chief (Acting), Branch 2
DNDP1/ONDP/OPQ



CHEMISTRY REVIEW



Executive Summary Section

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments**
Sterility	Process, container closure integrity, (b) (4)	High	(b) (4)	Low	
Endotoxins	Drug substance source, process, container integrity	Medium		Low	
Assay	Process testing, inhomogeneity	Low		Low	
Potential genotoxic impurities	Drug substance, process, proposed deletion of tests	Medium		Low	(b) (4)
Physical stability (solid state)	Process, storage	Low		Low	
Dose uniformity	Filling, container, formulations, prevention of factors that may block needles (e.g. agglomeration)	Medium		Low	
Content uniformity	Process, filling, intermediate storage	Medium		Low	
Osmolality	Formulation, process	Low		Low	



CHEMISTRY REVIEW



Executive Summary Section

From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking*	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments**
pH	Formulation, storage	Low	(b) (4)	Low	
Particle size distribution	Process	Medium		Low	
Particulate matter	Process, storage	Medium		Low	
Leachables/extratables	Container	Medium		Low	(b) (4)
Re-dispersability	Formulation, process	High		Low	
Dissolution	Formulation, stability	High		Low	
Appearance (color)	Formulation, drug substance/excipient interactions or degradation	Low		Low	
Device Functionality	n/a	n/a		Human factors studies demonstrate device functions as designed and delivers the intended dose; End product testing for break loose force and glide force at release and on stability	Low

Chemistry Assessment

A Product Quality Discipline Review Letter issued on 29-APR-2015 outlined the following requests for information to address deficiencies noted during the review:

1. Revision of the drug product post-approval stability protocol
2. Justification for the proposed (b) (4) hold time for the bulk (b) (4) drug substance
3. Justification for the proposed drug product shelf-life
4. Submission of executed batch records for the drug product registration stability batches
5. Revision of the drug product dissolution acceptance criteria
6. Definition of (b) (4) and (b) (4)
7. Justification and supporting data for the defined design space for (b) (4)
8. Evidence of suitable product performance when the syringe contents are (b) (4)
9. Updated drug product photostability results
10. Revision of the SPL data elements for the kit and pre-filled syringe

The applicant adequately addressed the deficiencies (May 15, 2015 and June 12, 2015 amendments). In the July 2, 2015 amendment, the applicant also revised the specification and analytical procedures for (b) (4) adding an assay test (NLT (b) (4) %). In the May 15, 2015 amendment, Alkermes also committed to include in the NDA annual reports results from the on-going stability analysis to assess the mechanical reliability of the fully assemble device over the shelf-life, as requested by CDRH.

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S DRUG SUBSTANCE [Aripiprazole Lauroxil, (b) (4)]

Revised (b) (4) Specification

The applicant revised the (b) (4) specification, as requested, to include a test for assay. The proposed acceptance criterion is NLT (b) (4) %. The (b) (4) used for (b) (4) will be used to determine assay. The applicant provided method validation results to support use of the (b) (4) for assay determination.

Evaluation: Adequate – The applicant commits to re-evaluating (b) (4) assay criterion after six batches. The method validation included specificity, linearity, accuracy, precision, stability, and robustness. Based on the method validation results, the (b) (4) is appropriate for use for assay determination.

Revised Threshold for Toxicological Concern (TTC)

The applicant revised the TTC for potentially genotoxic impurities as part of the July 2, 2015 amendment as well. The new TTC that impurity content will be evaluated against is (b) (4) ppm based on ICH M7.

Evaluation: Adequate – The revised TTC reflects the TTC from the nonclinical team.

NDA 207533

Aripiprazole Lauroxil Injectable Suspension

P**DRUG PRODUCT [Aripiprazole Lauroxil Injectable Suspension, Alkermes]****1. Revision of the drug product post-approval stability protocol**

The applicant revised the drug product post-approval stability protocol to include testing at accelerated conditions (b) (4) and to include testing (b) (4) at long-term conditions (b) (4)

Evaluation: Adequate – Section 3.2.P.8.2 of the submission was updated to reflect the revision (see Appendix 1 for final post-approval stability protocol).

2. Justification for the (b) (4) hold time for the bulk (b) (4) drug substance

(b) (4)

Evaluation: Adequate – (b) (4)

(b) (4)

(b) (4)

3. Justification for the proposed drug product shelf-life

The applicant agreed to a 27 month drug product shelf-life.

Evaluation: Adequate – (b) (4)

4. Submission of executed batch records for the drug product registration stability batches

The applicant provided executed batch records for Lots 453-0020, 453-0021, and 453-0018.

Evaluation: Adequate – Section 3.2.R.1 was updated with the EBRs.

5. Revision of the drug product dissolution acceptance criteria

The applicant agreed to the revised dissolution specification based on (b) (4) % acceptance criterion.

Evaluation: Adequate – See the Biopharmaceutics Review Addendum for additional information (June 18, 2015, Elsbeth Chikale). Sections 3.2.P.5.1, 3.2.P.5.6, and 3.2.P.8.3 of the submission reflect the revised dissolution criteria. See Appendix 2 for the final regulatory drug product specification.

6. Definition of (b) (4) and (b) (4),,

(b) (4)

Evaluation: Adequate.

7. Justification and supporting data for the defined design space for (b) (4)

The applicant confirmed that the submission did not include a proposal for a design space as defined by ICH Q8. (b) (4) The applicant confirmed that any changes to the (b) (4) will be evaluated via the change management procedure and reported to the Agency prior to implementation.

Evaluation: Adequate.

8. Evidence of suitable product performance when the syringe contents are (b) (4)

The applicant referenced product development studies included in the submission (Report 702-03392) that investigated potential failure modes (b) (4). The impact of (b) (4) dose delivery for both the 882 mg and 441 mg strength prefilled syringes were evaluated as part of these studies. The results showed that (b) (4) had no impact on product performance, (b) (4) had no impact of product performance, and (b) (4) had no impact on product performance.

Evaluation: Adequate – The development studies demonstrate that the product is suitable for use, irrespective of (b) (4).

9. Updated drug product photostability results

The applicant provided updated photostability results that compared the quality attributes for exposed and dark controls samples. The quality attributes tested included description, assay, impurities (total and specified), dissolution, in vitro initial release, break loose force, glide force, particle size distribution, pH, and (b) (4) content.

Evaluation: Adequate – The data was comparable across test conditions. (b) (4)

NDA 207533

Aripiprazole Lauroxil Injectable Suspension

10. Revision of the SPL data elements for the kit and pre-filled syringe

The applicant revised the SPL data elements to denote that the product is a combination product containing a pre-filled syringe.

Evaluation: Adequate.

Revised Drug Product Justification of Specifications

The applicant included a commitment to evaluate the impact of any future formulation or process changes proposed on the formation of (b) (4). Sections 3.2.P.5.2.3.2 and 3.2.P.5.6.2.1 were updated to reflect this commitment (b) (4) will be reported as supportive information for post-approval changes only).

Evaluation: Adequate – This revision is aligned with the guidance provided as part of the late-cycle meeting and supports removal of a drug product specification test for (b) (4)

Overall Microbiology Recommendation

Dr. Vinayak Pawar recommended approval on August 8, 2015. (refer to Product Quality Microbiology review).

Overall Facilities Recommendation

The overall facilities recommendation is approve (July 7, 2015).

The screenshot displays the 'Overall Manufacturing Inspection Recommendation' form within the CDER Manufacturing Facility Inspection system. The form is titled 'Overall Manufacturing Inspection Recommendation' and includes a 'Task Summary' tab. The main content area shows a list of inspection items with details such as the facility name, product name, and approval dates. The items listed are:

- ALKERMES CONTROLLED THERAPEUTICS II | 1000142940 | OXA DEVICE KIT ASSEMBLER | Approve facility - 2015-08-22 - (b) (4)
- ALKERMES CONTROLLED THERAPEUTICS II | 1000142940 | SVS STERILE FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility - 2016-08-15 - (b) (4)
- (b) (4) CTL CONTROL TESTING LABORATORY | Approve Facility - 2016-09-26 - (b) (4)
- (b) (4) SVS STERILE FILLED SMALL VOLUME PARENTERAL DRUGS | Approve Facility - 2016-01-15 - (b) (4)

Below the list, there is a section for 'Overall Manufacturing Inspection Recommendation' with radio buttons for 'Approve' (selected) and 'Withhold'. The 'Overall Application Re-evaluation Date' is set to 8/22/15. On the right side, there is a sidebar with 'Assigned To' information for Ruo (Rose) Xu, who is the 'OPF Reviewer'. It shows that the task was completed on Jul 7, 2015, and the status is 'Complete'. The reference number is 2055621.

Labeling

The June 26, 2015 amendment included revised commercial and sample syringe labels, carton labels, and instructions for use as requested by DMEPA (June 11, 2015 Information Request).

Evaluation: Adequate – There are no needed revision to the syringe or carton labels from a CMC perspective. Any edits to the IFU or PI will be communicated through the division's labeling comments.

Appendix 1 – Drug Product Post-Approval Stability Protocol
(copied from submission)

Table 1: Study Design in Support of First Three Production Batches

--

(b) (4)

Appendix 2 – Drug Product Specification
(copied from submission)

Table 1: Proposed Specifications for Commercial Product

Attribute ^a	Test Method	Proposed Acceptance Criteria	Test Category		
Description	Visual	Syringe Package: Colorless plastic syringe with a gray rubber plunger and tip cap free from visual defects Product: White to off-white suspension	R, S		
Identification #1	HPLC	Retention time of sample corresponds to retention time of standard	R		
Identification #2	FTIR	Spectrum of the sample corresponds to spectrum of standard	R		
Uniformity of Dosage Units – Content Uniformity	HPLC	Meet USP <905>	R		
Dose Delivery Assay (Label Claim)	HPLC	(b) (4) % of Label Claim	R, S		
Impurities	HPLC	Total Impurities: NMT (b) (4) % Individual Impurities: NMT (b) (4)	R, S		
Dissolution	HPLC	Dose	R, S		
		441 mg		Sampling Time	% Drug Dissolved
				6 hr	(b) (4)
				24 hr	
				96 hr	
		662 mg		6 hr	
				24 hr	
				96 hr	
		882 mg		6 hr	
				24 hr	
				96 hr	
		Particle Size Distribution		Laser Diffraction	Dv[10]: NMT (b) (4) μm Dv[50]: (b) (4) μm Dv[90]: NMT (b) (4) μm
Break Loose Force	Compressive Force	NMT (b) (4) N	R, S		
Glide Force	Compressive Force	NMT (b) (4) N	R, S		
pH	pH	(b) (4)	R		
Osmolality	Osmolality	(b) (4) nOsm/kg	R		
Bacterial Endotoxins	LAL	441 mg Dose: NMT (b) (4) EU/mL 662 mg Dose: NMT (b) (4) EU/mL 882 mg Dose: NMT (b) (4) EU/mL	R, S		
Sterility	Sterility	No evidence of microbial growth	R, S		

^a Note: full descriptions of the methods listed in the above table are provided in Section 3.2.P.5.2. NMT = not more than; N/A = not applicable; R = at release; S = on stability.

NDA 207533

ARISTADA

**Aripiprazole Lauroxil Injectable Suspension, Extended-Release
(One Month Injection)**

Alkermes, Inc.

