

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022549Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: 20 DEC 2012

FROM: David J. Claffey, PhD

SUBJECT: Clarification of prior CMC AP Recommendation for NDA 22-549

In a previous memo (5 DEC 2012) an approval recommendation was made from a CMC perspective based on CDER Office of Compliance's (OC) "acceptable" recommendation of 29 NOV 2012. On 14 DEC 2012 CDER OC withdrew this "acceptable" recommendation as they determined that they had not yet consulted with CDRH OC.

On 20 DEC 2012 CDER OC re-entered an overall recommendation of "acceptable" into EES (Attachment). Therefore an approval recommendation from a CMC perspective can be made once again for NDA 22-549.

ATTACHMENT

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 22549/000	Sponsor:	ALEXZA PHARMS
Org. Code:	130		2091 STIERLIN CT
Priority:	3		MOUNTAIN VIEW, CA 94043
Stamp Date:	11-DEC-2009	Brand Name:	Staccato (loxapine) for Oral Inhalation
PDUFA Date:	21-DEC-2012	Estab. Name:	
Action Goal:		Generic Name:	LOXAPINE
District Goal:	22-OCT-2012	Product Number; Dosage Form; Ingredient; Strengths	
			001; AEROSOL; LOXAPINE; EQ 5MG BASE
			002; AEROSOL; LOXAPINE; EQ 10MG BASE
FDA Contacts:	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	C. TELE	Team Leader	3017961762

Overall Recommendation:	ACCEPTABLE	on 20-DEC-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 17-DEC-2012	by EES_PROD		
	PENDING	on 14-DEC-2012	by EES_PROD		
	PENDING	on 02-JUL-2012	by EES_PROD		
	PENDING	on 02-JUL-2012	by EES_PROD		
	WITHHOLD	on 23-APR-2012	by D. SMITH	(HFD-323)	3017965321
	WITHHOLD	on 31-JAN-2012	by EES_PROD		
	PENDING	on 27-JAN-2012	by EES_PROD		
	WITHHOLD	on 05-OCT-2010	by EES_PROD		

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

Establishment: CFN: 3007119522
ALEXZA PHARMACEUTICALS, INC.
MOUNTAIN VIEW, , UNITED STATES 940434655

DMF No: AADA:

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

Profile: AEROSOL DISPERSED MEDICATION OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 23-NOV-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Profile: ELECTRONIC ASSEMBLY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 20-DEC-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 30-SEP-2011

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 29-NOV-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

/s/

DAVID J CLAFFEY
12/20/2012

CHHAGAN G TELE
12/20/2012

MEMORANDUM

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

DATE: 4 DEC 2012
FROM: David J. Claffey, PhD
SUBJECT: **NDA 22-549** CMC Recommendation (third review cycle)

An approval recommendation can be made from a CMC perspective as CDER Office of Compliance issued an overall acceptable recommendation on 29 NOV 2012 (Attachment) for the manufacturing sites.

It is also noted that data were provided in the amendment dated 24 OCT 2012 which support the proposed 24 month expiry period for the drug product. Data was provided through 18 months for the Primary Stability Lots. No significant changes were noted (b) (4)

Supportive data through 36 months was also provided for the RSLs – they met the specification at each time point.

2 Pages Have Been Withheld As A Duplicate Copy Of The "FDA CDER EES ATTACHMENT" dated December 20, 2012 Which Is Located In The Chemistry Review Section Of This NDA Approval Package

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

/s/

DAVID J CLAFFEY
12/05/2012

KASTURI SRINIVASACHAR
12/05/2012

MEMORANDUM

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

DATE: 30 JUL 2012

FROM: David J. Claffey, PhD

SUBJECT: Evaluation of Impact of failures in the process
validation

(b) (4)

(b) (4)

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

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

/s/

DAVID J CLAFFEY
08/06/2012

RAMESH K SOOD
08/06/2012

MEMORANDUM

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

DATE: 23 APR 2012

FROM: David J. Claffey, Ph.D., ONDQA

SUBJECT: **Update #2 on outstanding CMC-related issues impacting final recommendation.**

A recommendation was made in a prior memo (19 MAR 2012) to approve this application from a CMC-perspective on receipt of an “Acceptable” recommendation from CDER Office of Compliance (OC). On 23 APR 2012 CDER OC issued a “WITHHOLD” recommendation for this application, therefore an “Approval” recommendation from a CMC-perspective can NOT be made at this time.

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

Application:	NDA 22549/000	Action Goal:	
Stamp Date:	11-DEC-2009	District Goal:	05-MAR-2012
Regulatory:	04-MAY-2012		
Applicant:	ALEXZA PHARMS 2091 STIERLIN CT MOUNTAIN VIEW, CA 94043	Brand Name:	Staccato (loxapine) for Oral Inhalation
		Estab. Name:	
		Generic Name:	LOXAPINE
Priority:	3	Product Number; Dosage Form; Ingredient; Strengths	
Org. Code:	130	001; AEROSOL; LOXAPINE; EQ 5MG BASE	
		002; AEROSOL; LOXAPINE; EQ 10MG BASE	
Application Comment:	<p>FOLLOWING A REVIEW OF AN ADDITIONAL RESPONSE FROM ALEXZA REGARDING DEVICE DEFICIENCIES, CDRH/OC CONTINUES TO RECOMMEND WITHHOLD ON THIS APPLICATION AND A RE-INSPECTION PRIOR TO APPROVAL. CDER/OC IS ENTERING A FINAL WH ON CDRH/OC'S BEHALF FOR THIS REVIEW CYCLE. (on 23-APR-2012 by D. SMITH (HFD-323) 3017969643)</p> <p>THIS IS A 505(B)(2) APPLICATION WITH LOXAPINE (WATSON PHARMACEUTICALS) LISTED AS THE REFERENCE LISTED DRUG (on 09-FEB-2010 by D. HENRY () 3017964227)</p> <p>THE PDUFA GOAL DATE FOR THIS APPLICATION IS OCTOBER 11, 2010 (on 08-FEB-2010 by D. HENRY () 3017964227)</p> <p>THE CONTACT PERSON FOR THE APPLICATION IS CHRISTINE WELCH, PHONE: 650-944-7030 (on 08-FEB-2010 by D. HENRY () 3017964227)</p>		
FDA Contacts:	T. BOUIE	Project Manager	3017961649
	D. CLAFFEY	Review Chemist	3017961343
	C. TELE	Team Leader	3017961762
Overall Recommendation:	WITHHOLD	on 23-APR-2012	by D. SMITH (HFD-323) 3017969643
	WITHHOLD	on 31-JAN-2012	by EES_PROD
	PENDING	on 27-JAN-2012	by EES_PROD
	WITHHOLD	on 05-OCT-2010	by EES_PROD

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

Establishment: **CFN:** ALEXZA PHARMACEUTICALS, INC. **FEI:** 3007119522

2091 STIERLIN COURT
MOUNTAIN VIEW, CA 940434855

DMF No: **AADA:**

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

Establishment Comment: CDER OC IS PREPARING A KNOWLEDGE TRANSFER MEMO (KTM) FOR THE INSPECTION OF THIS SITE. (on 21-MAY-2010 by C. CRUZ (HFD-323) 3017963254) (10/6/2011) **NOTE: THE CMC REVIEWER PARTICIPATED IN THE FIRST INSPECTION AND WOULD LIKE PARTICIPATE IN THE REINSPECTION OF THIS SITE. (1/27/2012) - THREE DEVICE PROFILE CODES APPLY TO THIS SITE - (b) (4) on 27-JAN-2012 by T. BOUIE () 3017961649)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE
ELECTRONIC ASSEMBLY POTENTIAL OAI

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-FEB-2010				HENRYD
SUBMITTED TO DO	17-FEB-2010	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	11-AUG-2010	Product Specific			RYOUNG
INSPECTION SCHEDULED	11-AUG-2010		12-AUG-2010		RYOUNG
INSPECTION PERFORMED	20-AUG-2010		20-AUG-2010		WMILLAR
(b) (4)					
DO RECOMMENDATION	23-AUG-2010			WITHHOLD	WMILLAR
(b) (4)					
OC RECOMMENDATION	05-OCT-2010			WITHHOLD	TGOOEN
BASED ON DO RECOMMENDATION OF SIGNIFICANT FINDINGS RELATING TO INADEEQUATE STABILITY PROGRAM AND TESTING, INADEQUATE LABORATORY TESTING AND DOCUMENTATION, AND INADEQUATE PROCESS CONTROL.				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	23-SEP-2011				BOUIET
SUBMITTED TO DO	30-SEP-2011	10-Day Letter			TOULOUSEM

