

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022549Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 022549

SUPPL # NA

HFD # 130

Trade Name: Adasuve

Generic Name: loxapine inhalation powder

Applicant Name: Alexza Pharmaceuticals, Inc.

Approval Date: December 21, 2012

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). (NDA); (NDA)

NDA# 017525

Loxitane capsule/tablet

NDA# 018039

Loxitane IM

NDA# 017658

Loxitane C oral concentrate

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 004-301: "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Efficacy and Safety Study of Staccato Loxapine for Inhalation in Schizophrenic Patients with Agitation

Study 004-302: "A Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Multi-Dose Efficacy and Safety Study of Staccato Loxapine for Inhalation in Patients with Bipolar I Disorder and Acute Agitation

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study 004-301  
Study 004-302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  
IND # 73248      YES       ! NO   
! Explain:

Investigation #2  
IND # 73248      YES       ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Kimberly Updegraff  
Title: Regulatory Project Manager  
Date: December 21, 2012

Name of Office/Division Director signing form: Mitchell Mathis  
Title: Director (acting)

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY S UPDEGRAFF  
12/22/2012

STEVEN D HARDEMAN  
12/28/2012

## DEBARMENT CERTIFICATION

Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View  
CA 94043.

### **Staccato<sup>®</sup> Loxapine for Inhalation New Drug Application Number 022549**

Alexza Pharmaceuticals, Inc hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application (NDA 022549).

Digitally signed by Christine Welch  
DN: o=VeriSign, Inc., ou=VeriSign Trust Network, ou=www.  
verisign.com/repository/RPA Incomp. by Ref.,LIAB.LTD(c)98,  
ou=Persona Not Validated, ou=Digital ID Class 1 - Microsoft  
Full Service, cn=Christine Welch, email=cwelch@alexza.com  
Reason: I attest to the accuracy and integrity of this  
document.  
Date: 2010.02.04 15:20:49 -08'00'

Christine Welch, M.S.  
Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc  
2091 Stierlin Court  
Mountain View, CA 94043  
Phone: (650) 944 7030  
Fax: (650) 944-7983

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 22549	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA
Proprietary Name: loxapine inhalation powder Established/Proper Name: Adasuve Dosage Form: powder for inhalation		Applicant: Alexza Pharmaceuticals Agent for Applicant (if applicable): NA
RPM: Kimberly Updegraff		Division: HFD-130 / Division of Psychiatry Products
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>	<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Loxitane (NDA 017525); Loxitane IM (NDA 018039)</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p style="padding-left: 40px;">This application provides for a new dosage form, from capsule or injectable, to powder for inhalation. This application also provides for a new indication, acute treatment of agitation associated with bipolar or schizophrenia and a new delivery route (inhalation).</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input checked="" type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input checked="" type="checkbox"/> This application relies on New clinical studies.</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input checked="" type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check: 12/21/2012</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>	
<b>❖ Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>12/21/2012</u></li> </ul>	<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR	

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>	CR 8/4/2011; CR 5/2/2012
<ul style="list-style-type: none"> <li>If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</li> </ul>	<input type="checkbox"/> Received
<ul style="list-style-type: none"> <li>Application Characteristics <sup>3</sup></li> </ul>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC         </p> <p>           NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)            Subpart I <input type="checkbox"/> Approval based on animal studies         </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request         </p> <p>           BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)            Subpart H <input type="checkbox"/> Approval based on animal studies         </p> <p>           REMS: <input type="checkbox"/> MedGuide  <input checked="" type="checkbox"/> Communication Plan  <input checked="" type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required         </p> <p>Comments:</p>	
<ul style="list-style-type: none"> <li>BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</li> </ul>	<input type="checkbox"/> Yes, dates
<ul style="list-style-type: none"> <li>BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Public communications (<i>approvals only</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: AP letter to be redacted and posted on web

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1)u <input checked="" type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input checked="" type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input checked="" type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes     No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

*If "Yes," skip to question (4) below. If "No," continue with question (2).*

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

*If "No," continue with question (3).*

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes     No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

*If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes     No

*If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).*

*If "No," continue with question (5).*

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	✓
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	<u>Actions and dates:</u> AP Cycle 3: 12/21/2012 CR Cycle 2: 5/2/2012 CR Cycle 1: 8/4/2011
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	12/17/2012
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	AP: 6/21/2012 CR 2: 8/4/2011 CR 1: 6/23/2010
<ul style="list-style-type: none"> <li>Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> <li>• Original applicant-proposed labeling</li> <li>• Example of class labeling, if applicable</li> </ul>	See below (Labels)
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	6/21/2012; 12/7/2012
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	10/10/12; 1/13/12; 5/6/10 10/5/12; 1/12/12; 5/6/10
<ul style="list-style-type: none"> <li>❖ Labeling reviews</li> </ul>	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA 10/12/12; 4/9/12; 3/12/12; 11/10/11 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 3/16/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 3/16/12 <input checked="" type="checkbox"/> SEALD 12/13/12 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews PMHT 3/27/12; 3/19/12
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	RPM Filing Review 3/4/2010 Memo of Filing Meeting 3/4/2010 505 (b)(2) Clearance: 10/22/2012; 4/23/2012; 9/27/2010 505(b)(2) Assessment Form: 12/19/2012
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics ( <i>approvals only</i> ) <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>4/11/12; 8/11/2010</u> If PeRC review not necessary, explain:</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	✓
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	12/17/10
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	7/14/09
• EOP2 meeting ( <i>indicate date of mtg</i> )	9/13/07
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	EOP2 CMC: 8/17/05; EOP2 CMC/CDRH: 12/12/06; CMC: 12/3/08 ROC: 10/14/11; 4/5/12 DSB: 11/16/11
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/>
• Date(s) of Meeting(s)	12/12/11
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	12/21/12; 5/1/12; 10/7/10
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	12/10/12; 4/25/12; 10/5/10
PMR/PMC Development Templates ( <i>indicate total number</i> )	5
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	See CDTL Memo(s)
• Clinical review(s) ( <i>indicate date for each review</i> )	11/27/12; 11/8/11; 4/9/12; 9/17/10
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	9/17/10 review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	DPARP: 11/26/12; 3/29/12; 8/27/10

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

	QT Study Review: 4/22/10 OSE – DEPI: 11/27/12; 11/3/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	See DRISK review dated 12/19/12 12/21/12 DRISK: 12/19/12; 4/2/12 OC: 11/9/12; 3/30/12
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	8/20/10; 8/27/10; 10/6/10
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	9/8/10
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	9/30/10; OCP Stat Review 9/27/10
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Supervisory Review(s) ( <i>indicate date for each review</i> )	9/16/10
• Pharm/tox review(s), including referenced IND reviews	9/14/10
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	12/20/12; 12/5/12; 8/6/12; 4/23/12; 3/23/12; 11/15/11; 9/10/10; 10/5/10
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	ONDQA-Pulmonary: 4/28/10/ 8/27/10 CDRH: 4/13/12; 3/19/12; 11/10/11; 10/8/10; 6/21/10; 5/14/10
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review dated 9/10/10
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: 12/20/12 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KIMBERLY S UPDEGRAFF  
12/22/2012

## NDA 022549

Adasuve (loxapine) inhalation powder 10mg  
Sponsor: Alexza Pharmaceuticals

PDUFA: December 21, 2012

### Final Email Agreement(s) for Approval Action:

- 1) Labeling (package insert): 12/17/12
- 2) Device label: 12/5/12
- 3) PMR-PMC: 12/4/12; 12/18/12
- 4) Special Reporting Requirements: 12/10/12

**From:** [Edwin Kamemoto](#)  
**To:** [Updegraff, Kimberly](#)  
**Cc:** [Lily Gong](#)  
**Subject:** RE: NDA 022549: Adasuve - labeling  
**Date:** Monday, December 17, 2012 6:14:55 PM  
**Attachments:** [emfalert.txt](#)

---

Dear Kim,

Reference is made to your email below containing the latest labeling changes. This is to confirm that Alexza is in agreement with these changes.

Regards,

Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

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**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Monday, December 17, 2012 1:56 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve - labeling

Dear Ed and Lily,

Please see the attached labeling. This version contains a few edits from our labeling team. The edits are noted in track changes. Please verbally confirm if you are in agreement with the edits.

Thank you,

Kim

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**From:** Edwin Kamemoto [mailto:ekamemoto@alexza.com]  
**Sent:** Tuesday, December 11, 2012 4:40 PM  
**To:** Updegraff, Kimberly  
**Cc:** Lily Gong  
**Subject:** RE: NDA 022549: Adasuve - labeling

Dear Kim,

With reference to your email below which contained minor edits to the labeling, Alexza is in agreement with these edits.

Please advise as to how to proceed with submission of the labeling, if necessary.

Regards,

Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

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**From:** Updegraff, Kimberly [<mailto:Kimberly.Updegraff@fda.hhs.gov>]  
**Sent:** Tuesday, December 11, 2012 11:48 AM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve - labeling

Dear Dr. Kamemoto,  
Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder. We also refer to your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.  
The attached labeling includes minor edits (see comments throughout the document), and is based on the last version of labeling you emailed to us on December 3, 2012.

Please let us know if you are in agreement with the attached labeling. We request a response by COB on Wednesday, December 12, 2012.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

30 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

**From:** [Edwin Kamemoto](#)  
**To:** [Updegraff, Kimberly](#)  
**Cc:** [Lily Gong](#)  
**Subject:** RE: NDA 022549: Adasuve - Device label IFU  
**Date:** Wednesday, December 05, 2012 3:30:20 PM  
**Attachments:** [emfalert.txt](#)

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Dear Kim,

Alexza will revise the picture in question as requested. If acceptable by you, Alexza will formally submit the updated Instructions for Use – Device Packaging in the same submission that will include the final PI and the final REMS documents. Therefore, when can we expect final FDA comments on the PI? Regarding the REMS documents, please confirm that there are no more comments on the *Steps for Safe Use of Adasuve*.

Regards,  
Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

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**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Wednesday, December 05, 2012 12:18 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve - Device label IFU

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder and your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.

We also refer to the Instructions for Use - Device Packaging that was submitted with the June 21, 2012 submission. We request that you remove the word "placebo" from the pictured device and add "10 mg" to appropriately depict the device as it will be labeled if/when marketed.

Please formally submit the updated figure(s) to the NDA as soon as possible.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**

**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

**From:** [Edwin Kamemoto](#)  
**To:** [Updegraff, Kimberly](#)  
**Cc:** [Lily Gong](#)  
**Subject:** RE: NDA 022549: Adasuve -- PMR/PMC Communication  
**Date:** Tuesday, December 18, 2012 4:03:52 PM  
**Attachments:** [emfalert.txt](#)

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Dear Kim,

This email confirms Alexza's agreement with the proposed change below.

Regards,  
Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

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**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Tuesday, December 18, 2012 12:09 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong  
**Subject:** RE: NDA 022549: Adasuve -- PMR/PMC Communication

Dear Ed,

In reviewing the PMR/PMC list for Adasuve, we would like to make the PMC below a PMR:

A single-dose GLP developmental juvenile rat tolerability and toxicokinetic study of loxapine by inhalation route that spans the corresponding ages for the pediatric clinical studies (ages 10 to 17 years). The study will evaluate the potential pharmacodynamic and pharmacokinetic differences among different ages in rats, and the results may apply to potential differences between adults and children.

Final Report Submission: [05/31/2013](#)

Please let me know if you are in agreement with the change.

Thank you,

Kim

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**From:** Edwin Kamemoto [mailto:ekamemoto@alexza.com]  
**Sent:** Tuesday, December 04, 2012 7:50 PM  
**To:** Updegraff, Kimberly  
**Cc:** Lily Gong  
**Subject:** RE: NDA 022549: Adasuve -- PMR/PMC Communication

Dear Kim,

With reference to your email below (dated December 4, 2012), Alexza agrees with the listed postmarketing requirements/commitments. As requested, dates for each PMR/PMC have been supplied where indicated.