**Sherita McLamore-Hines, Ph.D.
Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Products
for
Division of Psychiatry Products**

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Chemistry Review Data Sheet

1. NDA: 207533
2. REVIEW: 01
3. REVIEW DATE: 22-APR-2015
4. REVIEWER: Sherita McLamore-Hines, Ph.D. (Drug Substance)
Wendy Wilson-Lee, Ph.D. (Drug Product)

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	-

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	10-APR-2015
Amendment	01-APR-2015
Amendment	13-MAR-2015
Amendment	06-MAR-2015
Amendment	02-FEB-2015
Amendment	19-DEC-2014
Amendment	25-NOV-2014
Original	22-AUG-2014

7. NAME & ADDRESS OF APPLICANT:

Name:	Alkermes, Inc.
Address:	852 Winter Street Waltham, MA 02451-1420
Representative:	Georgianna Harris
Telephone:	781-609-6336

8. DRUG PRODUCT NAME/CODE/TYPE:

- | | |
|---|-----------------------|
| a) Proprietary Name: | ARISTADA |
| b) Non-Proprietary Name (USAN): | Aripiprazole Lauroxil |
| c) Code Name/# (ONDQA only): | ALKS 9072; RDC-3317 |
| d) Chem. Type/Submission Priority (ONDQA only): | |
| • Chem. Type: | 1 |
| • Submission Priority: | Standard |

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

Executive Summary Section

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	107249	Aripiprazole lauroxil
Site Master File	Sharp Corporation	Labeling, (b) (4) Packaging
510(k)	(b) (4)	(b) (4)
510(k)	(b) (4)	(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Pending		
DMEPA	N/A		
EA	Categorical exclusion granted	20-APR-2015	W. Wilson-Lee
Microbiology	Pending		

Chemistry Review for NDA 207533

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 207533 can be approved, from a CMC perspective, pending labeling, resolution of the outstanding deficiencies (bulk hold stability, post-approval stability protocol) and information requests (clarification of terms) along with completion of the facilities inspections and reviews by the biopharmaceutics and CMC-microbiology team.

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

None

II. Summary of Chemistry Assessments

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

ARISTADA (aripiprazole lauroxil) is a (b)(4), white to off-white, (b)(4), extended-release suspension provided as a single-use, 5 mL pre-filled syringe combination product in dosage strengths of 441 mg, 662 mg, and 882 mg. Aripiprazole lauroxil is a covalently bonded modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. *In vivo* conversion of aripiprazole lauroxil to aripiprazole is governed by slow dissolution of the drug particles followed by hydrolysis, resulting in extended systemic exposure of aripiprazole. The (b)(4) vehicle ((b)(4)) contains sorbitan monolaurate (b)(4), polysorbate 20 (b)(4), sodium chloride (b)(4) and Water for Injection, USP (WFI).

Aripiprazole lauroxil is a new molecular entity and is the active pharmaceutical ingredient in this application. It is (b)(4) and is presented as a white to off-white solid. (b)(4)

Based on the stability data provided in the submission and in accordance with ICH Q1E, we assign a 27 month drug product expiry for ARISTADA when stored at the recommend storage condition in the commercial container closure.

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

Aripiprazole lauroxil is indicated for the treatment of schizophrenia. ARISTADA will be administered once monthly by a health care professional in a clinical setting as an intramuscular injection by either the deltoid (441 mg) or gluteal route (442 mg, 662 mg, and 882 mg). The drug product is supplied as a kit containing the pre-filled syringe and safety needles. The single-use syringe components consist of a (b)(4) syringe fitted with a (b)(4) cap and plunger. The 441 mg strength kit contains a 1-inch 21 gauge needle, a 1½-inch 20 gauge needle, and a 2-inch 20 gauge needle. The 662 mg and 882 mg strength kits each contain a 1½-inch 20 gauge needle and a 2-inch 20 gauge

Executive Summary Section

needle. ARISTADA should be stored at USP controlled room temperature. The suspension requires resuspension via tapping and shaking prior to administration.

C. Basis for Approvability or Not-Approval Recommendation

NDA 207533 can be approved, from a CMC perspective, pending labeling, resolution of the outstanding deficiencies (bulk hold stability, post-approval stability protocol) and information requests (clarification of terms) along with completion of the facilities inspections and reviews by the biopharmaceutics and CMC-microbiology team.

III. Administrative

Sherita D. Mclamore -A

Digitally signed by Sherita D. Mclamore -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=1300148713,
cn=Sherita D. Mclamore -A
Date: 2015.04.22 12:01:02 -04'00'

Wendy I.
Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300396790,
cn=Wendy I. Wilson -S
Date: 2015.04.22 12:28:39 -04'00'

Olen
Stephens -S

Digitally signed by Olen Stephens -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Olen Stephens -S,
0.9.2342.19200300.100.1.1=2000558
826
Date: 2015.04.22 12:34:46 -04'00'

NDA 207533

Aripiprazole Lauroxil Injectable Suspension

Chemistry Assessment

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data

S DRUG SUBSTANCE [Aripiprazole Lauroxil, (b) (4)]

Aripiprazole Lauroxil is a new molecular entity and is the active pharmaceutical ingredient in this application. The applicant includes all relevant information pertaining to the manufacture and control of this drug substance in the application.

S.1 General Information

S.1.1 Nomenclature

Chemical Name: 7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl)methyl dodecanoate

USAN Name: Aripiprazole Lauroxil

INN: n/a

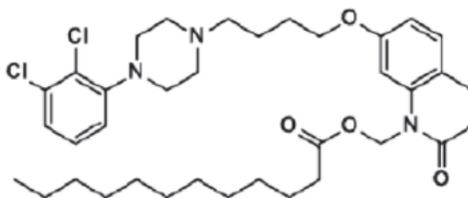
CAS No: 1259305-29-7

Code No: ALKS 9072, RDC-3317

S.1.2 Structures

Molecular Formula: $C_{36}H_{51}Cl_2N_3O_4$

Molecular Weight: 660.71



S.1.3 General Properties

This drug substance is a (b) (4) white to off-white solid with a molecular formula $C_{36}H_{51}Cl_2N_3O_4$ of and a molecular mass of 660.71. (b) (4)

(b) (4) The drug substance solubility profile is included below in tables 1 and 2.

Table 1: Drug Substance Aqueous Solubility Profile

(b) (4)

(b) (4)

Table 2: Drug Substance Solubility in Organic Solvents

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Aripiprazole Lauroxil Injectable Suspension

Solvent	Concentration, mg/mL	Solubility Description
(b) (4)		

Evaluation: Adequate

The applicant has provided adequate general information (i.e. names, structure, molecular formula, molecular weight, physico-chemical properties) about the drug substance. The information provided pertaining to the general description of the drug substance is sufficient to support this application. ^{(b) (4)}

S.2 Manufacture

S.2.1 Manufacturers

Manufacturing, in-process, packaging, release and stability testing of the drug substance will be performed by:

Name:	(b) (4)	
Address:		
Phone:		
Fax:		
Facility Establishment Identifier:		
DUNS:		

The commercial drug substance will be manufactured, packaged, stability and released tested by ^{(b) (4)} The site was entered into the EES system in December of 2014 and the recommendation is pending. . .

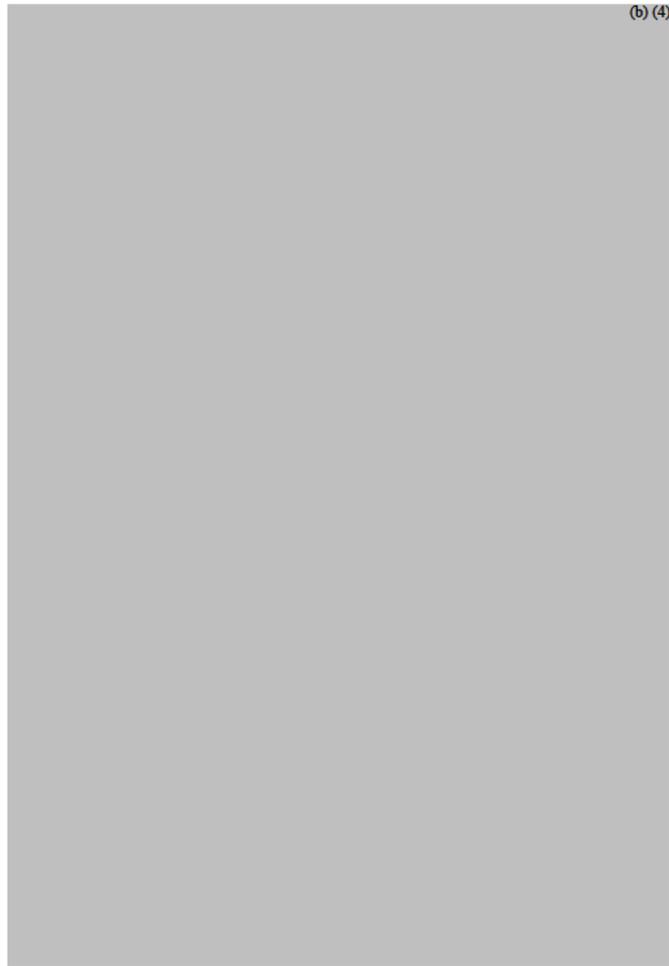
S.2.2 Description of Manufacturing Process and Process Controls

The drug substance is ^{(b) (4)} The flow diagram of the manufacturing process for the drug substance is reproduced below.

Diagram 1: Flow Diagram of the Drug Substance

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Aripiprazole Lauroxil Injectable Suspension

Figure 1: Manufacturing Process Overview**Evaluation:** *adequate*

The applicant has provided a detailed description of the each of the steps involved in the synthesis of the drug substance (b) (4)



The sponsor referenced in DMF (b) (4) for the manufacture and control of Aripiprazole (LoA 6/23/14) and includes specifications for (b) (4) from an approved supplier. DMF (b) (4) was reviewed in conjunction with this NDA and was found acceptable to support its approval.

Figure: Drug Substance (b) (4)

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(b) (4) Oil Injectable Suspension



S.2.3 Control of Materials

The materials used in the manufacture of the drug substance are included in the table below.



CHEMISTRY REVIEW TEMPLATE

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Aripiprazole Lauroxil Injectable Suspension

Table: Aripiprazole Specifications

No.	TESTS	REQUIREMENTS	METHODS	METHOD No
1.	Appearance	a white to off-white, crystalline powder	visual examination	
2.	Identification: - IR spectrum - HPLC	(b) (4)	USP <197K> USP	M/2-0113.24 M/2-0113.24
3.	Assay calculated on the dried basis (HPLC)	(b) (4)	USP	M/2-0113.24
4.	Residue on ignition	not more than (b) (4)%	USP <281>	M/2-0113.24
5.	Heavy metals	not more than (b) (4)ppm	USP <231> Method II	M/2-0113.24
6.	Organic impurities (b) (4)	not more than (b) (4)% not more than % not more than % not more than %	USP	M/2-0113.24
7.	Chromatographic purity (method II) (b) (4)	not more than (b) (4)% not more than % not more than % not more than %	(b) (4)	M/2-0113.17
8.	Loss on drying	not more than (b) (4)%	USP <731>	M/2-0113.24
9.	Residual solvents (b) (4)	not more than (b) (4) ppm not more than ppm	(b) (4)	M/2-0113.20
10.	Residual solvents (b) (4)	not more than (b) (4) ppm	(b) (4)	M/2-0113.22
11.	Bacterial endotoxins ²	less than (b) (4) /mg	USP	<65>
12.	Particle size ³	for information	(b) (4)	M/2-0113.19
13.	Microbiological purity ^{3b, 4} - total aerobic microbial count (TAMC) - total combined yeasts/moulds count (TYMC)	not more than (b) (4) fu /g not more than fu /g	USP	<61>
14.	Microbiological purity ^{3b} - total aerobic microbial count (TAMC) - total combined yeasts/moulds count (TYMC)	not more than (b) (4) fu /g not more than fu /g	USP	<61>

(b) (4)

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Aripiprazole Lauroxil Injectable Suspension

Table:

(b) (4) Specification

(b) (4)

**Evaluation:** *adequate*

The applicant has provided test methods and specifications to control the quality of each of the starting materials and reagents used in the manufacture of the drug substance. With the exception of (b) (4) and (b) (4) each of the materials included in the table above are commonly used and readily available. The specifications for (b) (4) are the same as those found in the referenced DMF. The specification for (b) (4) is devoid of an acceptance criterion for assay. The specifications for all other reagents and starting materials are adequate to control the quality of the referenced material. While the specifications are adequate to control the quality of each of the referenced material, the applicant has not provided certificates of analyses for these materials. The applicant was asked to update the (b) (4) specification to include a test for assay and to provide certificates of analyses for each of the reagents and starting materials used in the manufacture of the drug substance (see response below).

Comment 6 from Agency's 2/23/2014 IR Letter:

Provide representative certificates of analyses for all starting materials and reagents used in the manufacture of the drug substance.

Applicant's Response included in 3/23/2015 Amendment:

The applicant included the requested information and referenced DMF (b) (4) for starting materials and reagents used to manufacture Aripiprazole. The information provided is adequate to support the approval of this NDA.