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

ASSIGNED INSPECTION TO IB	30-SEP-2011	Product Specific		WMILLAR
INSPECTION SCHEDULED	21-NOV-2011			WMILLAR
INSPECTION PERFORMED	12-DEC-2011	12-DEC-2011	(b) (4)	WMILLAR
DO RECOMMENDATION	16-DEC-2011		ACCEPTABLE INSPECTION	WMILLAR
PRODUCT IS DRUG/DEVICE UNDER A NDA. 10-ITEM 483 ISSUED, FIRM LACKS PROCESS VALIDATION. LACK OF PV CITED UNDER 21 CFR 820.				
OC RECOMMENDATION	01-FEB-2012		ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
FOR DRUG CGMPs ONLY				
SUBMITTED TO OC	27-JAN-2012			BOUIET
SUBMITTED TO DO	27-JAN-2012	10-Day Letter		CRUZC
PLEASE EVALUATE EER FOR DEVICE ASSEMBLY WITH MOST RECENT EVALUATION.				
DO RECOMMENDATION	27-JAN-2012		WITHHOLD PRODUCTION/PROCESS CONTROLS	WMILLAR
OC RECOMMENDATION	20-MAR-2012		WITHHOLD DISTRICT RECOMMENDATION	SMITHDE
ON BEHALF OF CDRH/OC, CDER/OC IS ENTERING A CONCURRENCE WITH RECOMMENDATION BASED ON A REVIEW OF THE EIR AND FIRM'S RESPONSE TO 483 FROM THE DECEMBER 2011 INSPECTION. CURRENTLY WE ARE WORKING WITH THE DISTRICT OFFICE TO GET ADDITIONAL INFORMATION FROM ALEXZA REGARDING DEVICE DEFICIENCY CORRECTIVE ACTIONS. IF THE RESPONSE IS ADEQUATE, A RE-INSPECTION WILL OCCUR PRIOR TO PDUFA IF POSSIBLE.				
EIR REVIEW-CONCUR W/DISTRICT INADEQUATE RESPONSE TO LETTER				

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: MICROBIAL LIMITS TESTING (on 23-SEP-2011 by T. BOUIE () 3017961649)
 Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-SEP-2011				BOUIET
OC RECOMMENDATION	30-SEP-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM

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

Establishment: CFN: (b) (4) FEI: (b) (4)
 (b) (4)

DMF No: AADA:

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

Establishment Comment: (b) (4)
 Profile: (b) (4) OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-FEB-2010				HENRYD
OC RECOMMENDATION	17-FEB-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	23-SEP-2011				BOUIET
OC RECOMMENDATION	30-SEP-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM

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

/s/

DAVID J CLAFFEY
04/23/2012

RAMESH K SOOD
04/23/2012

MEMORANDUM

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

DATE: 19 MAR 2012

FROM: David J. Claffey, Ph.D., ONDQA

SUBJECT: **Update on outstanding CMC-related issues impacting final recommendation.**

Background: A recommendation was made in CMC Review #2 (15 NOV 2011) to approve this application from a CMC-perspective pending an acceptable recommendation from CDRH ODE and CDER Office of Compliance. Furthermore, at that time there was insufficient data to support the proposed (b) (4) drug product expiry period.

Update:

CDRH ODE found the response adequately addressed the “device/engineering related issues” (Review date: 4 NOV 2011, DARRTS date: 10 NOV 2011). A final recommendation on the requested human factors studies has not yet been received; however evaluation of these data will be made by CDRH in conjunction with DMEPA.

A CDRH ODE review of product labeling (Review date: 5 MAR 2012, DARRTS date: 19 MAR 2012) recommended that the labeling include detailed information on drug product particle size distribution (Attachment 1). ONDQA recommends that these data not be included in product labeling as it has not been CDER practice to do so and it is unclear how Health Care Professionals or Patients could use these data. Further, as these data are part of the drug product specification, they are generally considered proprietary in nature.

Updated stability data were provided in an amendment dated 13 JAN 2012. These were evaluated and were found to support the proposed (b) (4) expiry period (refer to Attachment 2)

A final CDER Office of Compliance recommendation remains pending.

A final recommendation from a CMC perspective will be made on receipt of the CDER Office of Compliance recommendation.

ATTACHMENT 1

CDRH ODE recommendation (5 MAR 2012) concerning drug product labeling:

Please request Alexza to address the following regarding their device labeling:

The Agency believes that your device labeling is an essential component in communicating the dosing specifications of the device. Accordingly, please include the particle specifications that you have established in your performance testing for the drug, including mass-median aerosol diameter (MMAD), total delivered dose, total respirable dose, respirable fraction and geometric standard deviation (GSD). For each of the specifications identified above, please include the range of measurements observed in your performance tests and provide the corresponding standard deviation. We recommend that you characterize particle size using three categories: course particles (>4.7 microns), fine particles (<4.7 microns), and extra-fine particles (<1 micron). As a function of the total dose delivered, please include specifications for the total mass and the fraction of each of these size ranges. Please note that each of the specifications listed in the labeling should be shown to have an appropriate level of statistical confidence as demonstrated by your performance tests.

ATTACHMENT 2

EVALUATION OF UPDATED STABILITY DATA (13 JAN 2012 amendment)

Appearance (Device): All lots met the criteria.

Appearance (surface markings): No significant changes are apparent in either individual surface markings or in total area of surface markings.

Device Functionality: At each time point each of the 16 devices successfully activated and actuated. One did, however initially fail to actuate. This was attributed to an analyst error, and did actuate at higher flow rate (“as instructed per test method”). The most likely cause of failure was stated to be “incorrect installation of the device to the test apparatus resulting in a leak”.

Coated Dose Assay: All samples remained within specified limits. The possible minor trend towards decreased assay observed in the previous review was no longer apparent when the nine- and 12-month data were considered.

Emitted Dose: All lots remained well within specified limits. No significant changes were noted.

Primary Package Leak Test: All lots met acceptance criteria.

Seal Strength: The results remained within specified limits through six months accelerated and 12 months long-term storage conditions. (b) (4)

(b) (4)
All data did however remain well within the acceptance criteria, and appear likely to remain so through the proposed (b) (4) expiry period.

“Mean” Aerosol Impurities: No impurities were found above the reporting threshold (0.1%). Except in one lot an unspecified impurity was found at the 9-month time point at (b) (4) it was not reported at the 12 month time point.

Aerosol Particle Size: (b) (4)

(b) (4)
Similar trends were noted in the RSL. These changes are unlikely to significantly impact product performance.

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

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

/s/

DAVID J CLAFFEY
03/23/2012

RAMESH K SOOD
03/23/2012

NDA 22-549

**STACCATO®
Loxapine Inhalation Powder**

Alexza Pharmaceuticals, Inc

Review #2

**David J. Claffey, PhD
ONDQA**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	3
The Executive Summary	7
I. Recommendations	7
A. Recommendation and Conclusion on Approvability	7
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	7
II. Summary of Chemistry Assessments.....	7
A. Description of the Drug Product(s) and Drug Substance(s)	7
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature.....	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment	12
S DRUG SUBSTANCE.....	24
P DRUG PRODUCT	29
A APPENDICES	78

Chemistry Review Data Sheet

1. NDA 22-549
2. REVIEW: #2
3. REVIEW DATE: 31 OCT 2011
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

IND 73,248 IND (b) (4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

N-026

4 AUG 2011

N-028

25 OCT 2011

7. NAME & ADDRESS OF APPLICANT:

Name: Alexza Pharmaceuticals
Address: 2091 Steirlin Court, Mountain View, CA
Representative: Christine Welch, MS

Chemistry Review Data Sheet

Telephone:

(650) 944 7030

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ADASUVE
- b) Non-Proprietary Name (USAN): loxapine inhalation powder
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Agitation associated with schizophrenia or bipolar disorder in adults

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: Rx OTC

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

SPOTS product – Form Completed

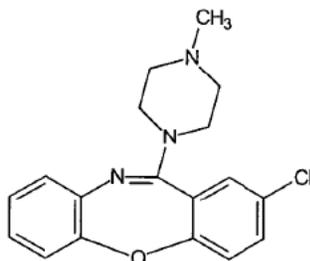
Not a SPOTS product

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

INN: loxapine base

Chemistry Review Data Sheet

Chemical Name: 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b, f][1,4]oxazepine
 CAS#: [1977-10-2]



C₁₈H₁₈ClN₃O
 327.81 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	adequate	31 OCT 2011	
				4			

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION



CHEMISTRY REVIEW



Chemistry Review Data Sheet

18. STATUS:

ONDC: (review cycle#1)

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	pending		Quynh Nhu Nguyen & Nayan Patel
EES	pending		
Pharm/Tox	Pending		
Biopharm	pending		
LNC	“loxapine inhalation powder”		
Pulmonary CMC	approval	27 AUG 2010	Craig Bertha, PhD

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-549

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend that this application be approved pending acceptable recommendations from CDER Office of Compliance and CDRH. There is insufficient stability data accumulated to-date to support the proposed (b) (4) drug product expiry period. The applicant stated that additional stability data would be provided during this review cycle. An expiry period will be assigned after evaluation of the additional stability data.