Regards,  
Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

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**From:** Updegraff, Kimberly [<mailto:Kimberly.Updegraff@fda.hhs.gov>]  
**Sent:** Tuesday, December 04, 2012 9:43 AM  
**To:** Edwin Kamemoto; Lily Gong  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve -- PMR/PMC Communication  
**Importance:** High

Dear Dr. Kamemoto,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder. We also refer to your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.

We would like to confirm your agreement with the following postmarketing requirements/commitments (please supply dates where indicated):

-

Postmarketing Requirements:

1. A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. A study to obtain pharmacokinetic data and provide information pertinent to dosing of ADASUVE in the relevant population.

Final Protocol Submission Date: 05/01/2013  
Study/Trial Completion Date: 07/18/2013  
Final Report Submission: 01/18/2014

2. A deferred pediatric study under PREA for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in pediatric patients ages 10 to 17 years. A study of the efficacy and safety of ADASUVE in the relevant pediatric population.

Final Protocol Submission Date: 10/01/2013  
Study/Trial Completion Date: 09/30/2014  
Final Report Submission: 03/30/2015

3. You are required to conduct a large, non-randomized, open-label, postmarketing observational study to assess the risks of bronchospasm and related respiratory adverse events and serious outcomes (e.g., hospitalization, intubation, mechanical ventilation, or rescue medication for the management of respiratory reactions) associated with ADASUVE treatment. The study must have a large sample size (approximately 10,000 patients exposed to ADASUVE), in order to adequately characterize the frequency, nature, and severity of the risk of bronchospasm (presumably a rare event). The study must assess the use of ADASUVE as used in clinical practice under the requirements of the ADASUVE REMS and per labeling. We must agree prospectively on all aspects of the protocol, including but not limited to: the study design, sample size calculation, patient selection criteria, primary and secondary endpoints, definitions of events, ascertainment of cases, methods for follow-up, required duration of follow-up post-dosing, and the types of patient characteristics and other data to be collected. You must submit all protocol amendments.

Final Protocol Submission: 06/01/2013  
Study Completion: 06/01/2015  
Final Report Submission: 12/01/2015

Postmarketing Commitment(s):

4. A single-dose GLP developmental juvenile rat tolerability and toxicokinetic study of loxapine by inhalation route that spans the corresponding ages for the pediatric clinical studies (ages 10 to 17 years). The study will evaluate the potential pharmacodynamic and pharmacokinetic differences among different ages in rats, and the results may apply to potential differences between adults and children.

Final Report Submission: 05/31/2013

5. Your agreement to implement, within 6 months of approval, the appropriate controls (routine extraction testing with acceptance criteria) for (b) (4) (b) (4) to ensure that levels remain below the levels that have been qualified by the risk assessments in Module 4.

Final Report Submission: 04/30/2013

We request a response no later than **noon on Wednesday, December 5, 2012**. Please let us know if you have any questions.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

**From:** [Edwin Kamemoto](#)  
**To:** [Updegraff, Kimberly](#)  
**Cc:** [Lily Gong](#)  
**Subject:** RE: NDA 022549: Adasuve - Special Reporting Requirements  
**Date:** Monday, December 10, 2012 2:12:20 PM  
**Attachments:** [emfalert.txt](#)

---

Dear Kim,

Reference is made to NDA 22549 for Adasuve (loxapine) inhalation powder and to your email dated December 7, 2012 (below).

The purpose of this email is to communicate Alexza's agreement with the 1) "Special Reporting Requirements for Respiratory Adverse Events" as described in your email and 2) to the requests outlined in the General Advice letter issued by the Agency (December 6, 2012) that was attached to your email.

Regards,  
Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

---

**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Friday, December 07, 2012 9:15 AM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve - Special Reporting Requirements

Dear Ed,

Please refer to your New Drug Application, NDA 22549, for Adasuve (loxapine) inhalation powder. We also refer to your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.

We are currently reviewing your application and we would like to confirm your agreement regarding the following:

- 1) "Special Reporting Requirements for Respiratory Adverse Events" described below;
- 2) The requests outlined in the attached copy of a letter recently issued by the Agency. You will receive the official copy of the letter by mail in a few days.

Special reporting requirements for respiratory adverse events:

- - a. Continue to submit all initial and follow-up adverse drug experiences pertaining to respiratory events, including but not limited to the following: asthma, COPD,

bronchospasm, wheezing, shortness of breath. Additionally, submit reports of respiratory events requiring intervention, such as treatment with a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (invasive and non-invasive), an emergency department visit/prolongation of an existing visit, or hospitalization/prolongation of an existing hospitalization as Postmarketing 15-day “Alert Reports” as defined under 21 CFR 314.80(c).

- b. In the periodic reports submitted for the first quarterly reporting period and each subsequent reporting period, include the following:

A summary and evaluation of all respiratory adverse events including but not limited to the following: preferred terms included in the Asthma/Bronchospasm SMQ, COPD, or Dyspnoea, as well as respiratory events requiring treatment with a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (invasive and non-invasive), an emergency department visit/prolongation of an existing visit, or hospitalization/prolongation of an existing hospitalization.

We request a response NLT COB on Monday, December, 10, 2012.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)



NDA 22549

**GENERAL ADVICE**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) dated and received on December 11, 2009, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) inhalation powder 10mg.

We also refer to your June 21, 2012, submission which constituted a complete response to our May 2, 2012, action letter. This new drug application, currently under review by the Division, provides for the use of Adasuve (loxapine) inhalation powder for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults.

This letter provides for recommendations for follow-up and reporting of postmarketing respiratory adverse events.

Current FDA guidance<sup>1</sup> recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up of postmarketing adverse event reports, especially for reports of serious events, and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning.

In order to improve the quality of individual case reports of respiratory adverse events, we request that you use the list of questions located in Appendix A to query reporters in order to obtain additional clinical information that fully characterizes these events. The list of questions should be part of your routine procedure for gathering follow-up information after the initial report of the respiratory adverse event. We believe that the clinical information collected in this manner will enhance the quality of adverse event reports submitted to FDA and facilitate our assessment of these reports.

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<sup>1</sup> *Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, page 4, March 2005.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071696.pdf>

In addition, we request that you propose how the additional data will be collected, analyzed, and reported. We request that you submit for agreement the final questionnaire, as well as your plan for implementation, analysis, and reporting prior to the launch of Adasuve.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D.  
CAPT, USPHS  
Director (acting)  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure  
Appendix A

## **Appendix A**

### **Adasuve: Respiratory Adverse Event Follow-Up Questionnaire**

#### **PAST MEDICAL HISTORY**

1. Was the patient's medical history captured prior to Adasuve administration? [Yes, No, Unknown] If yes, who provided the history (e.g., patient, patient advocate, medical records, other)? If no, provide reason why.
2. Has the patient previously received Adasuve? [Yes, No, Unknown] If yes, when? If unknown, provide reason why.
3. If the patient previously received Adasuve, did the patient have a respiratory event following any of the previous administrations?
4. Was it subsequently determined that the patient had a previous history of pulmonary disease, or was taking respiratory medications? If so, what is the history/medications?
5. What is the patient's smoking history? Specify never smoker, current smoker (pack-years), past smoker (pack-years).

#### **MANAGEMENT OF AGITATION EPISODE**

1. What was the name of the healthcare facility at which Adasuve was administered to the patient?
2. What medications were administered, in addition to Adasuve, to treat this episode of agitation?
3. Was a physical exam performed prior to Adasuve administration? [Yes, No, Partial, unknown] If No or Partial, provide reason why e.g., not cooperative
4. Provide any vitals and physical exam results that were obtained prior to and after Adasuve administration related to the risk of a respiratory adverse event.
5. Was the patient observed, monitored and periodically assessed after Adasuve administration? [Yes, No, unknown] If yes, for how long and at what frequency? If no, provide reason why.

#### **RESPIRATORY ADVERSE EVENT**

1. How was the respiratory adverse event detected (e.g., patient or patient advocate report of symptoms, auscultation, vital signs, observation, other)?
2. What were the signs and symptoms of the respiratory adverse event?
3. Was sedation a factor in the patient's ability to report respiratory symptoms?
4. What was the time to onset of the respiratory event after Adasuve administration?

#### **TREATMENT OF RESPIRATORY ADVERSE EVENT**

1. Did the respiratory event require the use of a bronchodilator or other rescue medications, oxygen, intubation, mechanical ventilation (non-invasive or invasive), an emergency department visit or hospitalization? Please list all that were used.
2. What was the outcome of the respiratory adverse event?
3. How much time passed between development of respiratory symptoms and initiation of the respiratory treatment?
4. Was the patient treated for the respiratory event at the facility where they received Adasuve? [Yes, No, Unknown] If no, why were they transferred?

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/s/  
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MITCHELL V Mathis  
12/06/2012

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/s/  
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KIMBERLY S UPDEGRAFF  
12/19/2012

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#)  
**Cc:** [Lily Gong](#); [Updegraff, Kimberly](#)  
**Subject:** NDA 022549: Adasuve -- REMS document changes (materials for 12/17/12 teleconference)  
**Date:** Tuesday, December 18, 2012 9:50:40 AM

---

Dear Ed,

We agree with your edits, please see below:

**1. REMS Website:**

Update to remove [REDACTED] (b) (4)

**2. Healthcare Provider Brochure:**

**Page 7: About ADASUVE**

- Administer only a single dose **per patient** within a 24-hour period.

**3. Education Program:**

Slide 2-3: ADASUVE™ Risk Evaluation and Mitigation Strategy (REMS)  
Education Program Content

- Administer only a single dose of ADASUVE **per patient** within any 24-hour period

**Slide 7: ADASUVE™: Product Information**

- Only a single dose **per patient** should be administered in any 24-hour period

**Slide 12: Pulmonary Safety Studies in Patients with Asthma and COPD**

Healthcare facilities must have policies in place to limit administration of ADASUVE to a single dose **per patient** in a 24-hour period.

**Slide 34-35: ADASUVE™ Education Program Summary**

- Administer only a single dose of ADASUVE **per patient** within any 24-hour period

**4. Order Set**

**Limit Adasuve use to a single dose **per patient** within a 24-hour period**

Best regards,

Kim

---

**From:** Edwin Kamemoto [<mailto:ekamemoto@alexza.com>]  
**Sent:** Monday, December 17, 2012 3:33 PM  
**To:** Updegraff, Kimberly  
**Cc:** Lily Gong  
**Subject:** RE: NDA 022549: Adasuve -- REMS document changes (materials for 12/17/12 teleconference)

Dear Kim,

Please confirm that no other REMS documents require revision as a result of the most recent changes to the REMS body.

Specifically:

- The Website includes the statement: [REDACTED] (b) (4)  
[REDACTED]  
[REDACTED] Please confirm that this statement is to be removed since it was removed from the REMS body.
- The Education Program, Brochure and Order Set contains the statement [REDACTED] (b) (4)  
[REDACTED] (or similar wording). Do you want us to add “per patient” to be consistent with the latest change to the REMS body? If so, please indicate the instances in which “per patient” is to be added.
  - Note that the Education Program contains multiple instances of the statement in question and that “per patient” is included in the statement on page 29 but not in the other instances.
  - The Brochure contains “per patient” on page 9 but not on page 7.