Comment 7 from Agency's 2/23/2014 IR Letter:

Update the specification for (b) (4) to include a test for assay.

Applicant's Response included in 3/23/2015 Amendment:

The applicant agreed to update the specification for (b) (4) to include a test for assay with an acceptance criterion of NLT (b) (4)%. The applicant indicates that the specification will be (b) (4) after 6 batches have been analyzed a the revised specification will be submitted to the agency in the form of

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a CBE-0 supplement. The applicant response is acceptable; however, was advised that (b) (4) the specification for (b) (4) is an annual reportable change.

S.2.4 Controls of Critical Steps and Intermediates

(b) (4)



S.2.5 Process Validation and/or Evaluation

Complete validation for aripiprazole lauroxil at production scale has been carried out using the following three successive batches: 101031228, 102031228 and 101051228. Validation for aripiprazole lauroxil at pilot plant scale has been carried out using the following three successive batches: 11111/P2, 21111/P2 and 31111/P2. All batches were manufactured via the commercial process at the intended commercial site (b) (4). Release and stability data have been provided for all batches. In all cases specification is met and the data from the batch analyses demonstrate that the drug substance can be manufactured in a manner that yields results that are reproducible and within the proposed specification limits. The process validation reports include a description of the manufacturing process including CPP, yields, batch sizes, test methods and equipment qualification documents.

S.2.6 Manufacturing Process Development

The CQAs for the drug substance are identified as appearance, identity, purity and microbiological purity (see table below).

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Aripiprazole Lauroxil Injectable Suspension

CQA	Attribute	CQA Rationale
Yes	Appearance	Aripiprazole lauroxil is a white to off-white solid. No other variations in appearance have been observed so this attribute is deemed critical to quality.
Yes	Identification	Identification is critical to quality.
No	(b) (4)	(b) (4)
No	(b) (4)	(b) (4)
Yes	Purity	(b) (4)
No	(b) (4)	(b) (4)
No	(b) (4)	(b) (4)
No	(b) (4)	(b) (4)
Yes	Microbiological purity	(b) (4)

Process development for the drug substance included (b) (4). The processes are defined as (b) (4) (commercial process). (b) (4) differ (b) (4). Comparisons of the processes are included in the scheme below.

Figure: Process Comparison Overview

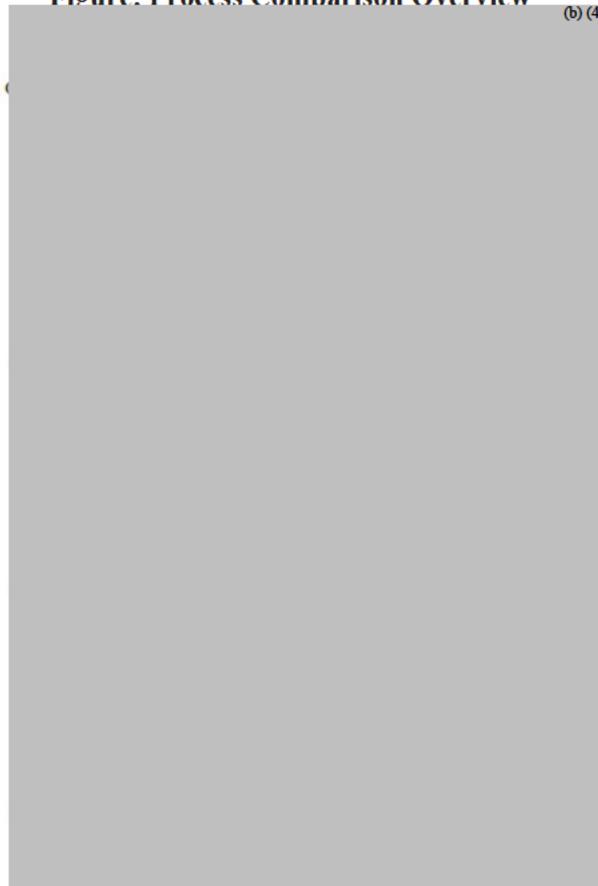


Table: Summary of Process modifications

Step	Description	(b) (4)	Rationale	Benefit
(b) (4)				

Table: Batch History of Process Development

Batch Number	Mfg. Site (Date)	Process	Scale (kg)	Use
26191-D-10-001	(b) (4)	A	(b) (4)	Nonclinical
60254-10-003	(b) (4)	A	(b) (4)	Phase 3 Clinical Nonclinical
10411	(b) (4)	B	(b) (4)	Nonclinical
11111/P2	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (pilot plant scale)
21111/P2	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (pilot plant scale)
31111/P2	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (pilot plant scale)
41111/P2	(b) (4)	B	(b) (4)	Phase 3 Clinical
51111/P2	(b) (4)	B	(b) (4)	Development
10212	(b) (4)	B	(b) (4)	Phase 3 Clinical
20212	(b) (4)	B	(b) (4)	Development
101031228	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (production scale)
102031228	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (production scale)
101051228	(b) (4)	B	(b) (4)	Phase 3 Clinical Primary Stability (production scale)
101071328	(b) (4)	B	(b) (4)	To be used for Development and Clinical Supply
101081328	(b) (4)	B	(b) (4)	To be used for Development and Clinical Supply

Evaluation: adequate

The changes outlined in the manufacturing process during development were very minor. The primary changes were employed to (b) (4)

(b) (4) During the process development, CPPs and CQAs were defined and established. The manufacturing process changes did not impact the purity profile of the final product. Impurities are removed during the manufacturing process or controlled within the finished product specifications.

The applicant has provided detailed information pertaining to the manufacturing process development. The information provided allows the reviewer to follow the evolution of the manufacturing process and understand the rationale behind each of the changes. The reviewer is also able to link the pre-clinical batches and the clinical batches to the exact process that was used to for manufacture. The information provided pertaining to the manufacture process development is complete and adequate to support this application.

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Aripiprazole Lauroxil Injectable Suspension

S.3 Characterization**S.3.1 Elucidation of Structure and other Characteristics****Structure Elucidation**

Batch 11111/P2 was used for all structure elucidation studies.

Elemental Analysis: C, H, N analyses (b) (4) was consistent with the theoretical tabulated data for C₃₆H₅₁Cl₂N₃O₄.

NMR Studies: NMR studies were performed in (b) (4) ¹³C NMR and ¹H NMR spectra and tabulated signal assignments are provided and are consistent with the proposed API molecular structure.

High Resolution Mass Spectroscopy: (b) (4)

FT-IR: (b) (4)

Evaluation: adequate

Batch 11111/P2 was used for structure elucidation studies. The drug substance has been described as a white to off-white solid (b) (4). The applicant includes the following characterization information as evidence of the chemical structure of the drug substance: elemental analysis, mass spectra, ¹H NMR, ¹³C NMR, and IR. The results from the various spectral analyses clearly confirm the molecular weight, functional groups and atom connectivity. All data presented were in accordance with the proposed structure. (b) (4)

The information provided pertaining to the characterization of the drug substance is acceptable and adequate to support the approval of this NDA.

S.3.2 Impurities

(b) (4)
The impurities (type and origin) are included in the table below which been reproduced from the application.

Table: Drug Related Impurities Observed in Aripiprazole Lauroxil

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(b) (4)



Evaluation: *adequate*

Related Substances

The structure and origins of the impurities are included in the table above.

(b) (4)



(b) (4)



(b) (4)

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Aripiprazole Lauroxil Injectable Suspension

(b) (4)

Residual Metals

(b) (4)

Results from the twelve batches manufactured to date clearly demonstrate the consistency of the manufacturing process that there is no risk or concerns with residual metal impurities in the drug substance.

(b) (4)



(b) (4)

**S.4 Control of Drug Substance****S.4.1 Specification**

There is no USP monograph for the drug substance. The drug substance specification is included in the table below which has been reproduced from the application.

Table: Drug Substance Specification

Test	Analytical Method	Acceptance Criteria
Description/Appearance	Visual Examination	White to off-white solid
Identification	IR Spectrum, USP <197>, M/2-0184.06 (b)(4)(HPLC), M/2-0184.11	(b)(4)
Assay	M/2-0184.11 (HPLC)	(b)(4)%
Chromatographic Purity Specified known impurities: (b)(4) Individual unidentified impurity Total Impurities	M/2-0184.11 (HPLC)	NMT (b)(4)% NMT % NMT % NMT % NMT % NMT % NMT % NMT % NMT %
Residue on Ignition	USP <281>	NMT (b)(4)%
Residual solvent: (b)(4)	M/2-0184.02 (GC)	NMT (b)(4) ppm
Bacterial Endotoxins	USP <85>	NMT (b)(4) EU/mg
Microbial limits Total aerobic microbial count Total combined yeast and molds count	USP <61>	NMT (b)(4) cfu/g NMT (b)(4) fu/g

Evaluation: adequate

The specification for the drug substance include tests and acceptance criteria for appearance by visual examination, assay by HPLC, identity by IR and HPLC, residue on ignition, heavy metals, impurities by HPLC, residual solvent (b)(4) by GC, bacterial endotoxins and microbial limits. The drug substance specification is consistent with ICH Q6A.

S.4.2 Analytical Procedures

The drug substance is a NME as such there is no USP monograph. The applicant includes a complete description of the analytical procedures for each of the tests. The description of the procedures includes the principle, reagents, equipment, evaluation, assessment and sample spectra where applicable.

Appearance: Determined by visual examination

Assay, Identification and Chromatographic Purity by HPLC: (b)(4)

(b)(4)

(b)(4)

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Aripiprazole Lauroxil Injectable Suspension

(b) (4)

Identification by IR: Determined by IR spectroscopy as per USP <197>

Residue on Ignition: Determined in accordance with USP <281>

Residual Solvent:

(b) (4)

Bacterial Endotoxins: Determined in accordance with USP <85>

Microbial Limit Testing: Determined in accordance with USP <61>

(b) (4) Content:

(b) (4)

(b) (4) Content:

(b) (4)

Evaluation: *adequate*

The proposed methods are appropriate for the proposed determinations. The applicant employs standard methodologies for the assays and residual solvent. Microbial limits, identification, bacterial endotoxin and residue on ignition all utilize compendial methods and the applicant references the appropriate USP chapters for each of these tests.

S.4.3 Validation of Analytical Procedures

Table: Assay, Identification and Purity by HPLC

Test	Determination of the Assay, Identification and Purity by HPLC	
Acceptance Criteria	Assay	(b) (4) %
	(b) (4)	NMT (b) (4)
		NMT %
Unspecified impurities	NMT	%
Total Impurities	NMT	

<p>Method</p>	<p align="right">(b) (4)</p>								
<p>Evaluation</p>	<p>Method validation for the determination of the assay, identification and purity of the drug substance by <i>HPLC</i> is provided herein. The validation of this method include sample preparation as well as the following validation characteristics: specificity, linearity, range, accuracy, precision, detection and quantitation limits, robustness and system suitability testing. The validation covered varying parameters such as the flow rate and column packing material in an effort to determine optimal running conditions and system suitability. The method is appropriate for the determination of the identity, assay and purity of the drug substance because of the following: 1) it ensures the identity of the analytes; 2) it is sensitive; 3) all components and degradants are well resolved from the each other; 4) the method is stability indicating (see sample chromatogram below).</p> <table border="1" data-bbox="467 1570 1295 1707"> <thead> <tr> <th>Validation Parameters</th> <th>Results</th> </tr> </thead> <tbody> <tr> <td>Limit of Quantitation (LOQ)</td> <td align="center">(b) (4)</td> </tr> <tr> <td>Limit of Detection (LOD)</td> <td align="center">(b) (4)</td> </tr> <tr> <td>Robustness</td> <td align="center">Demonstrated</td> </tr> </tbody> </table>	Validation Parameters	Results	Limit of Quantitation (LOQ)	(b) (4)	Limit of Detection (LOD)	(b) (4)	Robustness	Demonstrated
Validation Parameters	Results								
Limit of Quantitation (LOQ)	(b) (4)								
Limit of Detection (LOD)	(b) (4)								
Robustness	Demonstrated								
<p>Deficiencies</p>	<p>None</p>								

Table: Determination of the Residual Solvents

<p>Test</p>	<p>Residual Solvents by GC</p>
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Aripiprazole Lauroxil Injectable Suspension

Acceptance Criterion	(b) (4) NMT (b) (4) ppm				
Equipment	(b) (4)				
Method	(b) (4)				
Evaluation	<p>Method validation for the solvents by GC is provided in section 3.2.S.4.2. The validation of this method included the following characteristics: accuracy, precision, linearity, repeatability, specificity and system suitability test. While only (b) (4) is specified in the drug product specification, the method was used to quantify (b) (4).</p> <p>The LoQ and LoD for each of these solvent are included below</p> <table border="1" data-bbox="472 814 1349 1171"> <tr> <td data-bbox="472 814 743 993">Limit of Quantitation (LOQ)</td> <td data-bbox="743 814 1349 993">(b) (4)</td> </tr> <tr> <td data-bbox="472 993 743 1171">Limit of Detection (LOD)</td> <td data-bbox="743 993 1349 1171">(b) (4)</td> </tr> </table>	Limit of Quantitation (LOQ)	(b) (4)	Limit of Detection (LOD)	(b) (4)
Limit of Quantitation (LOQ)	(b) (4)				
Limit of Detection (LOD)	(b) (4)				
Deficiencies	None				

Evaluation: adequate

The applicant provided method validation for the following non-compendial methods: determination of the identity, assay and impurities by HPLC and the determination of residual solvents by GC. The methods do not include sample spectra; however, the applicant did include the RRT for the impurities. Accordingly, the information pertaining to the method validation is adequate to support this application.