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

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE: The original NDA (17-525) for loxapine (as the succinate) was approved in 1975 for dosage strengths up to 50 mg as orally administered capsules and tablets. NDA 17-658 was approved in 1976 for the HCl salt. NDA 18-039 was approved in 1979 for an intramuscular formulation of the HCl salt. All of these applications have been discontinued. Several generic products have been approved and remain active for loxapine succinate up to 50 mg strength as an orally administered capsule (ANDA 72-206 is the current RLD). (b) (4)

(b) (4) manufactured all lots that were used in the pivotal Phase III studies (Clinical Version 2). All subsequent and future lots (for Commercial Versions of the drug product) were manufactured by (b) (4). Drug product manufactured from drug substance from both suppliers were comparable. Drug substance data was provided in DMF (b) (4) and was found to be inadequate to support this application in the initial review cycle due to the lack of control over (b) (4). The drug substance specification was amended to include a control (u) (4) at (b) (4). This adequately resolved this issue.

DRUG PRODUCT: The proposed drug product is a hand-held, single-dose, single-use drug/device combination product with CDER being the lead review center. Inhalation through the product initiates the heating of a film of excipient-free loxapine coated on a heat package component to form a vapor which condenses into aerosol particles of a

Executive Summary Section

specified particle size distribution appropriate for deep lung deposition. Absorption of the drug through the lung provides peak plasma levels in the systemic circulation shortly after administration.

The principal components of the product are as follows:



(b) (4)



(b) (4)

Executive Summary Section

Immediately prior to administration, the health care provider pulls the activation tab, (b) (4)

The battery then charges a capacitor on the printed circuit board, which when fully charged causes an LED light on the device to illuminate. This indicates that the product is ready for administration. If not used within 15 minutes the light will turn off indicating that the device has self-deactivated. The patient is instructed to exhale fully then to inhale through the mouth piece with a “steady deep breath”, then to remove the mouth piece and to hold their breath “briefly”. Successful actuation is signaled by the extinction of the green LED light. Actuation is accompanied by a ‘clicking’ sound and a visible flash of light –both produced by the incendiary reaction within the heat package.

(b) (4)

The product’s “label-claim” strength (b) (4) 9.1 mg which represents the target amount of drug emitted from the (b) (4) 10 mg strength product (b) (4) (b) (4) 10 mg represents the target amount of drug present in the product will appear on the device/pouch labels. The labeled strength represents the amount of drug that the device is designed to deliver to the patient (i.e. the delivered or emitted dose, ca. 90%) and is derived from historical data through product development.

The drug product specification includes typical tests such as appearance, identity, assay as well as more specific tests for this product such as emitted dose, emitted dose uniformity, aerosol particle size distribution and aerosol particulates. Impurity levels (including (b) (4) levels) are measured in the aerosol rather than the drug film – the proposed limits are in agreement with ICH Q3B recommendations. Three critical quality attributes were identified - emitted dose, aerosol purity and aerosol particle size distribution. These attributes were tested during design verification testing after modifications were made to the product during development.

Executive Summary Section

Evaluation of this application was complicated by the numerous iterations of the device that were used during development. A single version of the product – Clinical Version 2- was used for all the pivotal Phase III clinical studies. A complete redesign of the device took place after completion of these studies – to give Commercial Version 1. (b) (4)

(b) (4) Data from a bioequivalence study and numerous in vitro characterization studies was provided to link the clinical performance of Commercial Version 1 to the product that was used in the pivotal clinical studies (Clinical Version 2). Further less drastic changes to Commercial Version 1 (b) (4) (b) (4) gave Commercial Version 2 which were used for the registration stability studies as well as other smaller clinical safety studies. Further revision involving (b) (4) gave Commercial Version 3 (aka Commercial Version 2.1). Further changes were proposed during the previous review cycle – (b) (4) this current version is termed Commercial Version 2.2. It should be noted that the version numbers were assigned at time of filing at this reviewer's request and the initial application generally referred to a single "Commercial Version".

This reviewer accompanied the investigator on the preapproval inspection at the drug product manufacturing site, Alexza Pharmaceuticals, Mountain View, CA during the first review cycle which resulted in a 'Withhold' recommendation from CDER Office of Compliance. Several issues were uncovered during the inspection that negatively impacted this reviewer's ability to make an approval recommendation from a CMC perspective at that time. These are detailed in Review #1. An outline of one of these issues (stability data) is included the executive summary of Review #1. The applicant resolved the main issues concerning the inappropriate stability storage conditions, (b) (4) and lack of link of stability studies to both the final commercial version by initiating new stability studies (b) (4) with the final commercial version of the device. Data through six-months storage at long-term and accelerated storage conditions was provided. No significant changes were detected thus far. The applicant expects to provide additional stability data to the application during this review cycle to support an (b) (4) expiry period. *An expiry period will be assigned after evaluation of the additional stability data.*

The remaining outstanding issues have been resolved by including or modifying in-process tests for weight of drug on tray-side, addition of controls (b) (4) changes (b) (4) controlled by the thermogram test and initiation of appropriate heat package stability studies.

CDRH is currently evaluating this submission. A recommendation regarding the approvability of this application from their perspective is pending.

Executive Summary Section

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

The drug product is a single use product and is expected to be administered with the aid of a health care professional. The recommended dose is 10 mg (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

DMF (b) (4) was found to be acceptable to support this application and the responses to the deficiencies listed in the 8 OCT 2010 CR letter were generally adequately addressed.

However an approval recommendation can not be made from a CMC perspective at this time until:

- An acceptable recommendation is received from the Office of Compliance.
- The application is found acceptable from a CDRH perspective.
- Data to support the proposed (b) (4) expiry period is provided.

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

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

C. CC Block

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

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

/s/

DAVID J CLAFFEY
11/14/2011

RAMESH K SOOD
11/15/2011

MEMORANDUM

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

DATE: October 5, 2010

FROM: David J. Claffey, Ph.D., ONDQA

SUBJECT: **Office of Compliance overall recommendation for NDA 22-549**

On October 5, 2010 CDER Office of Compliance issued an overall “Withhold” recommendation for NDA 22-549 (Attachment). Two sites were evaluated – the drug substance manufacturing site [REDACTED] ^{(b) (4)} was found to be acceptable “based on profile”, however a “withhold” recommendation was issued for the drug product manufacturing site (Alexza pharmaceuticals, Mountain View, CA).

An approval recommendation from a CMC perspective can not be made until this and the other issues listed in CMC Review #1 are resolved.

ATTACHMENT
FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22549/000	Sponsor:	ALEXZA PHARMS
Org. Code:	130		2091 STIERLIN CT
Priority:	3		MOUNTAIN VIEW, CA 94043
Stamp Date:	11-DEC-2009	Brand Name:	
PDUFA Date:	11-OCT-2010	Estab. Name:	
Action Goal:		Generic Name:	LOXAPINE
District Goal:	12-AUG-2010	Product Number; Dosage Form; Ingredient; Strengths	
			001; AEROSOL; LOXAPINE; EQ 5MG BASE
			002; AEROSOL; LOXAPINE; EQ 10MG BASE
FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	D. CLAFFEY	Review Chemist	301-796-1343
	T. OLIVER	Team Leader	301-796-1728

Overall Recommendation: WITHHOLD on 05-OCT-2010 by T. GOOEN (HFD-320) 301-796-3257

Establishment: CFN: ALEXZA PHARMACEUTICALS, INC.
2091 STIERLIN COURT
MOUNTAIN VIEW, CA 940434655 FEI: 3007119522

DMF No: AADA:

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

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** POTENTIAL OAI

Last Milestone: OC RECOMMENDATION

Milestone Date: 05-OCT-2010

Decision: WITHHOLD

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-FEB-2010

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

/s/

DAVID J CLAFFEY
10/05/2010

RAMESH K SOOD
10/05/2010

NDA 22-549

**STACCATO®
Loxapine Inhalation Powder**

Alexza Pharmaceuticals, Inc

Review #1

**David J. Claffey, PhD
ONDQA**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	13
C. Basis for Approvability or Not-Approval Recommendation.....	13
III. Administrative.....	13
A. Reviewer's Signature.....	13
B. Endorsement Block.....	13
C. CC Block	14
Chemistry Assessment	15
S DRUG SUBSTANCE.....	15
P DRUG PRODUCT	26
A APPENDICES	199
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1	200
A. Labeling & Package Insert	201
B. Environmental Assessment Or Claim Of Categorical Exclusion	205
The applicant claimed a categorical exclusion under 21 CFR 25.31(b). Calculated loxapine levels were (b) (4) entering publicly owned treatment works, several orders of magnitude less than the required limit (1 ppb). A similar level was calculated for (b) (4) and (b) (4) (b) (4) components.....	205
Evaluation: Adequate.	205
III. List Of Deficiencies To Be Communicated.....	205



CHEMISTRY REVIEW



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

Chemistry Review Data Sheet

1. NDA 22-549
2. REVIEW: #1
3. REVIEW DATE: 10 SEP 2010
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

Document Date

IND 73,248 IND (b) (4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Document Date

N-000	11 DEC 2009
N-001 (response to CMC IR)	1 FEB 2010
N-002 (response to CMC IR)	3 FEB 2010
N-005 (delineation of commercial versions)	10 MAR 2010
N-009 (drug product stability update)	20 MAY 2010
N-010 (response to CMC IR)	8 JUN 2010
N-013 (response to main CMC IR)	2 JUL 2010
N-015 (header, ds spec update)	19 JUL 2010
N-018 (b) (4) issue)	31 AUG 2010