Ed

Edwin S. Kamemoto, Ph.D.  
Vice President, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: (650) 944-7071  
Fax: (650) 944-7983

---

**From:** Updegraff, Kimberly [<mailto:Kimberly.Updegraff@fda.hhs.gov>]  
**Sent:** Monday, December 17, 2012 10:07 AM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve -- REMS document changes (materials for 12/17/12 teleconference)

Dear Dr. Kamemoto,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder

and your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.

We also refer to your submission dated December 7, 2012, containing amendments to the REMS/REMS Documents. Please see the table below for the revised REMS documents and notes.

In reference to the REMS document, please note the revision to move the Dear Healthcare Professional (DHCP) Letter to a component of a Communication Plan. Since the target audience for the DHCP letter is broader than the healthcare professionals (HCP) at certified healthcare facilities, the addition of a Communication Plan containing only the DHCP letter is recommended. This change will not affect the operation of the REMS, the REMS Assessment Plan or any of the appended REMS materials. The only affected documents are the REMS document and the REMS supporting document, which we have revised and attached.

In order to facilitate timely review of these materials, FDA proposes a teleconference today at approximately 2:30 PM EST to discuss the changes proposed and a timeline for submission of final materials.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

Document	Latest FDA Comments Provided	Attached Files (PDF redlined and Word Clean)	Notes
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1. REMS

- Revision to move the DHCP letter to a component of a Communication Plan.
- Removal of the phrase (b) (4) from 3 HCF requirements.
- Addition of the phrase “per patient” to the requirement that HCF limit administration to a single dose per patient in a 24-hour period.
- Removal of (b) (4)
- Minor edits to align with PI.

2. REMS Supporting Document

- Revision to move the DHCP letter information to a component of a Communication Plan.
- Edits to the Assessment Plan section.
- Item 9 contained 2 separate items. These must be separated into Item 9 and Item 10.
- Item number 9 text refers to item 9 (a-c) instead of item 8 (a-c).

Healthcare Facility  
3. Enrollment Information and Form

- Revisions to align HCF attestations to edits in the REMS document.

Wholesale /  
4. Distributor Enrollment Form

- Revisions to align Wholesaler/Distributor attestations to edits in the REMS document.

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/s/  
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KIMBERLY S UPDEGRAFF  
12/19/2012

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#)  
**Cc:** [Lily Gong](#); [Updegraff, Kimberly](#)  
**Subject:** NDA 022549: Adasuve - Device label IFU  
**Date:** Wednesday, December 05, 2012 3:17:33 PM

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Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder and your June 21, 2012 submission, containing a complete response to our May 2, 2012, action letter.

We also refer to the Instructions for Use - Device Packaging that was submitted with the June 21, 2012 submission. We request that you remove the word "placebo" from the pictured device and add "10 mg" to appropriately depict the device as it will be labeled if/when marketed.

Please formally submit the updated figure(s) to the NDA as soon as possible.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF

12/17/2012

Email dated 12/5/12

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#); [Lily Gong](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 22549: Adasuve REMS Documents  
**Date:** Wednesday, November 14, 2012 3:25:24 PM  
**Attachments:** [1-16-proposed-rems-body-10.31.2012 \(3\).doc](#)  
[1-16-proposed-rems-support-doc-body-10.31.2012.doc](#)  
[dhcp-ltr-10.31.2012.doc](#)  
[hcp-brochure-text-copy-10.31.2012 \(2\).doc](#)  
[hcf-enroll-info-ltr-form-10.31.2012.doc](#)  
[ed-prog-slideset-proposed-final-10.31.2012.pdf](#)  
[ed-prog-slideset-text-copy-10.31.2012.doc](#)  
[steps-for-safe-use-10.31.2012.doc](#)  
[wholesaler-distributor-form-10.31.2012.doc](#)  
[website-screenshot-proposed-final-10.31.2012.pdf](#)  
[order-set-template-proposed-final-10.31.2012.pdf](#)

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Dear Ed,

Please refer to your New Drug Application, NDA 022549, for loxapine inhalation powder. We also refer to your submission dated and received on September 28, 2012, containing REMS documents. We have reviewed your submission and we have the following requests/comments (please refer to the "Notes" field in the chart below):

Document	Latest FDA Comments Provided	Attached File (s)	Notes
1. REMS	9Sept2012	We accept the changes to the REMS document submitted on 28 Sept 2012. See attached redlined word document for minor FDA edits related to labeling changes.	
2. REMS Supporting Document	9Sept2012	See attached redlined word document for FDA edits and comments. Changes include grammatical corrections and changes to the REMS Assessment Plan and Audit Plan.	
3. Dear Healthcare Professional Letter	9Sept2012	FDA accepts the DHCP letter submitted on 28 Sept 2012.	
4. Healthcare Provider Brochure	9Sept2012	See attached redlined word document for FDA edits and comments.	
5. Healthcare Facility Enrollment Information and Form	9Sept2012	See attached redlined word document for FDA edits and comments. Include fax and phone number on final submitted document.	
6. ADASUVE Educational Program	9Sept2012	See attached redlined word document for FDA edits and comments.	
7. Steps for Safe Use of ADASUVE	9Sept2012	See attached redlined word document for FDA edits.	

Of note, all other REMS materials that contain the Steps for Safe Use of Adasuve should be adjusted to reflect these changes (i.e. Adasuve Education Program, Adasuve Healthcare Provider Brochure, Adasuve REMS Website, etc.)

Submit this document electronically in Word as well as in it's final formatted version.

- |  |           |   |
|--|-----------|---|
| 8. Wholesale / Distributor Enrollment Form | 9Sept2012 | See attached redlined word document for comments. Add phone and fax number to the form. |
| 9. REMS Website                            | 9Sept2012 |   |

FDA accepts document submitted on 28 Sept 2012

10. Order Set 9Sept2012 FDA accepts document submitted on 28 Sept 2012

Please let me know if you have any questions. We request that you respond by COB on *Tuesday, November 20, 2012*.

Best regards,

*Kim*

.....

Kimberly Updegraff, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
CDER/ODE1  
(301)796-2201  
[Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
11/14/2012

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#)  
**Cc:** [Lily Gong](#); [Updegraff, Kimberly](#)  
**Subject:** NDA 022549: Adasuve -- Request (labeling)  
**Date:** Wednesday, October 03, 2012 11:15:14 AM

---

Dear Dr. Kamemoto,

Please refer to your New Drug Application, NDA 022549, received on December 11, 2009 for loxapine inhalation powder. We also refer to our action letter dated May 2, 2012, and your complete response dated and received on June 21, 2012.

We are currently reviewing the product labeling submitted on June 21, 2012 and we have the following request:

***In Section 6.1, last sentence under COPD Patients, you provide a comment that "the CSR 004-108 Table 18 shows 4 subjects rather than 3; therefore, 15% is the correct value." Per FDA analysis, we are only able to identify 3 unique patients in the placebo group who received rescue medication (11%). Please clarify the number of placebo patients who received rescue medication by providing a data listing of the patient ID numbers of these patients and the number of separate treatments each of these placebo patients received. If there were only 3 unique patients, modify the sentence to read "11% of patients in the placebo group."***

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF

11/06/2012

Email dated 10/3/2012



NDA 022549

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

ATTENTION: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) dated December 11, 2009, received December 11, 2009, submitted under section 505(b) (2) of the Federal Food, Drug, and Cosmetic Act for Loxapine Inhalation Powder, 10 mg.

We also refer to:

- October 8, 2010: FDA Complete Response Letter
- August 4, 2011: Alexza Class 2 Resubmission of NDA
- October 24, 2011: Alexza Request of Review of Proposed Proprietary Name, Adasuve
- January 13, 2012: FDA Proprietary Name Request Conditionally Acceptable letter
- May 2, 2012: FDA Complete Response Letter
- June 20, 2012: Alexza Class 2 Resubmission of NDA,

Lastly, we refer to your July 16, 2012, amendment received July 17, 2012, requesting re-review of your proposed proprietary name, Adasuve, due to changes in your product characteristics such as (b) (4) updated indication, and more restrictive frequency of administration.

We have completed our review of your proposed proprietary name, Adasuve, and have concluded that it is acceptable.

The proposed proprietary name, Adasuve, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. Additionally, if **any** of the proposed product characteristics as stated in your July 16, 2012, submission are altered prior to approval of the marketing application, the proprietary name must be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Updegraff, at 301-796-2201.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
10/10/2012

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 022549: ADASUVE REMS Documents  
**Date:** Sunday, September 09, 2012 10:04:36 PM  
**Attachments:** [4.9.2012\\_1-16-proposed-rems-body.doc](#)  
[30\\_8\\_2012\\_proposed-rems-support-doc-body-12jul2012.doc](#)  
[4.9.2012\\_dhcp-ltr-12jul2012.doc](#)  
[4.9.2012\\_prescriber-brochure-text-copy-12jul2012.doc](#)  
[4.9.2012\\_hcf-enroll-info-ltr-form-12jul2012.doc](#)  
[4.9.2012\\_ed-prog-slideset-12jul2012.doc](#)  
[4.9.2012\\_steps-for-safe-use-12jul2012.doc](#)  
[4.9.2012\\_wholesaler-distributor-form-12jul2012\\_NO\\_EDITTS.doc](#)  
[4\\_9\\_2012\\_SCREENSHOT\\_of\\_website-23apr2012\\_\(2\).pdf](#)  
[4\\_9\\_2012\\_website-screenshot-12jul2012.doc](#)  
[4.9.2012\\_order-set-template-12jul2012.doc](#)

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Dear Ed,

Please refer to your New Drug Application, NDA 022549, for loxapine inhalation powder. We also refer to your submission dated and received on July 17, 2012, containing REMS documents. We have reviewed your submission and request the following:

- Submit all materials 2 weeks after receiving this communication.
- Submit all materials electronically, as Word documents and in the final formatted versions. For example, the ADASUVE Education Program should be submitted in Word as well as PDF or another format as slides with graphics included.
- Provide 4 hardcopies of the Steps for Safe Use poster to the FDA for review.

Table 1

Document	Latest FDA Comments Provided	Attached File (s)	Notes
1. REMS	12April2012		We accept the changes to the REMS document submitted on 21 July 2012. See attached redlined word document for minor FDA edits.
2. REMS Supporting Document	18April2012		See attached redlined word document for FDA edits and comments.
3. Dear Healthcare Professional Letter	12April2012		We accept the changes to the DHCP letter submitted on 21 July 2012. FDA has one formatting change shown in this redlined word document.
4. Healthcare Provider Brochure	18April2012		See attached redlined word document for FDA edits and comments.
5. Healthcare Facility Enrollment Information and Form	12April2012		See attached redlined word document for FDA edits and comments. Of note, increase the font on HCF attestations to at least 11 pt.
6. ADASUVE Educational Program	18April2012		See attached redlined word document for FDA edits and comments.
7. Steps for Safe Use of ADASUVE	12April2012		See attached redlined word document for FDA edits and comments.

Of note, all other REMS materials that contain the Steps for Safe Use of Adasuve should be adjusted to reflect these changes (i.e. Adasuve Education Program, Adasuve Healthcare Provider Brochure, Adasuve REMS Website, etc.)

Submit this document electronically in Word as well as in its final formatted version. In addition, submit 4 hard copies for FDA review of the final product.

8. Wholesale / Distributor Enrollment Form 12April2012 See attached redlined word document for minor FDA edits and comments.

9. REMS Website 12April2012

FDA has comments and edits to the REMS website. We have included comments on both the PDF file and in the word document. After making revisions, please submit landing page, in PDF, for FDA review.