S.4.4 Batch Analyses

Evaluation: adequate

The applicant provided batch analyses for thirteen batches of each drug substance (8 pilot scale and 5 commercial scale). The batch sizes ranged from (b) (4) kg. Twelve of the thirteen batches were manufactured at the proposed manufacturing site ((b) (4)) and one batch was manufactured at (b) (4). All results were within the prescribe specification limit. The batch numbers, use, size and site of manufacture are included in the table below. The results for each of these batches are included in the tables in section S.4.1 in the electronic submission.

Table: Batch Analyses Summary

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Aripiprazole Lauroxil Injectable Suspension

Batch Number	101031228	102031228	101051228	101071328	101081328				
Batch Size	(b) (4)								
Date of Manufacture	March 28, 2012	March 29, 2012	May 9, 2012	July 10, 2013	August 3, 2013				
Site of Manufacture	(b) (4)								
Use	Ph 3 Clinical Supplies, Primary Stability		Ph 3 Clinical Supplies, Primary Stability		Ph 3 Clinical Supplies, Primary Stability		To be used for Development and Clinical Supply		To be used for Development and Clinical Supply
Batch Number	60254-10-003	11111/P2	21111/P2	31111/P2	41111/P2	51111/P2	10212/P2	20212/P2	
Batch Size	(b) (4)								
Date of Manufacture	Sept 28, 2010	Nov 8, 2011	Nov 12, 2011	Nov 15, 2011	Nov 18, 2011	Nov 21, 2011	Feb 10, 2012	Feb 11, 2012	
Site of Manufacture	(b) (4)								
Use	Ph 3 Clinical Supplies	Ph 3 Clinical Supplies, Primary Stability	Ph 3 Clinical Supplies, Primary Stability	Ph 3 Clinical Supplies, Primary Stability	Ph 3 Clinical Supplies	Development	Ph 3 Clinical Supplies	Development	

S.4.5 Justification of Specification

Justification was provided for the following acceptance criteria: appearance, identification, assay, impurities, residue on ignition, residual solvents, microbial limits. Justification was also provided for the following tests (b) (4)

Appearance: Qualitative test which describes the visual appearance of the drug substance. The acceptance criterion is based on batch history and is consistent with a purity of at least (b) (4) %.

Identification: The identification is based on (b) (4) of the drug substance compared to that of the reference standard. The identity is determined via two methods as per ICH Q6A and provides unambiguous identification of the active.

Assay: Acceptance criterion was set based on manufacturing process capability and stability data and is consistent with industry standard.

Residue on Ignition: Based on USP <281> for residue on ignition requirement is consistent with industry standard.

Bacterial Endotoxins: Based on USP <85> for bacterial endotoxin requirements is consistent with industry standard.

Microbial Limits: Based on USP <61> for microbial limit requirements is consistent with industry standard.

Residual Solvents: (b) (4)

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Ariniprazole, Lauroxil Injectable Suspension

Batch #	(b) (4)
11111/P2	(b) (4)
21111/P2	
31111/P2	
41111/P2	
51111/P2	
10212/P2	
20212/P2	
101031228	
102031228	
101051228	
101071328	
101081328	
Manufacturing Step	
Class	

^{100%} values are the Limit of Detection

The acceptance criterion for (b) (4) was set according to ICH requirements. While this limit is not consistent with the manufacturing capabilities, it is consistent with ICH limits. (b) (4)

The information provided is acceptable and justifies the proposed residual solvent specifications.

Impurities: The applicant indicates that the specified impurities have been identified (b) (4). As such, based on a daily intake of less than (b) (4) ng/day, the limits for the specified impurities were set at NMT (b) (4)% based on ICH Q3A. Similarly, the acceptance criteria for the unspecified impurities were set at NMT (b) (4)%. The proposed levels are consistent with the ICH Q3B(R) identification and qualification limits at the maximum daily dose. Stability data demonstrate that the levels of the impurities do not increase over time. The reviewer notes that the release data for the impurities supports the proposed acceptance criteria for all impurities except impurity (b) (4).

Accordingly, the specification for (b) (4) and all other specified impurities is acceptable. The acceptance criterion for the total impurities is based on the manufacturing history and capability and variability of the drug substance impurity content. This proposed limit is also acceptable.

(b) (4)

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Aripiprazole Lauroxil Injectable Suspension

A total of twelve GMP lots have been manufactured, validated and placed in the stability protocol: seven (b) (4) kg pilot scale and five (b) (4) kg commercial scale. The proposed regulatory specifications were largely based on the stability results, manufacturing process capability and the established regulatory limits. The applicant has provided adequate justification for the inclusion and exclusion of the tests included in the drug substance specification.

S.5 Reference Standards or Materials

Reference Standard	Standard Number
Aripiprazole Lauroxil	2711/13.01
(b) (4)	(b) (4)

Table: Aripiprazole Lauroxil Reference Standard (Batch 2711)

TEST	SPECIFICATION	RESULTS
Appearance		(b) (4)
Identification		
IR spectrum		
Assay		
Chromatographic purity (HPLC)		
Impurity (b) (4)		
Impurity		
other single unidentified impurity (listed by RRT)		
total impurities		
Water		
(b) (4)		
Heavy metals		
(b) (4)		
Residual solvents (GC)		
(b) (4)		
Potency of standard substance		

Internal working standard established from batch 11111/P2.

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Table: (b) (4) Reference Standard

Test	Results
(b) (4)	

Table: (b) (4) Reference Standard

Test	Results
(b) (4)	

Evaluation: adequate

The drug substance reference standard is designated as batch 2711. Batch #2711 is an aliquot from batch 11111/P2. (b) (4) were used in the method for the determination of assay and impurities. As such, the applicant has provided reference standards for these compounds as well. The information provided pertaining to the reference standards is adequate to support approval of this application.

S.6 Container Closure System

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The drug substance is packaged into (b) (4). The applicant includes a complete description of the (b) (4) including CFR references, manufacturer, COAs, dimensions and composition components. The applicant includes representative label, an analytical certificate for the (b) (4) and a declaration of conformity with EU directives.

(b) (4) **Specifications:**

No.	PARAMETERS	REQUIREMENTS
1.	(b) (4)	
2.	(b) (4)	
3.	(b) (4)	
4.	(b) (4)	
5.	(b) (4)	

Evaluation: *adequate*

The applicant has provided a complete description of the container that will be used to store and ship the drug substance. (b) (4)

The applicant will be asked to provide additional information to support the use of the aforementioned container closure system.

Comment 8 from Agency's 2/23/2014 IR Letter:

Provide a description of the (b) (4) container closure systems.

Applicant's Response included in 3/23/2015 Amendment:

(b) (4)
The applicant's response is adequate to support approval of this application.

S.7 Stability

S.7.1 Stability Summary and Conclusions

The applicant includes 24 months of long term and six months of accelerated stability data for three pilot scale (batch number 11111/P2, 21111/P2 and 31111/P2) and three production scale (101031228, 102031228 and 101051228) batches of aripiprazole lauroxil. The pilot scale batches were approximately (b) (4) kg and the commercial scale batches ranged between (b) (4) kg. All batches were manufactured at (b) (4) according to the commercial process. The pilot scale batches were manufactured in late 2011 and the commercial scale batches were manufactured in early 2012. All six batches were packaged in packaging which simulates the commercial container closure system (i.e. (b) (4) and tested for appearance, assay, impurities, (b) (4) content and bacterial endotoxins (performed annually). In addition to the primary data, the applicant also included results from forced degradation and photostability studies. The forced degradation studies included testing under (b) (4) conditions. Photostability samples were assessed on lot 101031228 according to Option 1 of ICH Q1B (i.e. (b) (4) and packaged in (b) (4). Samples were tested for description, assay and impurities. A summary of the stability data is included below.

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Table: Stability Conditions and Time points

Condition	Temperature	Relative humidity	Test Period	Test Frequency (months)
Accelerated	40°C ± 2°C	(b) (4)	6 months	0, 1, 3, 6
Intermediate ^a	30°C ± 2°C		12 months	0, 6, 9, 12
Long-term	25°C ± 2°C		36 months	0, 1, 3, 6, 9, 12, 18, 24, 36

^a If called for as a result of significant change at accelerated conditions, 4 time points (e.g., 0, 6, 9, 12) are required.

Table: Stability Batches

API Batch (Link to Stability Study)	Manufacturing Date	Batch Size (kg)	Stability Study No.	Stability Interval Submitted
11111/P2	Nov. 8, 2011	(b) (4)	SJ/BS/097/1	Nov. 28, 2011 – Nov. 28, 2013
21111/P2	Nov. 12, 2011		SJ/BS/097/1	Nov. 28, 2011 – Nov. 28, 2013
31111/P2	Nov. 15, 2011		SJ/BS/097/1	Nov. 28, 2011 – Nov. 28, 2013
101031228	March 28, 2012		SJ/BS/097/1	April 4, 2012 – April 4, 2014
102031228	March 29, 2012		SJ/BS/097/1	April 4, 2012 – April 4, 2014
101051228	May 9, 2012		SJ/BS/097/1	May 17, 2012 – May 17, 2014

The results of the primary stability studies demonstrate that the drug substance can be stored for up to (b) (4) months under long term conditions as no stability trends were observed and no new impurities were observed. Based on the results of the primary stability studies the applicant has proposed a minimum retest period of (b) (4) months.

S.7.2 Post approval Stability Protocol and Stability Commitment

The post approval stability program is included below in the table below which has been reproduced from the application.

Table 24: Post Approval Stability Plan

(b) (4)	
---------	--

(b) (4)

As such the proposed post-approval stability plan is acceptable.

S 7.3 Stability Data

The drug substance stability data is summarized below.

Proposed Storage Condition: (b) (4)

Proposed Test Intervals: (b) (4)

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(b) (4)

Proposed Test: appearance, assay, impurities, water content, (b) (4) content and bacterial endotoxins (performed annually)

Packaging (primary): (b) (4).

Appearance:

After 24 months under long term and 6 months under accelerated conditions, the result for all batches remained the same (off white solid).

Water Content:

There were no increases or stability trends observed in the water content. The results for the water content remained under long term and accelerated conditions.

Assay:

The assay results ranged from (b) (4) % for all batches under all conditions. All values were acceptable and within the prescribed specification with no stability trend observed.

Drug Related Impurities:

There were no new impurities and no increases in the individual any of the specified or unspecified for any of the batches under either storage condition. The total impurities ranged from (b) (4) % with no stability trends observed. The reviewer notes that the acceptance criteria included for each of the specified impurities and for the single unidentified impurity in the stability table is NMT (b) (4) %. The applicant was advised that the release and stability specification for the drug substance must be congruent (see comment and response below).