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: Alexza Pharmaceuticals
Address: 2091 Steirlin Court, Mountain View, CA
Representative: Christine Welch, MS
Telephone: (650) 944 7030

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: ADASUVE
- b) Non-Proprietary Name (USAN): loxapine inhalation powder
- c) Code Name/# (ONDC only):
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type:
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment of Agitation associated with schizophrenia or bipolar disorder in adults

11. DOSAGE FORM: inhalation powder

12. STRENGTH/POTENCY: 5 mg and 10 mg

13. ROUTE OF ADMINISTRATION: inhalation

14. Rx/OTC DISPENSED: x ___ Rx ___ OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
_____SPOTS product – Form Completed

Chemistry Review Data Sheet

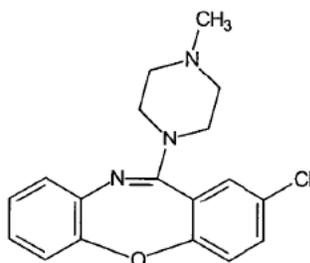
 x Not a SPOTS product

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

INN: loxapine base

Chemical Name: 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b, f][1,4]oxazepine

CAS#: [1977-10-2]



C₁₈H₁₈ClN₃O
327.81 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	inadequate	SEP 2010	
				4			Advised applicant to reconsider proposed (b) (4)

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

Chemistry Review Data Sheet

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CDRH	pending		Quynh Nhu Nguyen
EES	pending		
Pharm/Tox	Pending		
Biopharm	pending		
LNC	“loxapine inhalation powder”		
Pulmonary CMC	approval	27 AUG 2010	Craig Bertha, PhD

19. ORDER OF REVIEW (OGD Only)

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

The Chemistry Review for NDA 22-549

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An approval recommendation from a CMC perspective can not be made until the issues listed at the end of the review for inclusion in the Action Letter are resolved.

The San Francisco District Office issued a 'withhold' recommendation at the conclusion of the preapproval inspection. The observations listed in the resulting 483 will require resolution before an approval from a CMC perspective can be made.

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

II. Summary of Chemistry Assessments

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

DRUG SUBSTANCE: The original NDA (17-525) for loxapine (as the succinate) was approved in 1975 for dosage strengths up to 50 mg as orally administered capsules and tablets. NDA 17-658 was approved in 1976 for the HCl salt. NDA 18-039 was approved in 1979 for an intramuscular formulation of the HCl salt. All of these applications have been discontinued. Several generic products have been approved and remain active for loxapine succinate up to 50 mg strength as an orally administered capsule (ANDA 72-206 is the current RLD). (b) (4)

(b) (4) manufactured all lots that were used in the pivotal Phase III studies (Clinical Version 2). All subsequent and future lots (for Commercial Versions of the drug product) were manufactured by (b) (4) (DMF (b) (4) Drug product manufactured from drug substance from both suppliers were comparable. Drug substance data was provided in DMF (b) (4) and was found to be inadequate to support this application.

DRUG PRODUCT: The proposed drug product is a hand-held, single-dose, single-use drug/device combination product with CDER being the lead review center. Inhalation through the product initiates the heating of a film of excipient-free loxapine coated on a heat package component to form a vapor which condenses into aerosol particles of a specified particle size distribution appropriate for deep lung deposition. Absorption of the

Executive Summary Section

drug through the lung provides peak plasma levels in the systemic circulation shortly after administration.

The principal components of the product are as follows:



Executive Summary Section

Immediately prior to administration, the health care provider pulls the activation tab, (b) (4)

The battery then charges a capacitor on the printed circuit board, which when fully charged causes an LED light on the device to illuminate. This indicates that the product is ready for administration. If not used within 15 minutes the light will turn off indicating that the device has self-deactivated. The patient is instructed to exhale fully then to inhale through the mouth piece with a “steady deep breath”, then to remove the mouth piece and to hold their breath “briefly”. Successful actuation is signaled by the extinction of the green LED light. Actuation is accompanied by a ‘clicking’ sound and a visible flash of light –both produced by the incendiary reaction within the heat package.



The product’s “label-claim” strengths are (b) (4) 9.1 mg which represents the target amount of drug emitted from the (b) (4) 10 mg strength product (b) (4) (b) (4) 10 mg represents the target amount of drug present in the product – these numbers will appear on the device/pouch labels. The labeled strength represents the amount of drug that the device is designed to deliver to the patient (i.e. the delivered or emitted dose, ca. 90%) and is derived from historical data through product development.

The drug product specification includes typical tests such as appearance, identity, assay as well as more specific tests for this product such as emitted dose, emitted dose uniformity, aerosol particle size distribution and aerosol particulates. Impurity levels (including (b) (4) levels) are measured in the aerosol rather than the drug film – the proposed limits are in agreement with ICH Q3B recommendations. Three critical quality attributes were identified - emitted dose, aerosol purity and aerosol particle size distribution. These attributes were tested during design verification testing after modifications were made to the product during development.

Executive Summary Section

Evaluation of this application was complicated by the numerous iterations of the device that were used during development. A single version of the product – Clinical Version 2- was used for all the pivotal Phase III clinical studies. A complete redesign of the device took place after completion of these studies – to give Commercial Version 1. (b) (4)

(b) (4) Data from a bioequivalence study and numerous in vitro characterization studies was provided to link the clinical performance of Commercial Version 1 to the product that was used in the pivotal clinical studies (Clinical Version 2). Further less drastic changes to Commercial Version 1 (b) (4) (b) (4) gave Commercial Version 2 which were used for the registration stability studies as well as other smaller clinical safety studies. Further revision involving (b) (4) gave Commercial Version 3 (aka Commercial Version 2.1). Further changes were proposed during this review cycle – (b) (4) a version number for this iteration has yet to be assigned. It should be noted that the version numbers were assigned at time of filing at this reviewer's request and the initial application generally referred to a single "Commercial Version".

Quality issues encountered during preapproval inspection (PAI):

This reviewer accompanied the investigator on the preapproval inspection at the final drug product manufacturing site, Alexza Pharmaceuticals, Mountain View, CA from August 2-11, 2010. At close of the inspection a 483 was issued with 10 observations. Several issues were uncovered during the inspection that negatively impacted this reviewer's ability to make an approval recommendation from a CMC perspective. These are detailed in the review. An outline of one of these issues (stability data) is included below. The remaining issues are listed below and outlined in Attachment 1 of this document.

Integrity of Registration Stability data:

(b) (4)

Executive Summary Section

(b) (4)

(b) (4)

This is a clear violation of cGMP (21 CFR 211.166 (a) (4)) and a breach of the stability protocol

These observations in combination with other previously known factors demonstrate that the lots used for the registration stability lots no longer adequately represent the proposed commercial drug product – and that they can not be used as primary stability data to assign an expiry period. A request will be forwarded to the applicant that data be generated with the final commercial iteration of the product packaged in the final iteration of the commercial packaging (under cGMP conditions).

(b) (4)

complete

resolution of this issue does not appear to be an unreasonable or burdensome request.

Other PAI issues: (refer to Attachment 1 and review document for details)

- Inappropriate storage of heat package stability samples
- Lack of in-process weight check for tray side for drug
- Lack of control over (b) (4) levels in drug film
- Questionable capability of drug (b) (4) operation
- Insufficient control over heat package heating (thermogram test)

It should be noted that this reviewer was one of a team that evaluated the quality aspects of this product. Evaluations by the other team members have been filed in DAARTS. Quynh-Nhu Nguyen found the application not acceptable from a CDRH perspective (email 9 SEP 2010, final review pending). Dr Craig Bertha recommended that this application be approved from a “CMC perspective related to the aspects of the

Executive Summary Section

drug uniquely associated with products for oral inhalation”. David Darr from CDRH Office of Compliance evaluated the data from a CDRH Office of Compliance perspective and forwarded recommendations to the ORA investigators. CDER Office of Compliance was alerted to this application via a Consideration for Inspections Memo by this reviewer resulting in a memo by Dr. Vibhakar Shah which was sent to the ORA SFDO. The preapproval inspection was led by Peter Baker who concentrated on the drug compliance issues. Mark E Chan concentrated on that device compliance issues. This reviewer and Dr Vibhakar Shah accompanied the ORA investigators.

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

The drug product is a single use product and is expected to be administered with the aid of a health care professional. The recommended dose is 10 mg (b) (4)

C. Basis for Approvability or Not-Approval Recommendation

An approval recommendation can not be made from a CMC perspective at this time until the outstanding issues outlined at the end of this document for inclusion in the action letter are resolved and until:

- An acceptable recommendation is received from the Office of Compliance.
- DMF (b) (4) is found to be acceptable to support this application.
- The application is found acceptable from a CDRH perspective.

Note: Dr Craig Bertha recommended that this application be approved from a “CMC perspective related to the aspects of the drug uniquely associated with products for oral inhalation”. Data for delivered dose uniformity, aerodynamic particle size distribution and leachables were evaluated by Dr Bertha.