10. Order Set 12April2012 See attached redlined word document for FDA edits and comments.

Best Regards,

***Kim***

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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/s/  
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KIMBERLY S UPDEGRAFF  
09/09/2012

**From:** [Updegraff, Kimberly](#)  
**To:** [Edwin Kamemoto](#)  
**Cc:** [Updegraff, Kimberly](#)  
**Subject:** NDA 022549: Adasuve (loxapine) inhalation powder - Trade name request  
**Date:** Tuesday, July 10, 2012 8:14:49 AM

---

Dear Ed,

Please refer to your submission dated June 21, 2012, containing a resubmission of your new drug application for Adasuve (loxapine) Inhalation Powder.

(b) (4)  
Therefore, we are requesting that you submit a request for proprietary name review.

Please see the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*,  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>  
for additional guidance.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
07/10/2012



NDA 022549

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr Kamemoto:

We acknowledge receipt on June 21, 2012, of your June 21, 2012, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder.

We consider this a complete, class 2 response to our May 2, 2012, action letter. Therefore, the user fee goal date is December 21, 2012.

If you have any questions, please call me, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY S UPDEGRAFF  
07/03/2012



NDA 022549

GENERAL ADVICE

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr Kamemoto:

Please refer to your New Drug Application (NDA) dated and received on December 11, 2009, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) inhalation powder 5 mg and 10 mg.

We also refer to your August 4, 2011 submission containing a complete response to our October 8, 2010, action letter and to our recent May 2, 2012, action letter informing you that we could not approve the application in its present form because of deficiencies found during an inspection of the Mountain View, CA manufacturing facility.

The findings were discussed with you during an informal teleconference with the Center for Devices and Radiological Health (CDRH) on May 9, 2012. As a follow-up to the teleconference, we would like to formally convey the following deficiencies:

1. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test that the process shall be validated with a high degree of assurance and approved according to established procedure, as required by 21 CFR 820.75(a).

For example:

[Redacted text block]

We reviewed your firm's response and conclude that it is not adequate.

[Redacted text block]

(b) (4)



(b) (4)



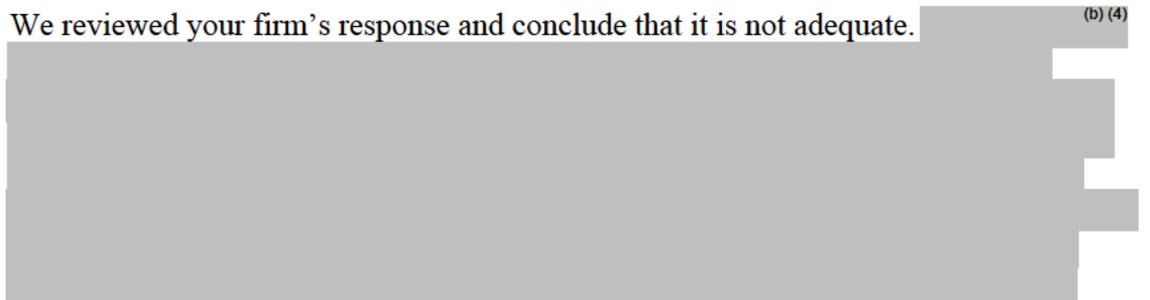
Your response is also inadequate since your firm has not performed a systemic corrective action to include reviewing other processes to ensure they have been adequately validated. You have addressed the processes identified in the 483 observation, but not other processes that may have also not been validated as required.

2. Failure to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA) to include identifying the actions needed to correct and prevent recurrence of nonconforming product and other quality problems, as required by 21 CFR 820.100(a)(3).

For example, (b) (4)



We reviewed your firm's response and conclude that it is not adequate. (b) (4)



[Redacted] (b) (4)

3. Failure to establish and maintain adequate procedures for implementing corrective and preventive action (CAPA) to include verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device as required by 21 CFR 820.100(a)(4). For example:

- a. [Redacted] (b) (4)
- b. [Redacted]

We reviewed your firm's response and conclude that it is not adequate. [Redacted] (b) (4)

[Redacted]

4. Failure to establish and maintain adequate procedures to ensure that complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803, Medical Device Reporting, as required by 21 CFR 820.198(a)(3).

For example, [REDACTED] (b) (4)

We reviewed your firm's response and conclude that it is not adequate. [REDACTED] (b) (4)

5. Failure to establish adequate procedures for identifying training needs and to ensure that all personnel are trained to adequately perform their assigned responsibilities, and have training documented, as required by 21 CFR 820.25(b).

For example, [REDACTED] (b) (4)

We reviewed your firm's response and conclude that it is not adequate. [REDACTED] (b) (4)

6. Failure to develop, maintain, and implement written Medical Device Reporting (MDR) procedures, as required by 21 CFR 803.17.

For example, [REDACTED] (b) (4)

We reviewed your firm's response and conclude that it is not adequate. [REDACTED] (b) (4)

If you have general questions regarding your submission, please contact the regulatory project manager, Kimberly Updegraff, at (301)796-2201. For questions or comments related to the inspection, contact Nazia Rahman, with the Office of Compliance in the Center for Devices and Radiological Health at (301)796-3849. Also, any submission regarding the outstanding deficiencies noted above should not be submitted to the application. Please address the response to both the San-District Office and the Office of Compliance in the Center for Devices and Radiological Health.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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THOMAS P LAUGHREN  
06/07/2012

## Updegraff, Kimberly

---

**From:** Updegraff, Kimberly  
**Sent:** Wednesday, April 11, 2012 8:17 PM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) inhalation powder - Carton / Container Labeling Comments

Dear Ed,

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) powder for inhalation 5 mg and 10 mg.

We also refer to your August 4, 2011 submission, containing a complete, class 2 response to our October 8, 2010 action letter, and your April 5, 2012 submission containing device, pouch, and carton labeling.

We have reviewed your April 5, 2012 submission and have the following comments regarding the pouch and carton labeling:

### A. Pouch Labeling (5 mg and 10 mg)

#### Front Side

1. Minimize the prominence of the graphic above the proprietary name by using smaller font size. Currently, the prominent graphic is brightly colored, and as a result, it distracts attention from the most important information on the label: the name of the drug, dosage form, strength, and route of administration.
2. Ensure that the strength of the product in the upper left corner and next to the dosage forms are consistent. Currently, the blue 10 mg pouch label states "5 mg" next to the product's dosage form.
3. We recommend increasing the prominence of the strength of the product next to the dosage form.
4. Add a colored box around the statement "(loxapine) inhalation powder, 5 mg" or "(loxapine) inhalation powder, 10 mg" consistent with the color of the strip provided for each strength (i.e., blue or (b) (4) to ensure that the two strengths are well-differentiated.

#### Back Side

5. Add the proprietary name and strength of the product to the back side of the pouch labeling to ensure that if the pouch's back side faces up, the correct strength is selected. Additionally, add the color block around the proprietary name and strength consistent with the color scheme used for 5 mg strength (i.e., (b) (4) or 10 mg strength (i.e., blue).
6. Add the phrase "Instruct patient to..." to steps 3, 4, and 5. For example, "Instruct patient to exhale".
7. Relocate the boxed statement in Step 4 to combine with the statement after step 5 as follows: "Important: Check that green lights turns OFF indicating the dose delivered. If light does not turn off, repeat steps 3-5 up to 2 more times."
8. Add the statement regarding the possible flash of light, clicking sound, or inhaler getting warm to Step 4.

### B. Carton Labeling (5 mg and 10 mg)

1. See A.1 and revise the carton labeling accordingly.
2. Currently the strengths presented next to the dosage form are not prominent and can be easily overlooked. Increase the prominence of the strength next to the dosage form, and present the proprietary name, established name, dosage form, and strength in the following manner:

Adasuve  
(loxapine) inhalation powder  
xx mg

3. Add a colored box around each strength, consistent with the color of the strip provided for each strength (i.e., blue or (b) (4) to ensure that the strength is well visible.
4. Delete the reference to the strength from the colored strip from each panel of the carton labeling (e.g., 10 mg Loxapine per single unit dose” or 10 mg), because the strength is already presented next to the dosage form, and the strength on the blue strip crowds the panels.
5. Delete the statement “10 mg Loxapine per single dose unit” or “5 mg Loxapine per single dose unit” prior to the net quantity from three panels of the carton labeling, because these statements are repetitive. Additionally, since these statements are located next to the net quantity, they may be misinterpreted as the net quantity and vice versa.
6. Include the route of administration on each panel of the carton labeling.
7. Delete the words “Dosage and Administration” from the principle display panel, because the full dosage and administration is not provided.
8. Add the statement “Usual Dosage:” next to the statement “See package insert”.
9. Decrease the prominence of the manufacturer “Alexza,” because this name is as prominent as the proprietary name of the product and distracts attention from the important information on the carton labeling.
10. Relocate storage information to the panel with the lot number and expiration date. Only the most important information should be placed on the principle display panel.

We have no further comments regarding the device label.

We request a response by COB on Monday, April 16, 2012. Please let me know if you have any questions.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF  
04/16/2012

## Updegraff, Kimberly

---

**From:** Updegraff, Kimberly  
**Sent:** Wednesday, April 11, 2012 8:35 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) inhalation powder - REMS Document Information Request

**Attachments:** 1-16-proposed-rem-s-body+FDAFinal2.pdf; 1-16-proposed-rem-s-body+FDAFinal\_Clean2.docx; 1-16-proposed-rem-s-support-doc-body+FDAFinal.pdf; DHCP letter+FDAFinal.pdf; DHCP letter+FDAFinal\_Clean.docx; prescriber-brochure-text-copy+FDAFinal.pdf; prescriber-brochure-text-copy+FDA Final\_clean12.4.9.docx; hcf-enroll-info-ltr-form+FDAFinal.pdf; hcf-enroll-info-ltr-form+FDAFinal\_Clean.docx; ed-prog-slideset+FDAFinal2.pdf; ed-prog-slideset+FDAFinal2\_Clean.doc; steps-for-safe-use+FDAFinal.pdf; steps-for-safe-use+FDAFinal\_Clean.doc; wholesaler-distributor-form+FDAFinal.pdf; wholesaler-distributor-form+FDAFinal\_Clean.docx; website-screenshot+FDAFinal.pdf; website-screenshot+FDAFinal\_Clean.docx; order-set-template+FDAFinal.pdf; order-set-template+FDAFinal\_Clean.docx

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) inhalation powder.

The documents in the table below contain DRISK's latest comments regarding the REMS documents/materials for Adasuve. The recommendations are based on the currently proposed labeling (emailed to you on 4/11/2012) and REMS. Please note that all REMS materials must be consistent with the final FDA approved labeling and REMS.

The table includes a list of all REMS Materials and the date of the FDA's most recent comment(s).

	Document	Latest FDA Comments Provided	Attached Files (PDF redlined and Word Clean)	Notes
1.	REMS	11April2012	 1-16-proposed-rem-s-body+FDAFin...  1-16-proposed-rem-s-body+FDAFin...	Please resubmit REMS document by 13 April 2012
2.	REMS Supporting Document	11April2012	 1-16-proposed-rem-s-support-doc...	Information for the Assessment section will be sent under separate cover

3.	Dear Healthcare Provider Letter	11April2012	 DHCP r+FDAFinal.pdf (83)	
			 DHCP r+FDAFinal_Clean.d	
4.	Healthcare Provider Brochure	11April2012	 prescriber-brochure -text-copy+...	
			 prescriber-brochure -text-copy+...	
5.	Healthcare Facility Enrollment Information and Form	11April2012	 hcf-enroll-info-ltr-fo rm+FDAFi...	
			 hcf-enroll-info-ltr-fo rm+FDAFi...	
6.	ADASUVE Educational Program	11April2012	 ed-prog-slideset+F DAFinal2.pdf...	
			 ed-prog-slideset+F DAFinal2_Cle...	
7.	Steps for Safe Use of ADASUVE	11April2012	 steps-for-safe-use +FDAFinal.pd...	
			 steps-for-safe-use +FDAFinal_Cl...	
8.	Wholesale / Distributor Enrollment Form	11April2012	 wholesaler-distribut or-form+FD...	
			 wholesaler-distribut or-form+FD...	