Comment 9 from Agency's 2/23/2014 IR Letter:

The acceptance criterion for each of the specified impurities and for the single unidentified impurity in the stability table is NMT (b) (4) %. The acceptance criteria for each of the specified impurities and for the single unidentified impurity in the drug substance specification are NMT (b) (4) % and NMT (b) (4) %, respectively. Be advised that release and stability specification for the drug substance must be congruent. As such we request that you provide a consolidated specification table with release and stability limits.

Applicant's Response included in 3/23/2015 Amendment:

The applicant confirms that the acceptance criteria for each of the specified impurities and for the single unidentified impurity are NMT (b) (4) % and NMT (b) (4) % as indicated in the drug substance specification. The applicant notes that the values included in the stability section were the values that were used in the phase 3 study. The applicant's response is adequate to support approval of this application.

(b) (4) Content:

The (b) (4) content ranged from (b) (4) ppm with no increases noted under any storage condition.

Bacterial Endotoxins :

Bacterial endotoxins are tested annually and all results were within the prescribed specification limits for all batches.

Force Degradation:

Results not include.

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Comment 9 from Agency's 2/23/2014 IR Letter:

Provide the results of the forced degradation studies

Applicant's Response included in 3/23/2015 Amendment:

The applicant provided the results of the degradation pathway together with the results of the forced degradation studies which were conducted under the conditions outlined in the table below.

DEGRADATION CONDITION	TEMP (°C)	TIME POINTS	METHOD VERSION
(b) (4)			

(b) (4)

(b) (4)

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(b) (4)



Evaluation: adequate

At the time tested under accelerated and long term conditions there were no stability trends observed for any of the six primary stability lots. The assay and water content remained virtually unchanged and there were no new impurities or increases in impurity levels for any of the batches. The applicant has proposed a (b) (4) month retest period for the drug substance. Based on the data presented from the primary and accelerated stability studies and what is known about the mechanism of degradation from the forced degradation studies, the reviewer feels that the applicant has provided sufficient data to support the proposed (b) (4) month re-test date as there are no stability trends observed and no imminent potential risks.

P DRUG PRODUCT [Aripiprazole Lauroxil Injectable Suspension, Alkermes]

P.1 Description and Composition of the Drug Product

Component	Function	Amount per Unit Dose Strength					
		mg			% w/w		
		441 mg	662 mg	882 mg	441 mg	662 mg	882 mg
(b) (4) aripiprazole lauroxil	Active pharmaceutical ingredient	441	662	882			(b) (4)
Sorbitan Monolaurate	(b) (4)	(b) (4)					
Polysorbate 20	(b) (4)	(b) (4)					
Sodium Chloride	(b) (4)	(b) (4)					
Sodium Phosphate Dibasic Anhydrous	(b) (4)	(b) (4)					
Sodium Phosphate Monobasic	(b) (4)	(b) (4)					
Water for Injection	(b) (4)	(b) (4)					
Total per unit dose strength							
Total volume per unit dose strength							-
Total weight in pre-filled syringe							-
Total volume in pre-filled syringe							-

Evaluation: Adequate – (b) (4)



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Aripiprazole Lauroxil Injectable Suspension

The drug product will be available in three strengths: 441 mg, 662 mg, and 882 mg. (b) (4)

The drug product is supplied as a kit containing the pre-filled syringe and safety needles. (b) (4)

The drug product is recommended for administration by health care professionals in a clinical setting only and is not intended for at home or self-administration.

P.2 Pharmaceutical Development

P.2.1 Components of the Drug Product

P.2.1.1 Drug Substance

Attributes	Property
Appearance	White to off-white
Melting Point	(b) (4)
Solubility*	
Hygroscopicity	
Polymorphism	
Particle Size Distribution*	
Surface Area*	
Sterility*	

*Considered critical quality attribute by reviewer

P.2.1.2 Excipients

Excipient	Regulatory Standard	Maximum Amount in Product	Approved Amount/Route/Dosage Form	Qualified for Use
Sorbitan Monolaurate	NF	(b) (4)	(b) (4)	Yes, based on p/t review of supporting nonclinical data
Polysorbate 20	NF			Yes, based on similar route of administration
Sodium Chloride	USP			Yes, based on similar route of administration
Sodium Phosphate, Dibasic Anhydrous	USP			Yes
Sodium Phosphate, Monobasic	USP			Yes
Water for Injection	USP			Yes
				(b) (4)
			Yes, complies with ICH Q3C	

P.2.2 Drug Product

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Aripiprazole Lauroxil Injectable Suspension

Target Product Profile (TPP)	Quality Target Product Profile (QTPP) ^a	Target QTPP ^a	Quality Attributes Identified	Critical Quality Attributes (CQAs) chosen to quantify QTPP ^b
Delivery, Efficacy, Safety	Dosage Form	Single use intramuscular injection suspension in a prefilled syringe individually packaged to ensure container closure integrity	Aspect Sterility	Aspect Sterility
Efficacy, Safety	Identity	Positive for active	Identity	Identity
Efficacy, Safety, Delivery	Dosage strength	441, 662 & 882 mg dose strength	Dose Delivered Content Uniformity	Dose Delivered
Efficacy, Safety	Patient Exposure	Consistent drug product when injected monthly intramuscularly	(b) (4)	
Efficacy, Safety	Impurities	Meets ICH guidelines or qualified	Impurities Particulate matter	Impurities
Safety	Tolerability	Consistent local and systemic responses	pH Osmolality Endotoxins Drug Product Particle size distribution	pH Osmolality Endotoxins
Delivery, Safety	Device Mechanical Reliability	Syringe and needle that reliably delivers required label claim	Break loose force Glide force	Break loose force Glide force

^a The QTPP is a quantitative surrogate for aspects of clinical safety and efficacy used to design and optimize the manufacturing process. It includes quantitative targets for impurities, stability, release profile (dissolution) and ease of use.

^b The defined CQAs are a list of physical, chemical and microbiological properties and the ranges that are required to ensure product quality.

P.2.2.1 Formulation Development

	Phase 1a	Phase 1b	Pivotal Clinical Studies	Primary Stability and Proposed Commercial
Formulation	Initial	Proposed Commercial		
Study Number(s)	ALK9072-001	ALK9072-002 ALK9072-101 ALK9072-102	ALK9072-003 ALK9072-003EXT ALK9072-003EXT2	Stability Protocols 105-00815 and 105-00855 (see Section 3.2.P.8.3, Table 1)
Container closure	Vial	Vial	Vial & PFS	PFS
Dose Strength (mg)	221 to 589	441 to 882	Vial: 441 and 882 PFS: 441 and 882	441, 662, 882

Phase 1a Formulation			Proposed Commercial Formulation		
Component	Amount (wt %)	Function	Component	Amount (wt %)	Function
(b) (4) drug substance	(b) (4)	Active	(b) (4) drug substance	(b) (4)	Active
(b) (4)	(b) (4)	(b) (4)	Sorbitan Monolaurate (SML)	(b) (4)	(b) (4)
Polysorbate 20 (PS20)	(b) (4)	(b) (4)	Polysorbate 20 (PS20)	(b) (4)	(b) (4)
Sodium Chloride	(b) (4)	(b) (4)	Sodium Chloride	(b) (4)	(b) (4)
Sodium Phosphate Dibasic Anhydrous	(b) (4)	(b) (4)	Sodium Phosphate Dibasic Anhydrous	(b) (4)	(b) (4)
Sodium Phosphate Monobasic	(b) (4)	(b) (4)	Sodium Phosphate Monobasic	(b) (4)	(b) (4)
WFI	(b) (4)	(b) (4)	WFI	(b) (4)	(b) (4)

Evaluation: Adequate – Two formulations were used during development. (b) (4)

**P.2.2.2 Overages**

The drug product does not contain overages.

P.2.2.3 Physicochemical and Biological Properties

Properties Impacting Performance	Observed Characteristic	Potential Impact	Control Strategy
(b) (4)			

Evaluation: Adequate – Alkermes has sufficient product understanding regarding physicochemical properties that impact product quality. (b) (4)



The instructions for use include directions to inject the total contents within 10 seconds. The 10 second time limit is supported by data from development and human factors studies. Dissolution will be evaluated by Biopharm.

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P.2.3

Manufacturing Process Development

Process Scale	Description	Clinical Study numbers
Small Scale (Section 3.1.2.1)	(b) (4)	ALK9072-001
Initial Pilot Scale (Section 3.1.2.2)		ALK9072-002 ALK9072-003 ALK9072-003EXT ALK9072-101 ALK9072-102
Final Pilot Scale (Section 3.1.2.3)		ALK9072-003 ALK9072-003EXT ALK9072-003EXT2 ALK9072-102
Commercial Scale (Section 3.1.2.4)		N/A

Table 7: Summary of Unit Operation Impact on Quality Attributes of Aripiprazole Lauroxil Injectable Suspension

Quality Attributes	Operations
	(b) (4)
Sterility	(b) (4)
Identity ^a	(b) (4)
Dose Delivered	(b) (4)
Dissolution	(b) (4)
Impurities	(b) (4)
pH	(b) (4)
Osmolality	(b) (4)
Bacterial Endotoxins	(b) (4)
Break Loose Force ^b	(b) (4)
Glide Force ^b	(b) (4)

Evaluation: Adequate, with Information Request – (b) (4)

(b) (4)

(b) (4)

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Process Parameter	CQA Potentially Impacted	Proposed/Target Range	Rationale	Control Strategy
(b) (4)				

Information Request – Clarify what is meant by the terms “(b) (4)” and “(b) (4)”, used to describe the control strategy in Section 3.2.P.2.3 Manufacturing Process Development. The meaning of these terms was not clearly defined in the submission. (b) (4)

Information Request – Clarify how the “defined design space” for the (b) (4) will be implemented as part of commercial manufacturing. It is unclear from the information provided in the submission if the “defined design space” represents a proposal for regulatory flexibility with respect to making changes to the (b) (4) without notification to the Agency.

P.2.4 Container Closure System

Summary of Container Closure Development/Suitability (copied from submission)

CHEMISTRY REVIEW TEMPLATE

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Table 12: Summary of the Development of the Container Closure System for ARISTADA

(b) (4)



Summary of Use Instructions (copied from submission)

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Step	Title	Function	Section
1	TAP and SHAKE the syringe	Resuspension of syringe contents	4.3.5.1.1
2	SELECT the injection needle	Needle selection based on dose, injection site and patient body type	4.3.5.1.2
3	ATTACH the injection needle	Needle attachment	4.3.5.1.3
4	PRIME the syringe to remove air	Air removal	4.3.5.1.4
5	ADMINISTER entire contents	Injection of selected dose intramuscularly	4.3.5.1.5
6	DISPOSE of the needle	Safe, disposal of needle	4.3.5.1.6

Evaluation: Pending – The contents of pre-filled syringe physically and chemically stable, supported by the drug product stability data. The packaging components are safe, compatible, and protect the product, supported by results from extractable and leachables testing, release testing, stability testing, testing of incoming packaging components (USP <88> Biological Reactivity Tests In Vivo, USP <661> Containers, USP <381> Elastomer Closures for Injection, USP <87> Biological Reactivity Tests In Vitro), manufacturer testing of assembled primary packaging components, and shipping evaluations. The supporting reviews by CDRH evaluating the function and design of the packaging components and Micro evaluating the ability of the packaging to maintain sterility are pending at the time of this review.

(b) (4)

Because vibration and gravity contribute to suspension settling, resuspension of the particles by shaking is required prior to injection. The Instructions For Use (IFU) are based on a laboratory study involving the pre-filled syringe exposed to extreme vibration and pressure conditions associated with shipping and in a worst case, tip down, orientation. Results showed that (b) (4) 10 taps followed by at least 30 seconds of vigorous shaking are required to achieve acceptable injection performance, assessed using the injectability test.

The IFU include directions to tap the syringe at least 10 times and to shake vigorously for a minimum of 30 seconds. Properly preparing the drug product for administration (sufficient tapping/shaking to resuspend) is considered a critical step. Key results from other human factors simulation studies showed that the majority of instances of non-compliance with the IFU were attributed to not seeing/using or not understanding the tapping/shaking instructions (Study I error rate – 13/32 (41%); Study II error rate – 3/9 (30%); Study III error rate – 6/15 (40%)), resulting in the drug product not being fully resuspended.