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

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

Executive Summary Section

C. CC Block

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

DAVID J CLAFFEY
09/10/2010

RAMESH K SOOD
09/10/2010

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

DATE: 23-AUG-2010

TO: N22549 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Ramesh Sood, Ph.D.
Branch Chief
ONDQA, Division I, Branch I



SUBJECT: Review of updated drug product stability data in the 20-MAY-2010, amendment; Review of response to CMC questions 1-12 of the 17-MAY-2010, information request letter submitted in the 07-JUN-2010, amendment; Review of the 29-JUL-2010, amendment for (b) (4) leachable method; Review of the 18-AUG-2010 amendment regarding the stability protocol for the process validation batches

BACKGROUND: The first review of the inhalation product aspects of this drug product resulted in a group of information request comments that were sent to the applicant in the information request letter dated 17-MAY-2010. The 07-JUN-2010, amendment is a response to these information request comments and will be evaluated in the current review below.

Additionally, the Agency agreed to allow the applicant to submit additional stability data during the review of the application. The 20-MAY-2010, submission provides the 9 and 12 month stability data (25°C/60%RH) for the six registration stability lots (Commercial Version 2), including leachables, as well as the 18 month data (25°C/60%RH) for the two supportive stability lots with the Commercial Version 1 configuration. The data for delivered dose uniformity (DDU), aerodynamic particle size distribution (APSD), and the leachables will be reviewed herein as well.

Recommendation

From the CMC perspective related to the aspects of the drug uniquely associated with products for oral inhalation, it is recommended that this application can be **approved**.

Post-Approval Commitment

There is one commitment that the applicant has agreed to fulfill post-approval, and this should be included in the action letter upon approval (see p. 10 below):

Alexza commits to implement, within 6 months of the date of approval of the application, the appropriate controls (routine extraction testing with acceptance criteria) for [REDACTED] (b) (4) to ensure that levels remain below the levels that have been qualified by the risk assessments in Module 4.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:

ONDQA/DIV 1/Branch II/CBertha/8/23/10

ONDQA/DIV 1/Branch I/DClaffey

ONDQA/DIV 1/Branch I/TOliver

ONDQA/DIV 1/Branch II/ASchroeder

ODEI/DPP/KUpdegraff

ODEI/DPP/DFegley

ONDQA/DIV 1/Branch I/RSood_____

ONDQA/DIV 1/Branch II/PPeri

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

CRAIG M BERTHA
08/23/2010

RAMESH K SOOD
08/27/2010

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

DATE: 26-APR-2010

TO: N22549 File

FROM: Craig M. Bertha, Ph.D.
Chemistry Reviewer
ONDQA, Division I, Branch II

THROUGH: Prasad Peri, Ph.D.
Acting Branch Chief
ONDQA, Division I, Branch II

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

SUBJECT: Review of CMC information and data specific for pulmonary inhalation drug products from the 11-DEC-2009, original submission and 03-FEB-2010, amendment (clarification of various commercial versions) of N22549



BACKGROUND: The combination product of NDA 22549, Staccato® (loxapine for inhalation) from Alexza Pharmaceuticals, Inc. is to be used for the rapid treatment of agitation associated with Schizophrenia or Bipolar Disorder. The drug product is a combination product, consisting of a device and drug formulation (neat drug), designed to produce an aerosol of loxapine to be delivered via oral inhalation for systemic uptake from the lungs of patients. Each combination product unit is for a single use and delivers (b) (4) 9.1 mg of aerosolized neat loxapine drug for oral inhalation. Figure 41 reproduced from P.2.2 below shows the components of the device. (b) (4)

The inhalation maneuver of the patient activates a mechanical flow switch and a capacitor charged by the battery ignites the starter assembly on the heat pack. The heat pack encloses thermite reactants which allow the immediate heating of the upper and lower surfaces of the pack to ~420°C, which quickly vaporizes the loxapine coating on the outside of the stainless steel surfaces of the heat pack. The resultant

loxapine vapor is entrained in the inhalation air stream where it is then inhaled by the patient for delivery to the systemic circulation via the lungs.

Figure 41. Schematic of Changes in the Commercial Version of *Staccato* Loxapine



Many of the characterization and quality control tests that have been performed in the development of this drug product are analogous to what is commonly done for other more typical oral inhalation drug products, such as inhalation aerosols (metered dose inhalers) and inhalation powders (dry powder inhalers). The Initial Quality Assessment for NDA 22549 has recommended that the assigned CMC reviewer (David Claffey, Ph.D.) consult with CMC reviewers that are familiar with the review of inhalation drug products for the Division of Pulmonary, Allergy, and Rheumatology Products. As a result, on 12-APR-2010, a meeting was held between the CMC-team assigned to review N22549 (Thomas Oliver, Ph.D., David Claffey, Ph.D.) and members of branch II of Division I that are familiar with the review of the CMC aspects of inhalation drug product applications (Prasad Peri, Ph.D., Alan Schroeder, Ph.D., Craig M. Bertha, Ph.D.). The meeting was chaired by Christine Moore, Ph.D. Based on discussion and agreement between the reviewers, Drs. Claffey and Bertha, it was outlined that Dr. Bertha would review the extractables/leachables information and data, drug product characterization studies, the delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) methods, and will evaluate and compare the *in vitro* dose performance data across the pertinent versions of the drug product.

The applicant used Clinical Version 2 of the drug product to conduct the pivotal phase III clinical studies. However, the applicant made revisions to that drug product configuration subsequent to these clinical studies. There are three distinct versions that followed Clinical Version 2, as shown in the table reproduced from the 03-FEB-2003, amendment below. These are Commercial Versions 1, 2, and 3.

Figure 1. Flow Chart of Commercial Device Versions and Incremental Changes

Use/Purpose	Version	Change
(b) (4)		

The bioequivalence study 004-103 was to provide a “link” of the Commercial Version 1 (“CV1” in plots and tables) product to the Clinical Version 2 product used in the phase III trials. However, the applicant changed (b) (4)

This yielded Commercial Version 2 (“CV2” in plots and tables), which was used in four clinical studies, for the drug product characterization studies, and for the manufacture of the six registration stability batches. A placebo version using the Commercial Version 2 device was also used to assess actuation reliability (study 004-R1). There was also one scale-up lot of this version produced (M0641-A).

Following Commercial Version 2, the applicant could no longer (b) (4)

This resulted in Commercial Version 3, which was originally the one planned for marketing. The extractables/leachables evaluation was done with the Commercial Version 3. Limited stability data were also obtained for the Commercial Version 3 of the product.

However, the CMC team considered the changes (b) (4) to be a relatively major change and recommended that these changes only be made post-approval. Based on that recommendation, the applicant now proposes to market Commercial Version 2, (b) (4) (see amendment dated 03-FEB-2010). This (b) (4) version can be referred to as Commercial Version 2/3 for the purpose of this review. It does not appear that there are any data for this particular configuration in the application, which is not unexpected considering the circumstances.

For inhalation drug products, the Agency has consistently and strongly recommended to sponsors that they use the final to-be-marketed versions of their drug product in the key clinical studies supporting the application, and to have their development of the drug product complete prior to the pivotal clinical studies. This was not the case for this development program. And although the changes made subsequent to the Clinical Version 2 used in phase III (b) (4) they could possibly complicate and confound the interpretation of the clinical results. As indicated above, the bioequivalence study 004-103 was performed to provide a link of Clinical Version 2 to the Commercial Version 1. Beyond that link, to help the clinical Division gauge the later changes made in going from Commercial Version 1 to Commercial Version 2 and then to Commercial Version 3, the *in vitro* drug delivery data available from the testing of these various versions will be compared. The main focus of this review will involve the comparison of the data from the important *in vitro* tests of delivered dose uniformity (DDU) and aerodynamic particle size distribution (APSD) by cascade impaction, to gauge the impact of the device changes that have been made. If the data from these (and the other specification parameters) are found to be comparable across the various device versions, that will then provide some level of assurance that the clinical performance might not be impacted by the various changes that have been made. It is recognized that there are cases that have been observed where *in vitro* dose delivery performance data obtained for devices of differing design are comparable, but where the measured systemic pharmacokinetic profiles are quite different.¹ However, in this case, the changes that have been made to the drug product through development were incremental, and have *not* involved changes in the basic function and overall design of the drug product, thus it is more likely that there is a reasonable correlation of the *in vitro* dose delivery performance and the *in vivo* behavior, such that an alteration of the *in vitro* performance would likely signal a change in the *in vivo* performance. To be clear, however, it is understood that the correlation of the *in vitro* performance to the *in vivo* delivery is not rigorously established with data in this application.

¹ Daley-Yates, PT; Parkins, DA; Thomas, MJ; Gillett, B; House, KW, Ortega, HG *Pharmacokinetic, Pharmacodynamic, Efficacy, and Safety Data From Two Randomized, Double-Blind Studies in Patients With Asthma and an In Vitro Study Comparing Two Dry-Powder Inhalers Delivering a Combination of Salmeterol 50 mcg and Fluticasone Propionate 250 mcg: Implications for Establishing Bioequivalence of Inhaled Products*. *Clinical Therapeutics*, **31** (2), 2009, pp. 370-385.