9.	REMS Website	11April2012	 website-screenshot +FDAFinal.pd...   website-screenshot +FDAFinal_Cl...	
10.	Order Set	11April2012	 order-set-template +FDAFinal.pd...   order-set-template +FDAFinal_Cl...	

We request that the designated REMS document(s) be submitted to us by Friday, April 13, 2012 and the remainder of the documents by Tuesday, April 17, 2012.

Please let me know if you have any questions.

Thanks,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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/s/  
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KIMBERLY S UPDEGRAFF  
04/16/2012

**From:** [Dar David](#)  
**To:** [Updegraff Kimberly](#)  
**Cc:** [Cathlin Charles](#); [Claffey David](#)  
**Subject:** RE: Question NDA 022549 - Inter-Center Consult Form  
**Date:** Wednesday, March 14, 2012 4:46:25 PM

---

Hello Kim,

Following on to our telephone conversation this afternoon regarding the inter-consult request, CDRH OC's review of the premarket device manufacturing information is complete and marked as adequate as of June 21, 2010. Thank you for keeping CDRH OC apprised.

David

---

**From:** Updegraff, Kimberly  
**Sent:** Thursday, February 23, 2012 12:41 PM  
**To:** Dar, David  
**Cc:** Cathlin, Charles; Claffey, David  
**Subject:** RE: Question NDA 022549 - Inter-Center Consult Form

Hi David,

Thank you for the response. We are aware of the problems with the medical device observations, but have been told that a reinspection will take place (March was mentioned).

We do plan to act on or before the PDUFA date of 5/4/2012.

Let me know if you need anything.

Thanks again,

Kim

---

**From:** Dar, David  
**Sent:** Wednesday, February 22, 2012 10:38 AM  
**To:** Updegraff, Kimberly  
**Cc:** Cathlin, Charles  
**Subject:** RE: Question NDA 022549 - Inter-Center Consult Form

Hello Kim,

I will review the NDA response. Also, a heads-up; the most recent Alexza EIR is under review and appears to be OAI for the medical device observations.

Regards,

David

---

**From:** Updegraff, Kimberly  
**Sent:** Wednesday, February 15, 2012 2:22 PM  
**To:** Dar, David  
**Subject:** RE: Question NDA 022549 - Inter-Center Consult Form

Thanks, David.

---

**From:** Dar, David  
**Sent:** Tuesday, February 14, 2012 4:33 PM

**To:** Updegraff, Kimberly  
**Cc:** Levin, Robert; Claffey, David  
**Subject:** RE: Question NDA 022549 - Inter-Center Consult Form

Kim,

Thanks. I will follow up on this and get back with you.

Regards.

David

---

**From:** Updegraff, Kimberly  
**Sent:** Tuesday, February 14, 2012 12:07 PM  
**To:** Dar, David  
**Cc:** Levin, Robert; Claffey, David  
**Subject:** Question NDA 022549 - Inter-Center Consult Form

Hi David,

The Division of Psychiatry Products sent this consult to CDRH/OC in October and I am trying to find out the status of the review. I contacted Charles Cathlin, but have not hear from him yet, so I thought I would send an email to you.

<< File: 022549 CDRH-OC consult 2nd cycle .pdf >>  
Do you know if your group will be providing feedback regarding this consult?

Thank you!

Kim Updegraff, RPM  
DPP

---

**From:** Dar, David  
**Sent:** Friday, October 14, 2011 5:38 PM  
**To:** Updegraff, Kimberly  
**Cc:** Covington, Vertleen J.; Cathlin, Charles; Nguyen, Quynh Nhu; Patel, Nayan; De, Sugato  
**Subject:** FW: Inter-Center Consult Form

Hello Kim,

Please see the links to the inter-center consults below. To issue a consult request, please send the completed form to Charles Cathlin to be reviewed by RANDB/DOE B/OC.

Thanks,

David

---

**From:** Tejero, Isabel  
**Sent:** Tuesday, September 20, 2011 3:08 PM  
**To:** Garvin, Terri T  
**Cc:** Flournoy, Valerie A (CDRH)  
**Subject:** RE: Inter-Center Consult Form

You can find the inter-center consult for a possible combination product here:  
<http://inside.fda.gov:9003/downloads/ProgramsInitiatives/CombinationProducts/ReviewerTools/UCM013277.pdf>

This is a fill in pdf form. For more information, you can visit the reviewer's tools page within the combination products website at:

<http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm>

**M. Isabel Tejero, M.D. Ph.D.**  
Consumer Safety Officer

General Hospital Devices Branch  
Division of Enforcement A  
Office of Compliance  
Center for Devices and Radiological Health  
Food and Drug Administration  
phone: 301-796-5322  
email: [Isabel.Tejero@fda.hhs.gov](mailto:Isabel.Tejero@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF

04/13/2012

Entered into DARRTS for CDRH/OC/DOEG/RANB consult

**Updegraff, Kimberly**

---

**From:** Updegraff, Kimberly  
**Sent:** Thursday, March 29, 2012 10:22 PM  
**To:** Edwin Kamemoto; Lily Gong  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) powder for inhalation - Pediatric Plan Information Request

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) powder for inhalation. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter. We are reviewing the proposed pediatric development plan for your deferred studies in the adolescent population and need confirmation regarding dates for protocol submission, study completion, and final report submission.

The pediatric plan submitted with your August 4, 2011 submission contains the following dates:

Pharmacokinetic study:

Final Protocol Submission Date: XXXXXXXX  
Study/Trial Completion Date: April 18, 2013  
Final Report Submission: September 18, 2013

Clinical efficacy and safety:

Final Protocol Submission Date: XXXXXXXX  
Study/Trial Completion Date: June 30, 2014  
Final Report Submission: December 31, 2014

Please add dates where needed and confirm those that are listed. We request a response by COB on Friday, March 30, 2012.

Best regards,

*Kim*

.....  
*Kimberly Updegraff, RPh, MS, RAC*  
*Senior Regulatory Project Manager*  
*Division of Psychiatry Products*  
*Center for Drug Evaluation and Research, FDA*  
*Office of Drug Evaluation*  
*Phone: (301)796-2201*  
*Email: Kimberly.Updegraff@fda.hhs.gov*

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/s/  
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KIMBERLY S UPDEGRAFF  
03/30/2012

## Updegraff, Kimberly

---

**From:** Updegraff, Kimberly  
**Sent:** Thursday, March 29, 2012 10:25 PM  
**To:** Edwin Kamemoto; Lily Gong  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) powder for inhalation - Information Request (Foreign Regulatory Status)

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) powder for inhalation. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter.

Please inform us whether or not Adasuve (loxapine) powder for inhalation is approved or under review in any other countries, and if any other regulatory authorities have raised concerns. If so, please let us know what those concerns are.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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/s/  
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KIMBERLY S UPDEGRAFF  
03/30/2012

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, March 01, 2012 6:04 PM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve - FDA REMS Comments  
**Attachments:** Adasuve FDA Resposne to 2-22-12 Sponsor REMS Comments edited.pdf

Dear Ed,

As a follow-up to our conversation this afternoon, please see the attached comments regarding your 2/22/2012 REMS Amendment. Our comments are highlighted in [blue](#).

We request a response by COB on March 2, 2012. Please let me know if you have any questions.

Best regards,

*Kim*

.....  
*Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov*

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/s/  
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KIMBERLY S UPDEGRAFF

03/30/2012

Late entry



NDA 022549

## INFORMATION REQUEST

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr Kamemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg.

We also refer to your August 4, 2011, submission, containing a complete, class 2 response to our October 8, 2010, action letter.

We have reviewed the reference material and have the following comments and requests regarding the device pouch and carton labeling:

### A. Foil Pouch Labeling (Front Side)

1. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and has the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
2. Increase the prominence of the proprietary and established names as they should be the most prominent information on the label. Currently, they can be overlooked by other information on the label.
3. Present the proprietary name followed by the established name immediately followed by the dosage form then the strength. Present in the following manner:  
Adasuve  
(loxapine) inhalation powder xx mg
4. Remove "loxapine" following the strength as the established name is already included following the proprietary name and as it crowds the label.
5. Include a space between the number and the unit in the presentation of the strength (i.e. 5 mg rather than 5mg).

6. Include the statement “Discard after one use” following the single dose unit statement.
7. Add the following prominent statement to the principle display panel “Adasuve is contraindicated in patients with acute respiratory signs/symptoms (e.g., wheezing) or who are taking medications to treat asthma or COPD.” This important statement serves as a reminder to healthcare practitioners not to administer Adasuve to patients with active airway disease. In order to accommodate placement of this statement to the principle display panel without overcrowding the panel, please minimize the prominence of the following information:
  - Manufacturer information
  - Storage information
  - PNL number and revision date
  - Lot Number and Expiration Date
8. Delete one of the NDC numbers as there are two of them printed on the principle display panel.
9. Consider additional differentiation between 5 mg and 10 mg strength of the Adasuve through additional use of color, boxing, or some other means. Presently, labeling for both strengths appear similar to each other for the exception of the colored strengths, which can lead to selection of the wrong strength.
10. Per 21 CFR 201.100(b)(2) or 201.55, include the usual dosage statement.
11. Per 21 CFR 201.100(b)(3), include the route of administration.
12. Delete the statement [REDACTED] <sup>(b) (4)</sup> as this statement crowds the label and does not represent a critical step in the correct administration of Adasuve.
13. Decrease the prominence of the “Rx Only” statement by relocating it to a less prominent position of the label.

## **B. Carton Labeling**

1. See comments B.1 through B.9 and revise the carton labeling accordingly.
2. Increase the prominence of the route of administration by using bigger font type or bolding as this important information may be overlooked because it appears in the same font size as other information on the label such as storage temperature.
3. Decrease the “Rx Only” statement by decreasing the font size as this statement completes with the most important information on the label such as proprietary and established name, dosage form, and strength.

In addition to the comments above, we remind you of the comments sent via email on February 16, 2012 regarding the Device Label.

NDA 022549

Page 3

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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THOMAS P LAUGHREN  
03/20/2012

## Updegraff, Kimberly

---

**From:** Updegraff, Kimberly  
**Sent:** Monday, March 19, 2012 1:32 PM  
**To:** Edwin Kamemoto; Lily Gong  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve REMS: DRISK Comments regarding REMS and REMS Documents

**Attachments:** 120316\_REMS\_redline.docx; 120316\_DHCP Letter .docx; 120316\_HCF Enrollment info and form.docx; 120316\_Steps for Safe Use.doc; 120316\_Distributor Enrollment.docx

Dear Dr. Kamemoto,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) Inhalation Powder. We also refer to your March 8, 2012 submission containing a response to Agency comments regarding the REMS sent on March 2, 2012. We acknowledge your agreement to our Comments 1 through 5 of the document, and have included a response to your proposal regarding Comment 6 at the end of this e-mail.

Please note that these are initial comments. The recommendations provided here are based on the currently proposed labeling and REMS documents. Additional revisions may be necessary as the documents go through the clearance process. Further, all REMS materials must be revised to be consistent with the final FDA approved labeling and REMS.

Please see the attached documents for DRISK's latest comments. The table below includes a list of all REMS Materials and of the date of the FDA's latest comment(s). A redline version of the REMS, and clean versions of the other documents (redline documents not available, due to submission format), are attached.