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These failures led to several iterations of labeling and packaging changes. The simulated use studies also showed that either tapping [REDACTED] (b) (4) were adequate to resuspend the suspension. The human factors validation study showed the final tapping/shaking instructions were adequate (15/15 (100%) of participants correctly prepared the syringe prior to injecting) to ensure proper performance of this critical step.

The instructions for use include directions for priming the syringe prior to administration. Development studies showed acceptable dose delivery irrespective of syringe priming. Priming the syringe is considered a non-critical step. The human factors simulation studies did not identify issues with priming the syringe as a key finding. The validation study showed a large variation in successful completion of the priming step (8/15 (53%) correctly primed the syringe). Failure to prime the syringe was attributed to various reasons such as forgetfulness, nervousness, and inaccurate visual assessment of the amount of air in the syringe. No additional changes to the IFU regarding priming were recommended because the risk to the patient safety (air embolism) is minimal as air is often added to push solutions through intravenous lines. Injection of ≤ 1 cc of air is expected to cause only mild injection site pain. This product does not require the use of an intravenous line for administration.

Development studies evaluated the effect of a lag time between when resuspension is completed and when the product is injected ("hold time") on injectability to support cases where the product is not administered immediately after resuspension. Results show that hold times of [REDACTED] (b) (4) minutes are associated with acceptable injection performance. Although longer times were found to be acceptable, a maximum hold time of 15 minutes is included in the use instructions along with an instruction to shake again if the suspension is not used within 15 minutes.

[REDACTED] (b) (4)

The applicant should comment on the expected performance of the drug product in this situation and provide any available data to support use under these conditions.

Information Request – [REDACTED] (b) (4)

[REDACTED]

It was not clear from the development studies or human factors evaluations if this potential in-use scenario was evaluated.

P.2.5 *Microbiological Attributes*

Microbiological attributes evaluated by Microbiology review team.

Evaluation: Pending

P.2.6 *Compatibility*

Summary of Leachables/Extractables Studies (copied from submission)

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(b) (4) ion



Species	Amount Delivered by Injection (mg/day)	Estimated Amount Normally in Human Body (mg)	% Amount in Human Body	Dietary Intake (mg/day)	% of Dietary Intake	Comments
(b) (4)						

Evaluation: Adequate – All of the primary packaging components have been shown to be biocompatible by the manufacturer. Stability data for appearance, pH, impurities, and glide force support compatibility of the container closure. Testing performed under excursion conditions of (b) (4) showed that the primary container closure components are compatible with the suspension and function as designed following temperature excursions. Photostability testing showed that the drug product is not light-sensitive.



P.3 Manufacture**P.3.1 Manufacturers**

Name and Address	Responsibility
Alkermes Inc. 265 Olinger Circle Wilmington, OH 45177 FEI: 1000142940 DUNS: 858582083	Bulk suspension manufacturing Primary packaging (b) (4) Raw Material and F ase Testing Stability Testing
Sharp Corporation (b) (4) DUNS: 143696495	Labeling (b) (4) Packaging
(b) (4)	Compendial raw material testing

P.3.2 Batch Formula (Copied from submission)**Evaluation: Adequate.****P.3.3 Description of Manufacturing Process and Process Controls (Copied from submission)**

2 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page



P.3.5 *Process Validation and/or Evaluation*

Process validation will be evaluated by the product quality microbiology review team.

P.4 *Control of Excipients*

P.4.1 *Specifications*

Excipient	Regulatory Standard	Manufacturer	Supplier
Sorbitan Monolaurate	NF		
Polysorbate 20	NF		
Sodium Chloride	USP		
Sodium Phosphate, Dibasic Anhydrous	USP		
Sodium Phosphate, Monobasic	USP		
Water for Injection	USP		

(b) (4)

(b) (4)

[Redacted]

(b) (4)

Evaluation: Adequate – The formulation excipients comply with current compendial monograph requirements. [Redacted]

(b) (4)

P.4.2 Analytical Procedures

See Section P.4.1 of this review for a summary of the analytical procedures used for the non-compendial excipients.

Evaluation: Adequate – The proposed analytical procedures used to control the quality of the non-compendial excipients are suitable to control the purity and identity of the excipients.

P.4.3 Validation of Analytical Procedures

Analytical Procedure	Validation Parameters
[Redacted]	

(b) (4)

Evaluation: Adequate – The validation results confirm that the proposed analytical procedures used to control the identity and purity of the non-compendial excipients are suitable for the intended use. [Redacted]

(b) (4)

P.4.4 Justification of Specifications

All excipients, with the exception of [Redacted], comply with the current USP/NF monograph requirements. As USP/NF, JP, or EP monographs do not exist for [Redacted] in-house specifications were established.

(b) (4)

Evaluation: Adequate – The in-house specifications control the identity and purity of the non-compendial excipients.

P.4.5 Excipients of Human or Animal Origin

The drug product does not contain any excipients of human or animal origin.

Evaluation: Adequate.

P.4.6 Novel Excipients

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Sorbitan monolaurate is considered a novel excipient in this drug product as it has not been used in approved drug products administered intramuscularly. The use of sorbitan monolaurate via intramuscular administration was qualified via nonclinical studies evaluating the safety, absorption, distribution, metabolism, and excretion of the parent sorbitan monolaurate and related sorbitan fatty acid esters.

Evaluation: Adequate – The pharm/tox evaluation of nonclinical qualification studies found that sorbitan monolaurate is qualified for use, in the proposed amount, for intramuscular administration.

P.5 Control of Drug Product

P.5.1 Specification(s)

Test	Method	Acceptance Criteria		Typical Ranges Observed
			<i>Pivotal Clinical</i>	<i>Registration Stability</i>
Description	Visual	<i>Syringe Package: Colorless plastic syringe with a gray rubber plunger and tip cap, free from visual defects</i> <i>Product: White to Off-white suspension</i>	Conforms	Conforms
Identification*	HPLC	<i>Retention time of sample corresponds to retention time of standard</i>	Conforms	Conforms
	FT-IR	<i>Spectrum of the sample corresponds to spectrum of standard</i>	Not tested	Not tested
Uniformity of Dosage Units – Content Uniformity*	HPLC	<i>Meets USP <905></i>		(b) (4)
Dose Delivery Assay (Label Claim)	HPLC	(b) (4) % of Label Claim		
Impurities	HPLC			
Individual		NMT (b) (4) %		

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Test	Method	Acceptance Criteria		Typical Ranges Observed
Total		(b) (4)		
Dissolution	HPLC			
6 hours				
24 hours				
96 hours				
Particle Size Distribution	Laser Diffraction			
Dv[10]		(b) (4)		
Dv[50]				
Dv[90]				
Break Loose Force	Compressive Force			
Glide Force	Compressive Force			
pH*	USP <791>			
Osmolality*	USP <785>			
Bacterial Endotoxins	USP <85> LAL			
441 mg Dose				
662 mg Dose				
882 mg Dose				
Sterility	USP <71>			
Development Tests**				
(b) (4)				

Evaluation: Pending – The proposed regulatory drug product specification is adequate, from a CMC perspective, to ensure the identity, purity, strength, and quality of the drug product. The typical ranges observed for the registration stability batches comply with the proposed specification limits and are within the range observed for the pivotal clinical batches. The specification clearly identifies the tests intended for release only testing. The reviews from Biopharmaceutics evaluating the dissolution specification and the need for keeping in vitro release testing as part of the specification along with the reviews from

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Microbiology (bacterial endotoxins and sterility limits) and CDRH (functional attributes glide force, break loose force).

The applicant provided adequate justification for not including [REDACTED] (b) (4)
[REDACTED] (March 13, 2015 response to
Information Request). [REDACTED] (b) (4)

[REDACTED] The applicant also revised the acceptance criterion for description of the drug product package to include “free from visual defects” as part of the response to the information request. The applicant provided adequate justification for not including [REDACTED] (b) (4)

P.5.2 Analytical Procedures

Release/Stability Tests

Description: Visual inspection of the product [REDACTED] (b) (4)

Identification by HPLC: Same as drug substance

Identification by FT-IR: Same as drug substance

Uniformity of Dosage Units – Content Uniformity: In accordance with USP <905> Uniformity of Dosage Units Content Uniformity Method; Sample analysis conducted via Assay HPLC method

Dose Delivery Assay: [REDACTED] (b) (4)

Impurities: Same as drug substance

Dissolution: Sample analysis using the Assay HPLC method

Particle Size Distribution: Laser diffraction

Break Loose Force: Compressive force

Glide Force: Compressive force

pH: In accordance with USP <791>

Osmolality: In accordance with USP <785>

Bacterial Endotoxins: In accordance with USP <85>

Sterility: In accordance with USP <71>

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In-Process Tests

(b) (4)

Evaluation: Adequate – The analytical procedures are appropriate to ensure the identity, purity, strength, and quality of the drug product. The analytical procedures either rely on compendial standards, standard techniques typically used for the attribute tested, or are based on the method used for the drug substance. Prior to drug product testing, dose preparation is required, including resuspension of the contents, needle attachment, and priming following the directions included in the IFU. (b) (4)

P.5.3 Validation of Analytical Procedures

Test	Validation Criteria	
	Release and Stability Tests	
Identification and Impurities by HPLC	(b) (4)	
Identification by FT-IR		
Dose Delivery Assay and Content Uniformity by HPLC		
Dissolution by HPLC		
Particle Size Distribution		
Break Loose Force		
Glide Force		
	In-Process Tests	
	(b) (4)	
	Development Tests	
	(b) (4)	
Impurity	LOD	LOQ
		(b) (4)

Evaluation: Adequate – The method validation supports the use of the analytical procedures for the intended purposes. All results for all methods complied with the pre-defined validation criteria.

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P.5.4

Batch Analyses

See Section P.5.1 of this review for a summary of the aripiprazole lauroxil injectable suspension batch analysis results. The following table (copied from the submission) summarizes the drug product batches manufactured using to establish clinical efficacy and safety as well as the registration stability batches.

Lot Number	Site of Manufacture	(b) (4)	Drug Substance Lot # (Alkermes Lot#)	Date of Manufacture	Scale	Container Closure System	Dosage Strength ^a	Purpose
453-0008AA	Alkermes - Wilmington		60254-10-003 (W1012031652)	13-Oct-11	(b) (4)	Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003
453-0008BA	Alkermes - Wilmington		60254-10-003 (W1012031652)	20-Oct-11		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-002 ALK9072-003
453-0009AA	Alkermes - Wilmington		60254-10-003 (W1012031652)	03-Nov-11		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003
453-0009BA	Alkermes - Wilmington		60254-10-003 (W1012031652)	09-Nov-11		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003
453-0012AA	Alkermes - Wilmington		60254-10-003 (W1012031652)	07-Feb-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003
453-0012BA	Alkermes - Wilmington		60254-10-003 (W1012031652)	15-Feb-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003EXT
453-0011AA	Alkermes - Wilmington		11111/P2 (W1201050957)	21-Feb-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-101 ALK9072-102
453-0011BA	Alkermes - Wilmington		11111/P2 (W1201050957)	06-Jun-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-002 ALK9072-003
453-0013AA	Alkermes - Wilmington		21111/P2 (W1201051006)	20-Jun-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-102 ALK9072-003 ALK9072-003EXT
453-0019AA	Alkermes - Wilmington		31111/P2 (W1201051010)	17-Oct-12		Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003EXT
453-0020AA	Alkermes - Wilmington		102031228 (W1207021640)	24-Jan-13		Pre-filled syringe	882 mg	Registration Stability
453-0020AB	Alkermes - Wilmington		102031228 (W1207021640)	24-Jan-13		Pre-filled syringe	441 mg	Registration Stability
453-0021AA	Alkermes - Wilmington		101031228 (W1207021645)	07-Feb-13		Pre-filled syringe	441 mg	Registration Stability
453-0021AB	Alkermes - Wilmington		101031228 (W1207021645)	07-Feb-13		Pre-filled syringe	882 mg	Registration Stability
453-0023AA	Alkermes - Wilmington		101051228 (W1207021650)	14-Feb-13		Pre-filled syringe	441 mg	Registration Stability
453-0023AB	Alkermes - Wilmington		101051228 (W1207021650)	14-Feb-13		Pre-filled syringe	882 mg	Registration Stability
453-0018AA	Alkermes - Wilmington		11111/P2 (W1201050957)	14-Mar-13		Pre-filled syringe	882 mg	Registration Stability
453-0024AA	Alkermes - Wilmington		31111/P2 (W1201051010)	18-Apr-13		Pre-filled syringe	441 mg	P3 Clinical ALK9072-003EXT ALK9072-003EXT2
453-0024AB	Alkermes - Wilmington		31111/P2 (W1201051010)	18-Apr-13		Pre-filled syringe	882 mg	P3 Clinical ALK9072-003EXT ALK9072-003EXT2
453-0025AA	Alkermes - Wilmington		10212/P2 (W1204201309)	25-Apr-13		Pre-filled syringe	441 mg	P3 Clinical ALK9072-003EXT
453-0025AB	Alkermes - Wilmington	10212/P2 (W1204201309)	25-Apr-13	Pre-filled syringe	882 mg	P3 Clinical ALK9072-003EXT		