Recommendation

The evaluation below is segmented in accordance with the CTD sections of the application from which they were included, such that these portions can be easily incorporated into the final CMC review of N22549. It is requested that the PM send the applicant the information request comments that are included in the attached draft letter on p. 54 of this review.

Craig M. Bertha, Ph.D.
CMC Reviewer, ONDQA

cc:

ONDQA/DIV 1/Branch II/CBertha
ONDQA/DIV 1/Branch I/DClaffey
ONDQA/DIV 1/Branch I/TOliver
ONDQA/DIV 1/Branch II/ASchroeder
ODEI/DPP/KUpdegraff
ONDQA/DIV 1/Branch I/RSood_____
ONDQA/DIV 1/Branch II/PPeri_____

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

CRAIG M BERTHA
04/26/2010

PRASAD PERI
04/26/2010
I concur

RAMESH K SOOD
04/28/2010

Initial Quality Assessment Branch I

OND Division: Division of Psychiatry Products
NDA: 22-549
Applicant: Alexza Pharmaceuticals, Inc.
Letter Date: 11-DEC-09
Stamp Date: 11-DEC-09
PDUFA Date: 11-OCT-10
Trademark: Staccato® Loxapine for Inhalation
Established Name: loxapine
Dosage Form: aerosol (5mg and 10 mg)
Route of Administration: Inhalation
Indication: Rapid treatment of agitation associated with schizophrenia and bipolar disorder
Assessed by: Thomas F. Oliver, Ph.D.

Summary

Staccato® Loxapine for Inhalation (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product that provides rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. *Staccato* Loxapine was developed under IND 73,248 and represents a new dosage form for loxapine, an antipsychotic that has been available in the United States (US) since 1975. Loxapine binds with high affinity to dopamine D₂ receptors and acts as an antagonist at this receptor, as well as binding with high affinity at serotonin 5-HT_{2A} receptors. The applicant had an EOP2 meeting (September 13, 2007) with the clinical division where the following CMC issues were discussed: heat package integrity, extractables/leachables, morphology, uniformity, and mechanical stability of the coated drug film, product characterization, measuring particle size distribution [REDACTED] (b) (4) drug product specifications, registration stability study protocol, and stability program. The applicant had a pre-NDA meeting (July 14, 2009) with the clinical division where the following CMC issues were discussed: particle size distribution and control, drug product stability data, organization/content of quality section of NDA. Minutes for both meetings can be found in DARTS and should be read by the reviewer.

Drug Substance

The NDA applicant references DMF # [REDACTED] (b) (4) [REDACTED] (b) (4) for information on loxapine (LoA dated 22-OCT-09). DMF # [REDACTED] (b) (4) (letter dated 30-SEP-09, received 02-OCT-09) has not been reviewed (DARTS). Loxapine will be manufactured by [REDACTED] (b) (4) [REDACTED] (b) (4)

Drug Product

Staccato® Loxapine for Inhalation will be available in 5 mg and 10 mg single-use disposable units for the treatment of agitation associated with schizophrenia or bipolar disorder in adults. [REDACTED] (b) (4)

Staccato® Loxapine for Inhalation is a drug-device combination product and is available in two doses: 5 mg and 10 mg. For the 5 mg dose, loxapine is coated onto one surface of the heat package. For the 10 mg dose, loxapine is coated onto both surfaces of the heat package. There are no excipients in the drug product. Oral inhalation through the product initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a thermally generated, highly pure drug vapor. The vapor condenses into aerosol particles with a particle size distribution (1.0 to 3.5 μm) appropriate for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after administration.

The interior surface of the stainless steel substrate of the heat package is coated with a (b) (4). When activated, this undergoes a controlled, gasless, oxidation-reduction (redox) reaction that liberates heat. The redox reaction is initiated by a battery-activated starter inserted into the heat package. Inhalation through the product is detected by the breath sensor, causing the starter to initiate the redox reaction and subsequent rapid heating of the substrate to approximately 400°C. Heat then transfers into the film of loxapine that is coated on the exterior surface of the substrate. The loxapine vaporizes in <1 second, thereby limiting thermal decomposition. The vapor cools in the airflow and condenses to form aerosol particles that are characterized by a mass median aerodynamic diameter in the range of 1.0 to 3.5 μm .

The applicant has developed three versions (clinical version 1, clinical version 2, and commercial version) of the inhalation through clinical development. The principal components of *Staccato* Loxapine are: 1) heat package: the sealed assembly, composed of a reactant coating on the interior surfaces of stainless steel substrates, that generates heat to vaporize the drug and produce the aerosol, 2) drug coating: the thin film of excipient-free loxapine coated on the exterior stainless steel surface(s) of the heat package [single-sided coating for the 5 mg dose and double-sided coating for the 10 mg dose], 3) breath sensor: the breath-activation mechanism that initiates actuation of the heat package, and 4) airway: the channel formed by the medical-grade plastic housings surrounding the heat package; it controls and directs the airflow over the vaporizing drug.

The manufacturing process involves (b) (4)

(b) (4) The Staccato® Loxapine for Inhalation will be manufactured by Alexza Pharmaceuticals, Inc. (Mountain View, CA).

(b) (4) manufactures and tests heat packages used for the commercial drug product in conformance with the specifications that have been provided by Alexza. The heat package specification includes testing for: appearance, mean surface temperature, surface temperature uniformity, and (b) (4) rate before actuation.

The proposed commercial batch size for Staccato® Loxapine for Inhalation (*Staccato Loxapine*) is (b) (4)

(b) (4) These representative batch sizes do not account for sampling or processing losses.

The Staccato® Loxapine for Inhalation (*Staccato Loxapine*) devices are packaged in a foil pouch to maintain cleanliness and provide environmental protection during the life cycle of the product. (b) (4)

(b) (4) The applicant has proposed a 24 month expiry.

Critical Issues for Review

• The NDA holder cross-references DMF # (b) (4) [(b) (4) for information on the drug substance, loxapine (LoA dated 22-OCT-09). DMF # (b) (4) (letter dated 30-SEP-09, received 02-OCT-09) has not been reviewed (DARTS). DMF (b) (4) will need to be evaluated and found acceptable.

• The proposed drug substance appearance criterion for loxapine (b) (4) (b) (4) The adequacy of this limit will need to be evaluated as it appears wide.

• The drug substance manufacturer was (b) (4) for the early clinical development, phase 3 clinical studies and the clinical bioequivalence study. The commercial drug substance manufacturer will be (b) (4) (b) (4)

(b) (4) was used in the manufacture of the registration stability lots and clinical trial material for various clinical safety studies (m5.3.5.1, CSR 004-105; m5.3.3.4, CSR 004-106; m5.3.4.1, CSR 004-107; and m5.3.5.1, CSR 004-108). Lot M0617 (a pre-registration stability lot used for design verification testing) was also manufactured using (b) (4) API. It will need to be determined whether the chemical and physical properties of loxapine are comparable between the two manufacturers.

- It will need to be determined whether there are adequate controls for morphology, uniformity, and mechanical stability of the coated loxapine drug film.

- The applicant had made a statement (during development) that (b) (4) In addition, data should be provided on the mechanical stability of the device (due to handling) and its effect on the delivered dose and the aerosol purity.

- The applicant has developed three versions (clinical version 1, clinical version 2, and commercial version) of the inhalation device through clinical development. (b) (4)

The applicant was told that they should evaluate failed devices (FMEA), determine causality and incorporate corrective actions. The reviewer will need determine whether the NDA holder has fixed observed problems.

- The commercial version of the device has a number of differences from the clinical version 2 device. These changes include: (b) (4)

The adequacy of these changes will need to be evaluated in regards to safety and any changes to the chemical and physical properties of the aerosol.

- The applicant has stated (b) (4) these changes include: (b) (4)

The acceptability of these changes will need to be determined.

- The applicant has the following release tests for the heat package: appearance, mean surface temperature, surface temperature uniformity, and (b) (4) rate before actuation. Based on the data generated and any information learned from device failures, the adequacy of these limits will need to be determined and whether any additional tests may be needed. How storage effects these parameters will also need to be evaluated. The

acceptability of the tests and specification lists will need to be determined in conjunction with the CDRH reviewer.

- The proposed specification range for heat package mean surface temperature is (b) (4). It will need to be determined if this specification range is supported in the generation of an aerosol with the desired chemical and physical properties.

- It will need to be determined whether the heat generated from the device resulted in any injuries (e.g., burns) to patients during the clinical program. If so, it will need to be determined whether corrective actions have fixed the problem and/or any labeling warnings are needed.

- (b) (4)

- (b) (4)

- The heat package contains: (b) (4). The leaching of these components into the aerosol will need to be determined as a function of time. Adequate controls will need to be in place to safeguard the purity of aerosol.

- (b) (4). The reviewer will need to evaluate whether the applicant has adequate controls for these factors. In addition, it will need to be determined the sponsor has adequate control on the coating process (b) (4).

- (b) (4). Based on the data generated and any information learned from device failures, the adequacy of these limits will need to be determined and whether any additional tests may be needed. How storage effects these parameters will also need to be evaluated.