	Document	Latest FDA Comments Provided	Attached File (s)	Notes
1.	REMS	16March2012	 120316_REMS_redline.docx (67 K...	
2.	REMS Supporting Document	pending		
3.	Dear Healthcare Provider Letter	16March2012	 120316_DHCP Letter .docx (31 K...	
4.	Healthcare Provider Brochure	pending		
5.	Healthcare Facility Enrollment Information and Form	16March2012	 120316_HCF enrollment info and..	Previously named <i>Healthcare Facility Information Letter</i>
6.	ADASUVE Educational Program	pending		

7.	Steps for Safe Use of ADASUVE	16March2012	 120316_Steps for Safe Use.doc ...	Previously named <i>Safe Use Checklist</i>
8.	Wholesale / Distributor Enrollment Form	16March2012	 120316_Distributor Enrollment....	
9.	REMS Website	pending		
10.	Order Set	pending		

**SUBMISSION INSTRUCTIONS:**

1. Submit all requested documents by COB on March 23, 2012.
2. For e-CTD submissions, include all files in the xml eCTD backbone, in *1.16 Risk Management Plans* (no subheadings are needed).
3. For e-CTD submissions, submit all requested documents as the “current” document. All previously submitted documents should be marked as “replaced.”
4. Document Organization
  - a) Individual Word files for the REMS and an individual file for each ‘material’ that is appended to the REMS (see Table 1). This will allow us to provide redline versions in our next round of comments.
  - b) Provide redline versions of any documents that have been modified.

**FDA Response to Comment 6:**

We have considered your proposal for modified language pertaining to Comment 6 as follows:



(b) (4)

Please see redlined REMS document with track changes for these revisions.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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/s/  
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KIMBERLY S UPDEGRAFF  
03/19/2012

**Updegraff, Kimberly**

---

**From:** Updegraff, Kimberly  
**Sent:** Thursday, February 16, 2012 5:19 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) Inhalation Powder - DMEPA Device Label Comments (follow-up to 12/3/2011 Advice Letter)

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter.

We are currently reviewing your submission and we have the following comments:

**Device Label**

1. Include the dosage form immediately following the established name, followed by the strength [i.e. (loxapine) inhalation powder, 10 mg]. The proprietary and established names, dosage form, and strength should be relocated to the side of the device that has the LED light. The lot number, expiration date, NDC, and PNL numbers can remain on the opposite side.
2. Per 21 CFR 201.10(g)(1), include brackets around the established name so that the relationship between the proprietary name and established name is clear.
3. Per 21 CFR 201.10(g)(2), ensure that the established name is at least half the size of the proprietary name and have the prominence commensurate with the prominence of the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.
4. Per 21 CFR 201.10(i)(iv), include the name of the manufacturer, packer, or distributor on the opposite side of the side with the product's name and LED light.
5. Per 201.100(b)(2), include the route of administration if space permits.

Comments regarding the Device Pouch and Carton Labeling will be conveyed in the future under a separate request.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: Kimberly.Updegraff@fda.hhs.gov**

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/s/  
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KIMBERLY S UPDEGRAFF  
02/16/2012

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, February 16, 2012 1:08 PM  
**To:** Edwin Kamemoto  
**Cc:** Lily Gong; Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) Inhalation Powder - REMS comments  
**Attachments:** ADASUVE REMS for sponsor.pdf

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter and your January 10, 2012 submission containing a REMS amendment.

The attached document contains a revised REMS document with comments from the Division of Risk Management (DRISK). Please note that this is a working document and there may be additional changes as the labeling process progresses.

We are not asking that you submit any documents at this time. Once we have agreement on the current draft of the REMS, we will provide comments on the remaining REMS documents and communication activities as well as let you know when to re-submit the materials.

Please let us know if you have any questions or comments on our proposal. We request that you respond no later than COB on 2/20/2012.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: Kimberly.Updegraff@fda.hhs.gov**

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KIMBERLY S UPDEGRAFF  
02/16/2012

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, February 02, 2012 2:11 PM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) Inhalation Powder - Clinical Email Request

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter.

We are currently reviewing your submission and we have the following request:

(b) (4)

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: Kimberly.Updegraff@fda.hhs.gov**

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/s/  
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KIMBERLY S UPDEGRAFF  
02/03/2012

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, January 27, 2012 1:18 PM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) inhalation powder - OCP labeling comments

Dear Ed,

Please refer to your New Drug Application (NDA) for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg. We also refer to your August 4, 2011 submission, containing a complete response to our October 8, 2010, action letter and to your January 12, 2012 submission containing amended labeling.

We are currently reviewing the labeling and the Office of Clinical Pharmacology (OCP) has the following comments/requests:

**Comment 1**



**Comment 2**

(b) (4)

Please let us know if you have any questions. We request a response by 9:00 am EST on February 2, 2012.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF  
01/31/2012



NDA 022549

**REVIEW EXTENSION –  
MAJOR AMENDMENT**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder, 5 mg and 10 mg.

On January 10, 2012, we received your January 10, 2012, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 4, 2012.

In addition and in accordance with the “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012”, any previously discussed timeline for communicating labeling changes and/or postmarketing requirements/commitments no longer applies and no new timeline will be provided.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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THOMAS P LAUGHREN  
01/19/2012



NDA 022549

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, California 94043

ATTENTION: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) dated December 11, 2009, received December 11, 2009, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Loxapine Inhalation Powder, 5 mg and 10 mg.

We also refer to your August 4, 2011, submission containing a complete, Class 2 response to the FDA's October 8, 2010, action letter.

Lastly, we refer to your October 24, 2011, correspondence, received October 25, 2011, requesting review of your proposed proprietary name, Adasuve.

We have completed our review of Adasuve and have concluded that it is acceptable.

Adasuve will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your October 24, 2011, submission are altered prior to approval of the marketing application, the proprietary name must be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Updegraff at 301-796-2201.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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/s/  
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CAROL A HOLQUIST  
01/13/2012

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, December 23, 2011 11:27 AM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 (Adasuve)

Dear Ed,

This email is in response to your December 18, 2011 email, in which you posed the following question regarding the Division's December 3, 2011 Information Request letter:

***Alexza requests clarification on what is envisioned for the validation. Alexza's assumption is that validation would take the form of another Human Factors study (and would include drafting of the study protocol, IRB submission and approval, conduct of the Human Factors study, and preparation of the study report), which would not be able to be completed within the PDUFA timeframe.***

The Agency recommends that the Human Factors Validation Testing be completed prior to the approval of the product similar to the one you have already conducted to test the alterations to the device and revisions to the Instructions for Use (IFU) outlined in the December 3, 2011 correspondence. The study would evaluate the revisions to the device and the IFU prior to the approval to ensure the new revisions reduce the number of errors and do not introduce new sources of error.

You should demonstrate effectiveness of design and labeling improvements through focused HF/usability validation, and may consider using a protocol similar to the one used for Supplemental Summative Usability Test. However, you will *not* need to include patients. Only healthcare practitioners will need to be tested with the revisions to the device and labels and labeling. Additionally, you should include a specific observation and question related to healthcare professional informing patients about the flash of light, clicking sound, or temperature change for the device during use.

Please let us know if you have additional questions.

Best regards,

*Kim*

.....  
**Kimberly Updegraff, RPh, MS, RAC**  
**Senior Regulatory Project Manager**  
**Division of Psychiatry Products**  
**Center for Drug Evaluation and Research, FDA**  
**Office of Drug Evaluation**  
**Phone: (301)796-2201**  
**Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)**

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/s/  
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KIMBERLY S UPDEGRAFF  
12/23/2011

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, October 14, 2011 1:44 PM  
**To:** Edwin Kamemoto  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) Inhalation Powder: Information request

Dear Dr. Kamemoto,

Please refer to your New Drug Application, NDA 022549, for Adasuve (loxapine) Inhalation Powder. In order to inform our review of the usability of your product, please provide a copy of the written instructions that were distributed to healthcare practitioners or patients during your clinical trials. Additionally, please specify whether any additional training (e.g. verbal instructions) was given to healthcare practitioners or patients. If yes, provide the additional training materials utilized, including scripts of any verbal instructions that were given.

We request a response by COB of October 18, 2011. The information can be submitted via email.

Best regards,

*Kim*

.....  
Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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/s/  
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KIMBERLY S UPDEGRAFF  
12/20/2011



NDA 022549

**INFORMATION REQUEST**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr Kamemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg.

We also refer to your August 4, 2011 submission, containing a complete, class 2 response to our October 8, 2010, action letter. We have reviewed the human factors validation study, as well as the postmarketing observational study protocol synopsis. We request a prompt response regarding the following comments and requests:

**1. Human Factors Validation Study**

- A. The administration of *Staccato* Loxapine is intended to be supervised by a healthcare provider (HCP) in a healthcare setting. HCPs are primarily responsible for preparing the device for use by an agitated patient with schizophrenia or bipolar disorder. Patients are responsible for following the HCP's instructions in order to actuate the device and inhale the drug.

For the HCP arm of the study, you have undertaken helpful measures to reduce the rate of task failures, use errors, close calls, and operational difficulty that were observed in the initial HF/usability validation study. You changed (b) (4)

[REDACTED]. The improvements are helpful but appear to be incomplete. Some task failures, use errors, close calls, and operational difficulty impacting successful dose delivery remain:

- HCP(s) were unaware of the need to check for the LED light to confirm proper device function upon activation (LED on) or successful dosing after inhalation (LED off)
- HCP did not provide adequate guidance to patients for the inhalation, exhaling before inhaling, and holding their breath after inhaling.

Furthermore, many of the HCPs provided comments regarding how the design could be further improved. For example:



While the Agency recognizes that you have taken helpful measures to minimize the occurrence of potential of task failures and use errors with intended users, the Agency requests that you take the results of these evaluations and use them to further optimize the device user interface including labeling/IFU so that use errors are effectively minimized. Please note that improvements should be demonstrated through focused HF/usability validation.

- B. In addition to your efforts for further improvements, we recommend including the following revisions to the device and IFU prior to conducting another HF validation study.

Product Design

1. We recommend relocating the product's label containing proprietary and established name, dosage form, and strength to the side where the LED button is located. We recommend this design change to help minimize wrong technique errors in which participants do not verify whether the LED light is illuminated or that the light is turned off, indicating that the device has been activated or that the dose has been delivered, respectively.



2. We recommend adding a label or embossment next to the LED light stating the significance of the LED light when it is lit and when it is turned off (e.g., "when green, inhaler ready to use"). This label/embossment should be prominently displayed to call the HCP's attention. You should develop language that will be recognized by

healthcare practitioners for this statement. We recommend this design change to signify the meaning of this feedback mechanism and to help minimize wrong technique errors in which participants do not verify whether the LED light is illuminated or that the light is turned off indicating that the device has been activated or the dose has been delivered, respectively.