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Lot Number	Site of Manufacture	(b) (4)	Drug Substance Lot # (Alkermes Lot#)	Date of Manufacture	Scale	Container Closure System	Dosage Strength ^a	Purpose
453-0026AA	Alkermes - Wilmington		10212/P2 (W1204201309)	16-May-13	(b) (4)	Vial	441 mg and/or 882 mg	P3 Clinical ALK9072-003 ALK9072-003EXT
453-0030AA	Alkermes - Wilmington		102031228 (W1207021640)	11-Jul-13		Pre-filled syringe	882 mg	P3 Clinical ALK9072-003EXT2
453-0031AA	Alkermes - Wilmington		20212/P2 (W1204240756)	25-Jul-13		Pre-filled syringe	441 mg	P3 Clinical ALK9072-003EXT ALK9072-003EXT2
453-0031AB	Alkermes - Wilmington		20212/P2 (W1204240756)	25-Jul-13		Pre-filled syringe	882 mg	P3 Clinical ALK9072-003EXT
453-0032AA	Alkermes - Wilmington		102031228 (W1207021640)	15-Oct-13		Pre-filled syringe	441 mg	P3 Clinical and Supportive Stability
453-0033AA	Alkermes - Wilmington		101031228 (W1207021645)	24-Oct-13		Pre-filled syringe	882 mg	P3 Clinical ALK9072-003EXT2 and Supportive Stability
453-0034AA	Alkermes - Wilmington		102031228 (W1207021640)	30-Oct-13		Pre-filled syringe	441 mg	Supportive Stability
453-0034AB	Alkermes - Wilmington		102031228 (W1207021640)	30-Oct-13		Pre-filled syringe	662 mg	TBD
453-0035AA	Alkermes - Wilmington		101051228 (W1207021650)	23-Jan-14		Pre-filled syringe	882 mg	TBD
453-0036AA	Alkermes - Wilmington		101051228 (W1207021650)	30-Jan-14		Pre-filled syringe	882 mg	TBD
453-0037AA	Alkermes - Wilmington		101051228 (W1207021650)	05-Feb-14		Pre-filled syringe	441 mg	TBD
453-0038AA	Alkermes - Wilmington		101051228 (W1207021650)	20-Feb-14		Pre-filled syringe	662 mg	TBD

^a For vial configuration, two dosage strengths of 441 mg and 882 mg were used in the P3 clinical studies. TBD: To be determined.

Evaluation: Adequate – The pivotal clinical studies supporting safety and efficacy are ALK9072-003, ALK9072-003EXT, and ALK9072-003EXT2. The registration stability batches are 453-0020AA, 453-0020AB, 453-0021AA, 453-0021AB, 453-0023AA, 453-0023AB, and 453-0018AA. The results demonstrate that the manufacturing process is capable of producing drug product that complies with the proposed regulatory specification.

P.5.5 Characterization of Impurities

All impurities are controlled in the drug substance and no additional impurities or degradation products are observed in the drug product. The same impurity method is used for drug substance and drug product.

Impurity	Structure	Origin	Maximum Amount Observed in Drug Product
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(b) (4)

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Impurity	Structure	Origin	Maximum Amount Observed in Drug Product
(b) (4)			

Evaluation: Adequate – On stability, the amount of (b) (4) did not increase at either long-term or accelerated conditions from the amount reported at release. The pharm/tox reviewer indicated that based on the (b) (4) and assuming 900 dosing days over a lifetime and a (b) (4) mcg daily dose, the limit for potentially genotoxic impurities is (b) (4) ppm. Based on this limit, the (b) (4) (b) (4) should be limited to (b) (4) ppm. (b) (4) The maximum amounts observed for (b) (4) and (b) (4) are below the (b) (4) ppm limit.

P.5.6 Justification of Specification(s)

Included Tests	Justification
Description	Qualitative test for discoloration and package integrity
Identification	Confirms the identity of the active component of the drug product
Uniformity of Dosage Units	Content uniformity of individual and average of 10 syringes controlled based on USP <905> criterion
Dose Delivery Assay	Consistent with FDA guidance; Based on the total amount of aripiprazole lauroxil ejected from the pre-filled syringe following performance of the dose preparation procedure in the (b) (4)
Impurities	Controlled based on ICH Q3B(R2); No additional impurities or degradants observed above the identification threshold in the drug product at release or on stability
Dissolution	PENDING Biopharm
Particle Size Distribution	Acceptance criteria based on current process capability, batch history results, analytical capability, and stability data
Break Loose Force	PENDING CDRH
Glide Force	PENDING CDRH
pH	(b) (4)
Osmolality	

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Included Tests	Justification
Bacterial Endotoxins	PENDING Micro
Sterility	PENDING Micro
Excluded Tests	Justification

(b) (4)

Evaluation: Pending –

(b) (4)

P.6 Reference Standards or Materials

The aripiprazole lauroxil drug substance reference standard is used in the drug product identification, purity, assay, dissolution, and in vitro initial release tests. Information on the drug substance reference standard is cross-referenced to Section 3.2.S.5 of the submission. All other reference standards are obtained through commercial sources.

Evaluation: Adequate.

P.7 Container Closure System

Drug Product

Type	Contact Surface	Description	Supplier	Regulatory Status	Tests
Syringe Barrel (DMF (b) (4))	Yes	(b) (4)		Primary syringe device component (21 CFR 820)	Particulates (USP <788>); Sterility; Bacterial Endotoxins; Identification (syringe barrel, tip cap); Visual inspection (intermixing,

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Type	Contact Surface	Description	Supplier	Regulatory Status	Tests
					<i>cleanliness, cosmetic defects, molding defects; dimensional testing</i>
<i>Tip Cap</i> (DMF (b) (4))	Yes	(b) (4)	(b) (4)	Primary syringe device component (21 CFR 820)	Tested as a mounted component of the syringe barrel
<i>Plunger</i> (DMF (b) (4) – composition; DMF (b) (4) – (b) (4); DMF (b) (4); (b) (4))	Yes	(b) (4)	(b) (4)	Primary syringe device component (21 CFR 820)	Identification (IR), Sterility, Bacterial Endotoxins, Visual inspection, dimensional testing, opalescence, color, acidity or alkalinity, absorbance, reducing substances, ammonia, extractable zinc, extractable heavy metals, volatile sulfides, residue on evaporation
Plunger Rod(s)	No	(b) (4)	(b) (4)	Syringe device component (21 CFR 820)	Visual inspection, dimensional testing (rod diameter, total length, clipping distance)
Finger flange (backstop)	No	(b) (4)	(b) (4)	Syringe device component (21 CFR 820)	Visual inspection, dimensional testing (total length, total height, notch width)
Tray	No	(b) (4)	(b) (4)	Packaging component (21 CFR 820)	None; Accepted based on supplier part number
Carton	No	(b) (4)	(b) (4)	Packaging component (21 CFR 820)	None; Accepted based on supplier part number
<i>Needle</i> (21G 1"; 20G 1.5", 20G 2")	Yes	(b) (4)	(b) (4)	Associated device component (21 CFR 820) 510(K) (b) (4) and (b) (4)	None; Commercially available

Bulk (b) (4) Drug Substance

Evaluation: Adequate – The syringe barrel and plunger are received and evaluated by the drug product manufacturer. All secondary packaging components (plunger rod, backstop, tray, and carton) are received and evaluated by the contract packager. (b) (4)

The expiration date of the entire kit, including all kit components is controlled through SOPs at Alkermes and (b) (4), the contract manufacturer used for labeling and kit assembly. Alkermes assigns the expiration date for each kit lot taking into account the shorter of the expiration date of the pre-filled syringe or the needle lots to be used. (b) (4) verifies that the kit components used in each lot do not expire prior to the assigned expiration date, and the expiration date is further verified as part of the Alkermes review of the (b) (4) batch records prior to release of the finished kit.

The status of the supporting DMFs is as follows:

- DMF (b) (4) – not reviewed, sufficient information was provided in the submission
- DMF (b) (4) – adequate 4/21/15
- DMF (b) (4) – adequate 3/27/15
- DMF (b) (4) – adequate 4/15/15

P.8 Stability

P.8.1 Stability Summary and Conclusion

The submission includes fifteen (15) months of long-term and 6 months of accelerated stability data for 7 commercial-scale registration batches representing 4 batches of the highest strength (882 mg) and 3 batches of the lowest strength (441 mg). One of the batches for the highest strength drug product is a stacked stability batch. All other batches are considered primary stability batches. The stability protocol follows an agreed upon bracketing and matrixing scheme with testing of all samples at Months 0, 6, 12, 24, and 36. In addition, the submission includes photostability data for one drug product batch, simulated shipping stability results for three batches at (b) (4)C over (b) (4) days, 2 batches exposed to (b) (4), and 2 batches exposed to either a (b) (4). Based on the available stability data, statistical analysis, and shelf-life estimation, the applicant proposes a drug product expiration date of (b) (4) months from (b) (4).

Evaluation: Adequate – The primary stability batches were manufactured at the same scale as proposed for the commercial manufacturing process. However, the proposed commercial process differs slightly from that used for the primary stability and pivotal clinical studies in that the commercial scale (b) (4)

The primary stability data is considered representative of the proposed commercial process.

The applicant revised the proposal to calculate the drug product expiry from (b) (4) to calculate the drug product expiry from (b) (4) in response to the information request (March 13, 2015 Response to Information Request). This approach is reasonable and is aligned with the current policy regarding establishing drug product expiry. The primary stability data has shown little to no change for the time period reported. The shelf-life estimation evaluated the CQAs considered stability-indicating – dose delivery, total related impurities, dissolution (6 hrs, 24, hrs, and 96 hrs), break loose force, glide force, and PSD (Dv[10], Dv[50], and Dv[90]). The proposed drug product expiration date and storage condition are supported by the primary stability data and supporting stability data.

P.8.2 Post approval Stability Protocol and Stability Commitment

The post-approval stability commitments include the following:

(b) (4)

Evaluation: Inadequate – Due to minor modifications of the commercial manufacturing process, the applicant commits to include the first three production batches in the stability program at long-term conditions. The applicant should revise the post-approval stability commitment and protocol to include testing of the first three production batches (b) (4) to include testing at accelerated condition (b) (4) and to include testing (b) (4) for the long-term condition.

Deficiency – Revise the post-approval stability protocol to include testing at accelerated conditions (b) (4) at accelerated conditions for the first three production batches (b) (4). Revise the proposed testing schedule for the long-term condition to include testing (b) (4). In accordance with ICH Q1A(R2) Stability Testing of New

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Drug Substances and Products, the post-approval stability protocol should include a commitment to test the first three production batches at long-term conditions through the proposed shelf life and at accelerated conditions through six months. In addition, ICH Q1A(R2) also states that the frequency of testing at the long-term condition should normally be every three (3) months over the first year.