- The materials used in the manufacture of (b) (4) will need to be evaluated. The leaching of these materials (or components or these materials) into the aerosol will need to be determined as a function of time. Adequate controls will need to be in place to safeguard the purity of aerosol.

- Assignment of the drug product expiry will need to take battery life into account. Data to support battery life will need to be evaluated along with any information from device failures. Applicant had agreed to provide data evaluating (b) (4) battery leakage as a function of time and temperature in the updated device.

- (b) (4)
Based on the data generated and any information learned from device failures, the adequacy of these limits will need to be determined and whether any additional tests may be needed. How storage effects these parameters will also need to be evaluated.

- The materials used in the manufacture of the (b) (4) will need to be evaluated. The leaching of these materials (or components or these materials) into the aerosol will need to be determined as a function of time. Adequate controls will need to be in place to safeguard the purity of the aerosol.

- (b) (4)
This information will need to be evaluated.

- It will need to be determined whether the sponsor has adequately characterized the observed extractables/leachables and has developed adequate specifications (test methods/ specification limits) for these extractables/leachables. The reviewer will need to work in conjunction with the pharm/tox group.

- The applicant has switched to the (b) (4) for measuring particle size distribution. During a meeting with the NDA holder they were told to generate “comparative data” from multiple batches using both (b) (4) methods. The specifications for Aerosol Particle Size Distribution (APSD) will need to be evaluated and will need to be based on what was used clinically. There should be a specification for mass balance.

- The applicant was told that the identification of foreign particles in the emitted aerosol should be determined and a safety assessment of these particles should be included in their NDA. An appropriate specification will need to be determined for foreign particles in conjunction with pharm/tox.

· In the pharmaceutical development section, the applicant states that (b) (4). However, no unit formula was provided; only a batch formula. As a result, the (b) (4) issue should be verified.

·As this product is a drug-device combination, the CMC reviewer and CDRH reviewer will need to determine which sections are reviewed by each discipline. As the drug-device product is quite complicated in nature with many facets, it will be imperative the two disciplines meet regularly to discuss areas of shared interest.

· The drug product manufacturing process utilizes (b) (4). It will to be determined that there are adequate controls in place so that levels of these (b) (4) in the drug product are acceptable.

· Any material or manufacturing differences between the 5 mg strength (one sided coating) and the 10 mg strength (two sided coating) should be determined. The physical and chemical properties of the both aerosol strengths should be evaluated.

· (b) (4)

· (b) (4) The adequacy of these controls will need to be evaluated.

·As this product is drug-device combination, the CMC reviewer and CDRH reviewer will need to determine which sections are reviewed by each discipline. As the drug-device product is quite complicated in nature with many facets, it will be imperative the two disciplines meet regularly to discuss areas of shared interest.

· The applicant utilizes (b) (4) in number of the drug product manufacturing steps. It will need to be determined whether there are adequate controls for the (b) (4) as loxapine will be delivered to the deep lung.

· The Staccato® Loxapine for Inhalation (*Staccato* Loxapine) devices are packaged in a foil pouch. (b) (4)

(b) (4) The acceptability of the drug product packaging will need to be determined.

• The applicant has an appearance specification for the drug product in the foiled pouch and removed from the foiled pouch. There appears to be no specific markings on the outside of the pouch which differentiates this product from other products. The reviewer should try to secure both a 5 mg and 10 mg drug product sample. The acceptability of the appearance specifications will need to be determined.

• The applicant has set the following specification for Emitted Dose Content Uniformity for the 5 mg strength.

1st Tier Testing (n = 10)

≤1 value outside (b) (4) of Label Claim

No value outside (b) (4) of Label Claim

If 2 or 3 values are in the range (b) (4)

and/or (b) (4) of Label Claim, conduct 2nd Tier Testing

2nd Tier Testing (n = 20; total n = 30)

≤3 values outside (b) (4) of Label Claim

No value outside (b) (4) of Label Claim

The adequacy of this specification will need to be evaluated along with the specification for the 10 mg strength.

• The applicant has set the following specification for Aerosol Particle Size Distribution:

Group 1: (b) (4) (b) (4)

Group 2: (b) (4) (b) (4)

Group 3: (b) (4) (b) (4)

It will need to be determined the acceptability of the aerosol particle size distribution specification.

• The applicant has set the following specification for Foreign Particulates in Aerosol:

(b) (4)

It will need to be determined the acceptability of the foreign particulates in aerosol specification.

• The applicant has set a drug product impurity specification for (b) (4) It will need to be determined the adequacy of this specification.

• The presence of foreign particulate and leachables will need to be evaluated as a function of time.

• The applicant has requested a 24 month expiry for the drug product. The applicant has provided 6 months of stability data from six registration stability lots (three 5 mg and three 10 mg lots) along with supportive stability data. (b) (4)

(b) (4)

It was stated that the 9 and 12 month stability updates will be submitted during the review process. It will need to be determined the acceptability of their proposed expiration date.

- The applicant agreed to test for foreign particulates in the updated device incorporating a variety of aged devices (new and stored devices) to determine if the presence of foreign particulates increases over time. In addition, the sponsor has agreed to provide data from this study and a rationale for not including this test as part of their stability program in their NDA.

It will need to be determined whether the foreign particulates specification limit is acceptable and whether testing needs to be studied until expiry or even further.

- Labeling will need to have adequate instruction on the disposal of the used device, as components could be at a temperature of 440°C.

- It appears the dosage strengths (5 mg and 10 mg) are correctly expressed as 5 mg and 10 mg loxapine in the label. However, the reviewer will need to verify this information.

Comments and Recommendation:

The NDA appears to be fileable from a CMC perspective. My recommendation would be for a single reviewer, but the reviewer will need to be experienced as this product has many facets to be considered. As Dr. Chhagan Tele has worked on this product throughout development, he would be the recommended reviewer. In accordance with 21 CFR §25.31, Alexza Pharmaceuticals, Inc. claims a categorical exclusion from the requirement for an Environmental Assessment or Environmental Impact Statement as the Expected Introduction Concentration (EIC) of the active moiety into the aquatic environment will be below 1 ppb. In addition the applicant states that to the best of their knowledge, no circumstances exist which would cause FDA's approval of *Staccato* Loxapine to significantly affect the quality of the human environment. The device will need to be consulted to CDRH. As this product is a drug-device combination, the CMC reviewer and CDRH reviewer will need to determine which sections are reviewed by each discipline. As the drug-device product is quite complicated in nature with many facets, it will be imperative the two disciplines meet regularly to discuss areas of shared interest. In addition, either a formal consult or an informal consult with ONDQA chemists with experience with drug delivered to the deep lung would also be recommended. The manufacturing, testing and packaging sites will need to be submitted into EES.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22549	ORIG-1	ALEXZA PHARMACEUTICA LS INC	Staccato (loxapine) for Oral Inhalation

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

/s/

THOMAS F OLIVER
01/20/2010

RAMESH K SOOD
01/20/2010

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

Application: NDA 22549/000
Stamp Date: 11-DEC-2009
Recovery: 21-DEC-2012

Action Goal:
District Goal: 22-OCT-2012

Applicant: ALEXZA PHARMS
2091 STIERLIN CT
MOUNTAIN VIEW, CA 94043

Brand Name: Staccato (loxapine) for Oral Inhalation
Estab. Name:
Generic Name: LOXAPINE

Priority: 3
Org. Code: 130

Product Number; Dosage Form; Ingredient; Strengths
001; AEROSOL; LOXAPINE; EQ 5MG BASE
002; AEROSOL; LOXAPINE; EQ 10MG BASE

Application Comment: THIS IS A 505(B)(2) APPLICATION WITH LOXAPINE (WATSON PHARMACEUTICALS) LISTED AS THE REFERENCE LISTED DRUG (on 09-FEB-2010 by D. HENRY () 3017964227)
THE PDUFA GOAL DATE FOR THIS APPLICATION IS OCTOBER 11, 2010 (on 08-FEB-2010 by D. HENRY () 3017964227)

THE CONTACT PERSON FOR THE APPLICATION IS CHRISTINE WELCH, PHONE: 650-944-7030 (on 08-FEB-2010 by D. HENRY () 3017964227)

FOLLOWING A REVIEW OF AN ADDITIONAL RESPONSE FROM ALEXZA REGARDING DEVICE DEFICIENCIES, CDRH/OC CONTINUES TO RECOMMEND WITHHOLD ON THIS APPLICATION AND A RE-INSPECTION PRIOR TO APPROVAL. CDER/OC IS ENTERING A FINAL WH ON CDRH/OC'S BEHALF FOR THIS REVIEW CYCLE. (on 23-APR-2012 by D. SMITH (HFD-323) 3017965321)

SUBMISSION RECEIVED JUNE 2012 HAS PDUFA DATE OF DECEMBER; HOWEVER REVIEW WOULD LIKE TO TAKE ACTION IN SEPTEMBER. PLEASE PLAN INSPECTIONS ACCORDINGLY IF POSSIBLE. (on 02-JUL-2012 by D. SMITH (HFD-323) 3017965321)