3. We recommend orienting the device in a pouch in such a manner, so that the LED light and the relocated label containing the proprietary and established names, dosage form, and strength are facing the same side as the IFU on the foil labeling. We recommend this change to ensure easy identification of the label and the LED light on the device as well as to help eliminate wrong technique errors in which participants do not verify whether LED light is illuminated or turned off. (b) (4)

[Redacted]

#### Instructions for Use

1. Revise the word (b) (4) to state “inhaler” throughout the IFU. The word (b) (4) is imprecise and could be confusing to healthcare practitioners or patients.
2. Step 2: Pull Tab
  - a. Include a box similar to that in Step 4, which includes information about the green light (e.g. IMPORTANT: Check that the green light is on before giving the inhaler to patients.) This box should be highlighted.
  - b. Add a sentence that reads “Discard the inhaler after one use” after the sentence “Use within 15 minutes after removing the tab to prevent automatic deactivation of the product.” We recommend this revision to ensure that healthcare providers dispose of the device after the patient uses it once.
3. Step 3: Exhale – Instruct the patient to exhale before giving the inhaler to patient. (b) (4)

[Redacted]

We recommend this revision to ensure that patients are not exhaling into the inhaler.
4. Step 4: Inhale
  - a. Include an instruction for HCP to inform patients regarding the fact that it is normal for the patient to see a flash of light, hear a clicking sound, or feel that the inhaler gets warmer while inhaling from the inhaler after the first sentence “Inhale through mouthpiece with a steady deep breath”. We recommend this revision to help ensure that patients inhale the medication correctly without being interrupted, startled, or frightened by flash of light, noise, or hotter temperature of the device. (b) (4)

[Redacted]

(b) (4)

- b. Add a second sentence in the box stating “The green light will automatically turn off after the medication has been delivered.” We recommend adding this sentence to help patients and practitioners identify that a dose has been delivered.
5. Step 5: Hold Breath
  - a. Revise the image, so that a person in the picture has puffy cheeks and pressed lips to imitate a person holding a breath. We recommend this revision because the graphic is misleading and may cause confusion. (b) (4)
  - b. Specify how long a patient should hold the breath (e.g., remove the mouthpiece from the mouth and hold breath for 5 seconds). (b) (4)
6. In the ‘NOTE’ section, specify how many times a patient can repeat steps 3 through 5. (b) (4)
7. Provide further instructions regarding the steps that should be taken if the LED light does not turn off after Steps 3 through 5 were performed by a patient a specified number of times. We recommend the addition of this important information, because it is unclear what the healthcare providers should do in the event that the device malfunctions or dosing errors occur (e.g., underdosing or omission of a dose).

#### Foil Pouch Labeling (Back Side with Instructions for Use)

1. Revise the word (b) (4) to state “inhaler” throughout the abbreviated IFU on the pouch labeling. The word (b) (4) is imprecise and could be confusing to healthcare practitioners or patients.
2. Step 2: Pull Tab
  - a. Include a box similar to that in Step 4 that provides information about the green light (e.g. IMPORTANT: Check that the green light is on before giving the inhaler to patients.) This box should be highlighted.
  - b. Add a sentence that reads “Discard the inhaler after one use” after the sentence, “Use within 15 minutes after removing the tab to prevent automatic deactivation

of the product.” We recommend this revision to ensure that healthcare providers dispose of the device after the patient uses it once.

3. Step 3: Exhale – Instruct the patient to exhale before giving the inhaler to the patient.

(b) (4)

[REDACTED] We recommend this revision to ensure that patients are not exhaling into the inhaler.

4. Step 4: Inhale

- a. If space permits, add the sentence “It is normal to see a flash of light, hear a clicking sound, or feel that the inhaler gets warmer as you inhale.” after the first sentence: “Inhale through mouthpiece with a steady deep breath”. We recommend this revision to help ensure patients inhale the medication correctly without being interrupted, startled, or frightened by flash of light, noise, or hotter temperature of the device.

(b) (4)

- b. In the box, add a sentence “Check the green light” prior to the sentence “The green light turns off after the medication is delivered”.

(b) (4)

5. Specify how long a patient should hold the breath (e.g., remove the mouthpiece from the mouth and hold breath for 5 seconds).

(b) (4)

## 2. Phase 4 Observational Study

We have reviewed the synopsis of the protocol that you have provided. In general, the study objectives are reasonable. The observational study must evaluate the use patterns and risks of pulmonary toxicity in real-world settings. The study must include a very large cohort of real-world patients. Important issues for review will include the patient population studied, use patterns, characterization of respiratory and other clinical adverse reactions, use of rescue medication and other interventions, usability of the product, and availability of medical history and records.

We request that you submit a complete protocol for review. Before initiating the study, we must reach agreement on the protocol. In addition, we suggest that you refer to the principles outlined in the draft guidance for pharmacoepidemiologic studies when developing the study protocol, which can be found at the following link:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>

Provide a rationale for the proposed study settings and the criteria to be employed in the selection of study sites. The study population should reflect the population intended to use this product in the real world setting as closely as possible. The study must include patients with past medical histories of chronic obstructive pulmonary disease and asthma. Provide detailed inclusion and exclusion criteria in the study protocol. In particular, discuss the inclusion and exclusion criteria that rely on the availability of medical history or subjects' ability to reliably report medical history. (b) (4)

[Redacted]

[Redacted] (b) (4)

. Provide details regarding how medical diagnoses or medical history will be determined for all patients and how the potential inability to determine diagnoses or medical history in some patients may impact the interpretability of study findings. In addition, discuss the generalizability of patients actually included in the study to the intended population of patients who would be treated with *Staccato* Loxapine in real world settings.

Accurate ascertainment of past medical history, which may be challenging in this patient population, is important for characterizing the comparison groups and identifying sub-groups who may be at increased risk of developing pulmonary toxicity. The study protocol must address the ability to accurately ascertain exposure (including dose and frequency of exposure), as well as use of concomitant medications. Additionally, the protocol must clearly address the ability to accurately ascertain: 1) the occurrence of adverse events (including type, frequency, and severity of adverse events), 2) the use of bronchodilator rescue medications and other medical interventions to treat pulmonary adverse reactions, and 3) patient disposition. The protocol must address efforts to minimize loss to follow-up and missing data due to transfer of patients to other facilities or to home.

The study design and analyses should minimize the potential for surveillance bias that could arise from (1) differential assessment and follow-up between study groups and (2) lack of comparability between study groups. (b) (4)

[Redacted]

Address the comparability of the proposed comparison groups as well as how any differences between study groups will be handled. Specify important confounders and how these would be handled in the analyses. For example, there may be differences in disease severity across comparison groups; patients able to use an inhaled medication may be less agitated than those receiving medications via injection. Discuss whether differential follow-up between treatment groups could impact the interpretability of study findings, and provide strategies to minimize/eliminate these discrepancies. For example, patients in a particular treatment group may be more likely to be discharged home prior to 24 hours post medication administration. Provide details regarding the methods for follow-up during the 24 hours after treatment.

Provide standard case definitions of serious and non-serious adverse events in the study protocol, including operational definitions for the pulmonary outcomes of interest. The protocol should describe the methods of outcome assessment across study groups, including frequency of assessments and the required expertise/training of the medical team performing the assessments of the outcomes of interest (e.g., auscultation of lung sounds may require trained medical professionals).

Provide detailed sample size calculations for each outcome. The power calculations must be based on the primary pulmonary safety events of interest. In addition, provide information regarding the reliability of the assumptions concerning background rates of respiratory adverse reactions (e.g., reference from literature or information from pilot studies). The number of patients included in the study must be large enough to allow for detection of clinically meaningful differences in pulmonary adverse reactions between study groups.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/  
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THOMAS P LAUGHREN  
12/03/2011



NDA 22549

**INFORMATION REQUEST**

CERTIFIED MAIL  
RETURN RECEIPT REQUESTED

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr. Kamemoto:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder.

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).<sup>1</sup> The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is

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<sup>1</sup> These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

**Please respond to this query within 30 days from the date of this letter.**

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs  
Center for Drug Evaluation and Research  
10903 New Hampshire Avenue  
Bldg. 22, Room 6300  
Silver Spring, MD 20993-0002

If you have any questions, email CAPT Steven D. Hardeman, R.Ph., Chief, Project Management Staff, at [Steven.Hardeman@FDA.HHS.GOV](mailto:Steven.Hardeman@FDA.HHS.GOV).

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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STEVEN D HARDEMAN  
09/13/2011  
signed for Dr. Laughren



NDA 022549

**ACKNOWLEDGE –  
CLASS 2 RESPONSE**

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto, Ph.D.  
Executive Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Dr Kamemoto:

We acknowledge receipt on August 4, 2011, of your August 4, 2011, resubmission of your new drug application submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (loxapine) Inhalation Powder 5 mg and 10 mg.

We consider this a complete, class 2 response to our October 8, 2010, action letter. Therefore, the user fee goal date is February 4, 2012.

If you have any questions, please call me, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, M.S.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/  
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KIMBERLY S UPDEGRAFF

08/18/2011

Corrected zip code, replaces 8/17/2011 letter.



NDA 022549

**MEETING MINUTES**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (Loxapine) Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on April 29, 2011. The purpose of the meeting was to discuss the content of product labeling to include the possibility of a Medication Guide and proposed REMS to support the safe use of Adasuve and to discuss a proposed post-marketing study.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

## MEMORANDUM OF MEETING

NDA 022549: Adasuve™ (loxapine) Inhalation Powder  
Alexza Pharmaceuticals  
Type C Meeting  
April 29, 2011

**Objective:** To obtain the Agency's guidance regarding the content of product labeling to include a Medication Guide and a proposed REMS submission to support the safe use of Adasuve™ (loxapine) Inhalation Powder and to discuss a proposed post-marketing observational study.

### Participants –

#### **FDA**

Robert Temple, M.D.	Office of Drug Evaluation I Director
Thomas Laughren, M.D.	Division of Psychiatry Products Director
Mitchell Mathis, M.D.	Deputy Director
Robert Levin, M.D.	Medical Team Leader
Frank Becker, M.D.	Medical Reviewer
Victor Crentsil, M.D.	Deputy Director of Safety, Division of Psychiatry Products
David Claffey, Ph.D.	Chemistry, Manufacturing and Controls Reviewer
Sally Seymour, M.D.	Division of Pulmonary, Allergy and Rheumatology (DPARP) Deputy Director for Safety
Theresa Michele, M.D.	Division of Pulmonary, Allergy and Rheumatology Products (DPARP) Team Leader
Anya Harry, M.D., Ph.D.	DPARP Reviewer
Simone Pinheiro, Sc.D., M.Sc.	Office of Pharmacovigilance and Epidemiology Division of Epidemiology I (DEI) Team Leader
Kendra Biddick	Office of Compliance (DCRMS)
Ida-Lina Diak, Pharm.D.	Office of Pharmacovigilance and Epidemiology Division of Pharmacovigilance I (DPI) Team Leader
Tracy Salaam, Pharm.D.	Office of Pharmacovigilance and Epidemiology Division of Pharmacovigilance I (DPI) Safety Evaluator
Megan Moncur, Pharm.D.	Office of Medication Error Prevention and Risk Management, Division of Risk Management (DRISK) Safety Evaluator
David Tran	Student
Terry Harrison, Pharm.D.	Safety Regulatory Project Manager
Kimberly Updegraff, M.S.	Regulatory Project Manager

#### **Sponsor**

Thomas King	President and CEO
James Cassella, Ph.D.	Senior Vice President, Research and Development

Robert Fishman, M.D., FCCP  
August Moretti

(b) (4)

Vice President, Clinical Development  
Senior Vice President, CFO and General Counsel

(b) (4)

Edwin Kamemoto, Ph.D.  
Christine Welch, M.S., RAC

Executive Director, Regulatory Affairs  
Senior Director, Regulatory Affairs

**Background:**

Adasuve™ (loxapine) inhalation powder (*Staccato* Loxapine) is a single-use, hand-held, drug-device combination product intended to provide rapid systemic delivery by inhalation of a thermally generated aerosol of loxapine. The sponsor, Alexza Pharmaceuticals, Inc, submitted NDA 022549 on December 11, 2009 to support the approval of Adasuve™ (loxapine) inhalation powder (*Staccato* loxapine) for the treatment of agitation associated with schizophrenia or bipolar disorder. The application was reviewed by various disciplines including clinical, CDRH, DPARP, CMC, pharmacology toxicology, statistics, and OCP. On October 8, 2010, the Division issued a CR letter to Alexza Pharmaceuticals citing pulmonary toxicity as the primary reason for the Complete Response action.

In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. To place these findings in perspective, one should note that the standard bronchoprovocation tests cause a decrease in FEV1 of 10-20%. In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV1 of >10%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%.