P.8.3 Stability Data

Primary Stability

Test	Method	Acceptance Criteria	Typical Ranges Observed	
			Long-Term Conditions (25°C/60% RH)	Accelerated Conditions (40°C/75% RH)
Description	Visual	<i>Syringe Package: Colorless plastic syringe with a gray rubber plunger and tip cap</i> <i>Product: White to Off-white suspension</i>	Conforms	Conforms
Dose Delivery Assay	HPLC	(b) (4) % of Label Claim	(b) (4) %	(b) (4) %
Impurities	HPLC			
Total		NMT (b) (4) %	(b) (4) %	(b) (4) %
Individual		NMT (b) (4) %	(b) (4)	

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Test	Method	Acceptance Criteria	Typical Ranges Observed	
			Long-Term Conditions (25°C/60% RH)	Accelerated Conditions (40°C/75% RH)
Dissolution	HPLC			
6 hours		(b) (4) %	(b) (4) %	
24 hours		(b) (4) %	(b) (4) %	(b) (4) %
96 hours		NLT (b) (4)	(b) (4) %	(b) (4) %
Break Loose Force	Compressive Force	NMT (b) (4)	(b) (4) N	(b) (4) N
Glide Force	Compressive Force	NMT (b) (4)	(b) (4) N	(b) (4) N
Particle Size Distribution	Laser Diffraction			
Dv[10]		NMT (b) (4) μm	(b) (4) microns	
Dv[50]		(b) (4) μm	(b) (4) microns	(b) (4) microns
Dv[90]		NMT (b) (4) μm	(b) (4) microns	(b) (4) microns
pH		(b) (4)	(b) (4)	(b) (4)
Bacterial Endotoxins	LAL			
441 mg Dose		NMT (b) (4) EU/mL	(b) (4) EU/mL	
662 mg Dose		NMT (b) (4) EU/mL	Not tested	
882 mg Dose		NMT (b) (4) EU/mL	(b) (4) EU/mL	
Sterility	Sterility	<i>No evidence of microbial growth</i>	No evidence of microbial growth	
Additional Tests				

(b) (4)

Photostability

(b) (4)

Temperature Excursions, Freeze/Thaw Cycle, Shipping Simulation

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(b) (4)

[Redacted]

(b) (4) Drug Substance Bulk Hold/Drug Product Stacked Stability

(b) (4)

[Redacted]

(b) (4)

[Redacted]

^b Per proposed commercial drug product specification.

Evaluation: Inadequate – The results of the primary stability, temperature excursion, freeze/thaw cycle, and shipping simulation studies support the proposed drug product expiration and storage condition. (b) (4)

[Redacted]

(b) (4)

[Redacted] Based on our evaluation of the data, we do not agree that the data supports the proposed (b) (4).

(b) (4)

(b) (4)

The applicant proposes a (b) (4) month expiry for the drug product. The submission includes only 15 months of primary stability data. Based on ICH Q1E, the maximum allowed drug product expiry based on 15 months data would be (b) (4) months. (b) (4)

The results for all other quality attributes were comparable across storage conditions. Because statistical analysis of the stability data was provided, we can still grant up to two-times the time period covered by stability data. However, it should not exceed X + 12 months. Therefore, we grant a drug product expiry of 27 months based on the stability data provided and in accordance with ICH Q1E.

Deficiency – Provide justification for the proposed (b) (4) hold time for the bulk (b) (4) drug substance. Provide additional bulk stability data, if available, for other bulk (b) (4) drug substance batches stored through (b) (4) at the proposed bulk hold storage condition along with results from the stacked stability protocol for the drug product batch manufactured using the (b) (4) bulk (b) (4) drug substance. Include as part of the justification, a statistical analysis of the available hold time stability data to support the proposed bulk hold time. The information provided in the submission represents one data point at the proposed bulk hold time and does not provide sufficient evidence that an (b) (4) bulk hold time will not negatively impact product quality. Additional justification and data is required to support the proposed bulk hold time.

Deficiency – The proposed drug product shelf life of (b) (4) months is not in accordance with ICH Q1E. The submission contained fifteen (15) months of long-term, primary stability data for the drug product. Based on ICH Q1E, the drug product expiry cannot exceed the time period covered by primary stability data plus twelve (12) months, in this case 27 months. Additional justification and drug product stability data is required to support the proposed (b) (4) month drug product shelf life.

Information Request – Provided updated drug product photostability results that include results for the dark control (b) (4). The results provided in the submission did not include the dark control data and included the data for the (b) (4). We cannot determine if (b) (4) impacts stability or compare the results to a control sample based on the data in the submission.

A APPENDICES

A.1 Facilities and Equipment (biotech only)

Not applicable

A.2 Adventitious Agents Safety Evaluation

Not applicable

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A.3 Excipients

Not applicable

R REGIONAL INFORMATION**R1 Executed Batch Records**

One executed batch record was provided for Lot 453-0023.

Evaluation: Inadequate – [REDACTED] (b) (4)

The drug product manufacturing description in Section 3.2.P.3 provides sufficient detail about the intended commercial process, including set points and operating ranges. The applicant did not provide executed batch records for all drug product used to conduct the primary stability data in accordance with 21 CFR 314.50(d)(1)(ii)(b).

Deficiency – Provide executed batch records for each batch of drug product used to conduct the primary stability study. 21 CFR 314.50(d)(1)(ii)(b) requires submission of batch records for each drug product primary stability batch. The submission includes an executed batch record for Lot 453-0023 but did not include batch records for Lots 453-0020 453-0021 and 453-0018.

R2 Comparability Protocols

None submitted for review.

R3 Methods Validation Package

Information on the samples, specifications, reference standards, analytical procedures, and method validation information is provided or hyperlinked to the appropriate section in the submission.

Evaluation: Adequate.**II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1****A. Labeling & Package Insert**Immediate Container Label

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Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (21 CFR 201.10(g)(2))	Included	Adequate – The proposed container label includes all required information except the equivalency statement. However, space limitations on the label may prevent addition of this information. We will ask the applicant if it is feasible to include the statement on the immediate container label and if so, they can implement the change with the submission of the final carton/container labels post-approval. The different product strengths are differentiated based on the color of the label – light blue (441 mg), green (662 mg), and burgundy (882 mg). The physician sample immediate container labels are comparable to the commercial labels and include the statement “Sample, not for resale.”
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
“Rx only” statement per 21 CFR 201.100(b)(1)		
Storage (not required)	USP controlled room temperature statement	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included	
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
Others	No equivalency statement to aripiprazole	

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled “sample”, “physician’s sample”, or a substantially similar statement and the contents of the package do not exceed 8 grams

**Not required for Physician’s samples The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements

Carton Label

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	Included	Adequate – The proposed commercial and sample carton and container labels are acceptable from a CMC perspective. The labels include statements “administer entire contents of syringe” and “single use only.” DMEPA may want to consider the applicant including the graphics/instructions regarding required tapping/shaking to reconstitute the drug product.
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables[201.10(a), 21CFR201.100(b)(5)(iii)]		
Sterility Information (if applicable)	No information included	
“Rx only” statement per 21 CFR 201.100(b)(1)	Included	
Storage Conditions	USP controlled room temperature	
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included	
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
“See package insert for dosage information” (21 CFR 201.55)		
“Keep out of reach of children” (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

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Prescribing Information (PI) Review

(a) “Highlights” Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer’s Comment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary: ARISTADA Established Name: aripiprazole lauroxil	Adequate
Dosage form, route of administration	Dosage: Extended-release injectable suspension Route: Intramuscular	
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended-release injectable suspension 441 mg, 662 mg, 882 mg Single use syringe	Adequate
Whether the drug product is scored (If the product is not scored, do not say “not scored.”)	N/A	

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer’s Comment
Available dosage forms	Extended-release injectable suspension; single use syringe	Adequate
Strengths: in metric system	441 mg, 662 mg, 882 mg	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White to off white aqueous suspension Table provided that distinguishes target muscle groups based on product strength (gluteal only vs gluteal or deltoid)	

#11: Description (21CFR 201.57(c)(12))

Item	Information Provided in NDA	Reviewer’s Comment
Proprietary name and established name	ARISTADA Aripiprazole lauroxil	Adequate
Dosage form and route of administration	Suspension, once monthly via intramuscular injection	
Active moiety expression of strength with equivalence statement for salt (if applicable)	441 mg equivalent to 300 mg of aripiprazole 662 mg equivalent to 450 mg of aripiprazole 882 mg equivalent to 600 mg of aripiprazole	
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	All inactives listed but no quantities provided	Adequate with Information Request – We will include a comment in the PI for the applicant to include the quantities of the inactive ingredients
Statement of being sterile (if applicable)	Included	Adequate – There are no additional chemical or physical characteristics that impact safety or efficacy that need to be communicated in the PI.
Pharmacological/ therapeutic class	Atypical antipsychotic	
Chemical name, structural formula, molecular weight	included	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Not included	

NDA 207533

Aripiprazole Lauroxil Injectable Suspension

Information Request – Update the SPL data elements package description to denote that the product is a combination product containing a pre-filled syringe (Type 2, prefilled drug delivery device/system). Also provide SPL data elements for the intended commercial kit. The proposed SPL data elements do not include information on the commercial kit or accurately reflect that the drug product is a combination product.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant claims categorical exclusion in accordance with 21 CFR 25.31(a) based on the expected introduction concentration for five years post approval being < (b) (4) ppb. The applicant certifies that there are no extraordinary circumstances in accordance with 21 CFR 25.15(d).

Evaluation: Adequate.

C. Establishment Inspection

The overall compliance recommendation regarding manufacturing facilities is pending.

III. List Of Deficiencies and Information Requests To Be Communicated

Deficiencies

1. Revise the post-approval stability protocol to include testing at accelerated conditions (b) (4) at accelerated conditions for the first three production batches (b) (4). Revise the proposed testing schedule for the long-term condition to include testing (b) (4). In accordance with ICH Q1A(R2) Stability Testing of New Drug Substances and Products, the post-approval stability protocol should include a commitment to test the first three production batches at long-term conditions through the proposed shelf life and at accelerated conditions through six months. In addition, ICH Q1A(R2) also states that the frequency of testing at the long-term condition should normally be every three (3) months over the first year.
2. Provide justification for the proposed (b) (4) hold time for the bulk (b) (4) drug substance. Provide additional bulk stability data, if available, for other bulk (b) (4) drug substance batches stored through (b) (4) at the proposed bulk hold storage condition along with results from the stacked stability protocol for the drug product batch manufactured using the (b) (4) bulk (b) (4) drug substance. Include as part of the justification, a statistical analysis of the available hold time stability data to support the proposed bulk hold time. The information provided in the submission represents one data point at the proposed bulk hold time and does not provide sufficient evidence that (b) (4) bulk hold time will not negatively impact product quality. Additional justification and data is required to support the proposed bulk hold time.
3. The proposed drug product shelf life of (b) (4) months is not in accordance with ICH Q1E. The submission contained fifteen (15) months of long-term, primary stability data for the drug product. Based on ICH Q1E, the drug product expiry cannot exceed the time period covered by primary stability data plus twelve (12) months, in this case 27 months. Additional justification and drug product stability data is required to support the proposed (b) (4) month drug product shelf life.

4. Provide executed batch records for each batch of drug product used to conduct the primary stability study. 21 CFR 314.50(d)(1)(ii)(b) requires submission of batch records for each drug product primary stability batch. The submission includes an executed batch record for Lot 453-0023 but did not include batch records for Lots 453-0020 453-0021 and 453-0018.

Information Requests

1. Clarify what is meant by the terms “(b) (4)” and “(b) (4)” used to describe the control strategy in Section 3.2.P.2.3 Manufacturing Process Development. The meaning of these terms was not clearly defined in the submission. It is unclear based on the information provided in the submission if these terms refer to (b) (4)
2. Clarify how the “defined design space” for the (b) (4) will be implemented as part of commercial manufacturing. It is unclear from the information provided in the submission if the “defined design space” represents a proposal for regulatory flexibility with respect to making changes to the (b) (4) without notification to the Agency.
3. Comment on the expected product performance in cases where (b) (4) Provide any available data demonstrating suitable product performance under these conditions. (b) (4) It was not clear from the development studies or human factors evaluations if this potential in-use scenario was evaluated.
4. Provided updated drug product photostability results that include results for the dark control (b) (4) The results provided in the submission did not include the dark control data and included the data for the (b) (4) We cannot determine if (b) (4) impacts stability or compare the results to a control sample based on the data in the submission.
5. Update the SPL data elements package description to denote that the product is a combination product containing a pre-filled syringe (Type 2, prefilled drug delivery device/system). Also provide SPL data elements for the intended commercial kit. The proposed SPL data elements do not include information on the commercial kit or accurately reflect that the drug product is a combination product.