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

Overall Recommendation:	ACCEPTABLE	on 20-DEC-2012	by D. SMITH	(HFD-323)	3017965321
	PENDING	on 17-DEC-2012	by EES_PROD		
	PENDING	on 14-DEC-2012	by EES_PROD		
	PENDING	on 02-JUL-2012	by EES_PROD		
	PENDING	on 02-JUL-2012	by EES_PROD		
	WITHHOLD	on 23-APR-2012	by D. SMITH	(HFD-323)	3017965321
	WITHHOLD	on 31-JAN-2012	by EES_PROD		
	PENDING	on 27-JAN-2012	by EES_PROD		
	WITHHOLD	on 05-OCT-2010	by EES_PROD		

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

Establishment: **CFN:** ALEXZA PHARMACEUTICALS, INC.
2091 STIERLIN CT
MOUNTAIN VIEW, CA 940434655
FEI: 3007119522

DMF No: **AADA:**

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

Establishment Comment: CDER OC IS PREPARING A KNOWLEDGE TRANSFER MEMO (KTM) FOR THE INSPECTION OF THIS SITE. (on 21-MAY-2010 by C. CRUZ (HFD-323) 3017963254)
(10/6/2011) **NOTE: THE CMC REVIEWER PARTICIPATED IN THE FIRST INSPECTION AND WOULD LIKE PARTICIPATE IN THE REINSPECTION OF THIS SITE.
(1/27/2012) - THREE DEVICE PROFILE CODES APPLY TO THIS SITE - (b) (4) (on 27-JAN-2012 by T. BOUIE () 3017961649)

Profile: AEROSOL DISPERSED MEDICATION **OAI Status:** NONE
ELECTRONIC ASSEMBLY NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-FEB-2010				HENRYD
SUBMITTED TO DO	17-FEB-2010	Product Specific			STOCKM
ASSIGNED INSPECTION TO IB	11-AUG-2010	Product Specific			RYOUNG
INSPECTION SCHEDULED	11-AUG-2010		12-AUG-2010		RYOUNG
INSPECTION PERFORMED	20-AUG-2010		20-AUG-2010		WMILLAR
(b) (4)					
DO RECOMMENDATION	23-AUG-2010			WITHHOLD	WMILLAR
(b) (4)					
OC RECOMMENDATION	05-OCT-2010			WITHHOLD	TGOOEN
BASED ON DO RECOMMENDATION OF SIGNIFICANT FINDINGS RELATING TO INADEEQUATE STABILITY PROGRAM AND TESTING, INADEQUATE LABORATORY TESTING AND DOCUMENTATION, AND INADEQUATE PROCESS CONTROL.				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	23-SEP-2011				BOUIET
SUBMITTED TO DO	30-SEP-2011	10-Day Letter			TOULOUSEM

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

ASSIGNED INSPECTION TO IB	30-SEP-2011	Product Specific	WMILLAR
INSPECTION SCHEDULED	21-NOV-2011		WMILLAR
INSPECTION PERFORMED	12-DEC-2011	12-DEC-2011	WMILLAR
(b) (4)			
DO RECOMMENDATION	16-DEC-2011	ACCEPTABLE	WMILLAR
PRODUCT IS DRUG/DEVICE UNDER A NDA. 10-ITEM 483 ISSUED; FIRM LACKS PROCESS VALIDATION. LACK OF PV CITED UNDER 21 CFR 820.		INSPECTION	
OC RECOMMENDATION	01-FEB-2012	ACCEPTABLE	STOCKM
FOR DRUG CGMPS ONLY		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	02-JUL-2012		SMITHDE
SUBMITTED TO DO	02-JUL-2012	10-Day Letter	SMITHDE
(b) (4)			
ASSIGNED INSPECTION TO IB	10-JUL-2012	Product Specific	WMILLAR
INSPECTION SCHEDULED	24-AUG-2012		WMILLAR
DO RECOMMENDATION	09-NOV-2012	ACCEPTABLE	LDESOUZA
INSPECTION CONDUCTED (b) (4) VAI; 2 ITEM 483 ISSUED. 21 CFR 211. LACK OF YIELD CALCULATIONS & MISSING REQUIRED BATCH RECORD COMPONENTS.		INSPECTION	
OC RECOMMENDATION	23-NOV-2012	ACCEPTABLE	SMITHDE
		DISTRICT RECOMMENDATION	
SUBMITTED TO OC	27-JAN-2012		BOUIET
SUBMITTED TO DO	27-JAN-2012	10-Day Letter	CRUZC
PLEASE EVALUATE EER FOR DEVICE ASSEMBLY WITH MOST RECENT EVALUATION.			
DO RECOMMENDATION	27-JAN-2012	WITHHOLD	WMILLAR
(b) (4)		PRODUCTION/PROCESS CONTROLS	
OC RECOMMENDATION	20-MAR-2012	WITHHOLD	SMITHDE
ON BEHALF OF CDRH/OC, CDER/OC IS ENTERING A CONCURRENCE WH RECOMMENDATION BASED ON A REVIEW OF THE EIR AND FIRM'S RESPONSE TO 483 FROM THE DECEMBER 2011 INSPECTION. CURRENTLY WE ARE WORKING WITH THE DISTRICT OFFICE TO GET ADDITIONAL INFORMATION FROM ALEXZA REGARDING DEVICE DEFICIENCY CORRECTIVE ACTIONS. IF THE RESPONSE IS ADEQUATE, A RE-INSPECTION WILL OCCUR PRIOR TO PDUFA IF POSSIBLE.		DISTRICT RECOMMENDATION	
		EIR REVIEW-CONCUR W/DISTRICT	
		INADEQUATE RESPONSE TO LETTER	
SUBMITTED TO DO	02-JUL-2012	10-Day Letter	SMITHDE
APPLICATION HAS BEEN RE-SUBMITTED. CDRH RECOMMENDS A F/U PAI BE CONDUCTED. PDUFA DATE IS 6 MONTHS BUT REVIEW WOULD LIKE TO TRY TO WRAP UP IN SEPTEMBER			

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

.IF POSSIBLE. INSPECTIONS WILL BE RATE-LIMITING STEP.

ASSIGNED INSPECTION TO IB	10-JUL-2012	Product Specific	WMILLAR
INSPECTION SCHEDULED	24-AUG-2012		WMILLAR
DO RECOMMENDATION	09-NOV-2012		ACCEPTABLE LDESOUZA
INSPECTION CONDUCTED (DRUG REGS).	(b) (4)	VAI, 2 ITEM 483 ISSUED PERTAINING TO 21 CFR 211	INSPECTION
OC RECOMMENDATION	20-DEC-2012		ACCEPTABLE SMITHDE
CDER/OC/OMPQ IS ENTERING AN APPROVAL RECOMMENDATION BASED ON THE CDRH CONSULT REVIEW OF THE EIR FOR DEVICE COVERAGE. PREVIOUS ISSUES IDENTIFIED DURING THE PREVIOUS PAI LEADING TO AN OAI STATUS FOR THIS APPLICATION HAVE BEEN RESOLVED. SEE MEMO SENT TO CDER EESQUESTIONS ON 12/20/12			DISTRICT RECOMMENDATION

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

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

Establishment Comment: MICROBIAL LIMITS TESTING (on 23-SEP-2011 by T. BOUIE () 3017961649)

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	23-SEP-2011				BOUIET
OC RECOMMENDATION	30-SEP-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM

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

Establishment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

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

Establishment Comment: Profile: (b) (4)

OAI Status: NONE

<u>Milestone Name</u>	<u>Milestone Date</u>	<u>Request Type</u>	<u>Planned Completion</u>	<u>Decision</u>	<u>Creator</u>
<u>Comment</u>				<u>Reason</u>	
SUBMITTED TO OC	17-FEB-2010				HENRYD
OC RECOMMENDATION	17-FEB-2010			ACCEPTABLE BASED ON PROFILE	STOCKM
SUBMITTED TO OC	23-SEP-2011				BOUIET
OC RECOMMENDATION	30-SEP-2011			ACCEPTABLE BASED ON PROFILE	TOULOUSEM
SUBMITTED TO DO	02-JUL-2012	GMP Inspection			SMITHDE
NEW PDUFA CYCLE - 6 MONTH CLOCK - REVIEW TARGETING APPROVAL IN SEPTEMBER (3 MONTHS EARLY) AS ONLY ISSUE DURING PREVIOUS REVIEW CYCLE WAS DEVICE COMPLIANCE OF FD SITE.					
ASSIGNED INSPECTION TO IB	22-JUL-2012	GMP Inspection			PHILPYE
INSPECTION PERFORMED	(b) (4)		(b) (4)		Kham.Phommachanh
					
INSPECTION SCHEDULED	04-OCT-2012		21-SEP-2012		IRIVERA
OC RECOMMENDATION	28-NOV-2012			ACCEPTABLE	PHILPYE

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

BASED ON FILE REVIEW

OC RECOMMENDATION

29-NOV-2012

ACCEPTABLE

SAFAAIJAZIR

DISTRICT RECOMMENDATION