In subjects with asthma or COPD, the FEV1 and respiratory findings were marked. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Furthermore, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms, often requiring rescue treatment with bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related in the safety studies. Subjects treated with a second dose of loxapine inhalation powder had greater decreases in FEV1 (compared to their first dose), which did not return to baseline at 24 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued from the study before receiving

the second dose, because they developed a decrease in FEV1 and/or they required rescue treatment of respiratory signs and symptoms

On December 17, 2010, the Division held an End of Review meeting with Alexza to discuss the key issues described in the Agency's October 8, 2010 action letter. At the meeting, Alexza proposed that the risks could be managed through labeling and a comprehensive REMS program. The Division requested that the sponsor provide a detailed proposal, including product labeling, a Medication Guide, a Communication Plan, and protocols for post-approval, observational studies.

The sponsor's primary purpose for the April 29 meeting is to obtain the Division's guidance on the content of product labeling, the medication guide, and the REMS program to support the safe use of *Staccato* loxapine. To that end, the sponsor has provided draft Prescribing Information, a Medication Guide, a draft proposed REMS (that includes a communication plan and timetable for assessments), and a synopsis for a proposed post-marketing observational study to collect information on the real-world use of *Staccato* loxapine.

(b) (4)

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

**Questions:*****Question 1***

Does the Agency agree that the draft product labeling (that includes the Medication Guide) and the proposed Communication Plan-based REMS provide a reasonable approach for adequately managing the risk of bronchospasm associated with *Staccato* loxapine?

***Preliminary Comments:*** *Based on the data you have provided, we do not agree that a Medication Guide and Communication Plan-based REMS will be adequate to ensure that the benefits of Staccato loxapine outweigh the risk of bronchospasm and potential respiratory distress. We do not feel that the true extent and severity of respiratory adverse events and decreases in pulmonary function in acutely agitated patients who receive Staccato loxapine doses at two hour intervals has not been adequately characterized. We do not believe that a Medication Guide will help mitigate the risk since patients will be acutely agitated and potentially psychotic when they are given Staccato loxapine. A Communication Plan may inform practitioners of the risks with Staccato loxapine, but a major concern is that Staccato loxapine be administered only in a continuously monitored setting where equipment and personnel trained in the management of respiratory distress are readily available. In addition, while screening and examining patients are useful, this cannot identify all patients with COPD or asthma who should not receive Staccato loxapine. Should you choose to resubmit your NDA, we*

would likely convene an advisory committee meeting to discuss the proposed approach for managing the risks. Should the agency and its advisors not be persuaded that the available data are sufficient to mitigate the risk of significant pulmonary toxicity associated with the use of this product, it is possible that the discussion may lead to a requirement to show some advantage of this product over already available products to treat agitation, in order to outweigh this risk that would be unique to your product. It is also possible that any REMS might need to include elements to assure safe use, e.g., a requirement for a certain level of monitoring and observation of patients who receive the product.

***Discussion at Meeting:*** The Agency stated that the main issue is whether, in the real-world, one can adequately identify patients at risk of pulmonary toxicity and those who should not be treated with Staccato Loxapine. The sponsor acknowledged that groups at risk for respiratory adverse events must be clearly identified. The sponsor believes that there is a low risk of respiratory adverse events in the non-pulmonary disease population, based on the completed studies. However, the Agency reiterated that the real-world setting was not studied. They were studied in controlled settings in which rescue treatment was readily available. In addition, it was likely that there were adequate medical records and history available to guide the decision about whether a patient would be eligible for treatment in the study. In addition, the Agency expressed concern that the device was not used as proposed in labeling (at up to 2 hour intervals). The sponsor acknowledged this, but stated that the majority of patients in the clinical trials did not need more than one dose to treat agitation. The Agency also pointed out that, in the real world, patients may be more acutely agitated than those studied in the clinical trials and may require more frequent dosing; safety data for Staccato Loxapine treatment under these circumstances are not available currently. The sponsor acknowledged that the dosing frequency will need to be addressed in the re-submission.

We reiterated that we will take the application to an advisory committee upon resubmission. The sponsor must address whether they have adequately characterized the extent and severity of pulmonary toxicity with Staccato Loxapine. In addition, it is likely that the advisory committee will have a discussion about whether the product has a clear benefit compared to existing therapies. The sponsor believes that one can demonstrate an advantage, because Staccato Loxapine has a rapid onset of effect, and it is non-invasive. The sponsor acknowledged that some severely agitated patients may not be candidates for Staccato Loxapine, but the sponsor also believes that some patients who could have benefited from Staccato Loxapine were too agitated to provide informed consent in the clinical trials. The sponsor agreed to provide an argument in support of these positions in the resubmission.

## **Question 2**

With regard to mitigating the risk of bronchospasm, does the Agency have any specific comments on the content of the draft Prescribing Information, the Medication Guide, and the Proposed REMS?

***Preliminary Comments:*** Please see response to Question 1. While it is premature to discuss labeling, there are several ideas you might consider in drafting labeling. It may be necessary to include a Boxed Warning describing the risk of bronchospasm and a recommendation that appropriate emergency equipment and personnel to handle respiratory distress should be available. Consider adding a recommendation for monitoring and provide justification for the proposed duration of monitoring. It may be necessary to include specific contraindications, e.g., the presence of acute respiratory signs/symptoms or current treatment with a bronchodilator. As noted for question 1, inclusion of elements to assure safe use may need to be considered. These will be review issues. A complete review of the proposed REMS in conjunction with the full clinical review of the re-submitted NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA.

***Discussion at Meeting:*** The main concern is whether such measures can provide assurance that healthcare practitioners will follow necessary guidelines and be able to use Staccato Loxapine safely and effectively in a real-world setting. How can one ensure that all practitioners do what is needed to use the product safely? These issues will likely be raised by an Advisory Committee, which will likely include Psychiatrists and Pulmonologists.

The Division stated that a Communication Plan might not provide adequate information to ensure the safe use of the product, and we suggested that the sponsor consider developing an Elements to Assure Safe Use (ETASU). An ETASU would include the minimal standards of care (e.g., availability of rescue medications, availability of resuscitation equipment, and prescribed monitoring and training) needed for the safe use of Staccato Loxapine. These elements should be in place prior to the medication being used in a facility. We discussed several important issues to address, including the challenges of communication within a hospital/clinical unit and the poor reliability of monitoring for bronchospasm through pulse oximetry.

The sponsor stated that psychiatric emergency experts have informed them that there are new standards for observation levels in emergency rooms. Furthermore, emergency rooms are well-equipped to provide appropriate monitoring for patients treated with Staccato loxapine. The Agency stated that elements to assure safe use may provide additional assurance that Staccato Loxapine will be used only in a setting where provisions are in place to ensure that patients can be effectively monitored and treated if respiratory signs or symptoms develop. The Agency emphasized that patients must be treated in a setting in which there is adequate monitoring and the capability for rapid treatment. In a psychiatric unit, for example, it is often difficult to have access to intravenous equipment, pulse oximetry, nebulizer treatment, etc. The sponsor noted that, in the pulmonary safety studies, pulse oximetry demonstrated no significant changes in oxygen saturation after treatment with Staccato Loxapine; however, the Agency pointed out that pulse oximetry was not monitored after albuterol rescue and, in any case, there are typically no changes until the patient has severe respiratory compromise. Therefore, we do not consider the absence of clinically significant change in oxygen saturation as

*measured by pulse oximetry reassuring. The use of pulse oximetry for respiratory monitoring of patients who have received Staccato Loxapine would not be adequate.*

*The Agency expressed concern about the need for prolonged monitoring in patients who receive multiple doses of Staccato Loxapine in various clinical settings. The sponsor stated that, in the pulmonary studies, respiratory symptoms (if they occurred) typically had a rapid onset (within 15 minutes of study drug administration). Symptoms reversed within 15 minutes of receiving rescue treatment with albuterol. None of the subjects were so excessively somnolent that they could not verbalize their symptoms. In the pivotal studies, the respiratory adverse reactions occurred only after the first dose, consistent with an irritant effect. Thus, the sponsor reasons that, if patients tolerated the first dose, there was a low probability of a respiratory adverse event after the second dose. Therefore, the sponsor concluded that a relatively short monitoring period should be adequate. The Agency suggested that the sponsor provide these arguments in the resubmission. The sponsor agreed to further investigate hospital procedures for monitoring and treatment of acutely agitated patients.*

### ***Question 3***

Does the Agency agree that, consistent with the Agency's recent new guidance on the inclusion of Medication Guides in a REMS, the Medication Guide need not be made part of the REMS for *Staccato* loxapine?

***Preliminary Comments:*** *See response to Question 1. It is premature to fully address the issue of what might be needed in a REMS.*

***Discussion at Meeting:*** *There was no further discussion.*

### ***Question 4***

Does the Agency agree that, consistent with the Agency's recent new guidance on the distribution requirements for Medication Guides and considering the role of the healthcare professional in administering *Staccato* loxapine, the Medication Guide can be distributed according to the proposal in [Table 10](#) of the Meeting Package?

***Preliminary Comments:*** *See responses to Question 1 and Question 3.*

***Discussion at Meeting:*** *There was no further discussion.*

### ***Question 5***

The Sponsor has outlined a post-marketing surveillance study to collect information on the real-life use of *Staccato* loxapine in the post-marketing setting. Does the Agency have any comments on the proposed study objectives, study population, study design, or the proposed data to be collected?

***Preliminary Comments:*** *See response to Question 1. In addition to evaluating use patterns of *Staccato* loxapine in real world settings, a post-marketing study evaluating*

*the risk and the extent of pulmonary decline among patients diagnosed with schizophrenia or bipolar disorder receiving Staccato loxapine compared to other agents for treatment of agitation may be desirable. The study population would need to be representative of patients receiving treatment for agitation related to schizophrenia or bipolar disorder in real world settings (including acute settings), and would need to include patients with past medical histories of chronic obstructive pulmonary disease and asthma. The number of patients included in the study would need to be large enough to allow for detection of clinically meaningful differences in pulmonary function decline between study groups; power calculations would need to be provided for the main adverse events of interest. Potential differences in disease severity across comparison groups (e.g. patients able to use an inhaled medication may be less agitated than those receiving medications via injection) would need to be addressed in the study design and analyses. Accurate ascertainment of past medical history, which may be challenging in this patient population, is important to both characterize the comparison groups as well as to identify sub-groups of patients who may be at increased risk of drug-associated pulmonary decline. The study protocol would need to address ability to accurately ascertain exposure, including dose and frequency of exposure, as well as use of other medications during the same admission course. Additionally, the study protocol would need to clearly address ability to accurately ascertain occurrence of adverse events, including type, frequency, and severity of adverse events, as well as use of bronchodilator rescue medications and patient disposition. Ideally, monitoring of pulmonary function (e.g. pulse oximetry, FEV measurements) should be implemented. The protocol should also address efforts to minimize loss to follow-up due to transfer of patients to other facilities.*

**Discussion at Meeting:** *The Agency stated that it would important to have an observational study evaluating the use patterns and risks of pulmonary toxicity in the real-world. The Division stated that such a study must include a very large cohort of real-world patients. Important issues for review will include the patient population included, use patterns, characterization of respiratory and other clinical adverse reactions, use of rescue medication, usability of the product, and availability of medical history and records. We discussed the question of whether the study should be conducted as a premarketing versus a postmarketing study. The advisory committee may wonder if this should be a premarketing study rather than a post-marketing study. We requested that the sponsor submit a proposed real-world, large cohort study for review.*

*The Agency stated that the advisory committee may ask about the potential advantage of Staccato Loxapine over other drugs to treat agitation. The relevant comparison should be considered in patients with mild to moderate agitation who are cooperative and could also take oral products (tablet, solution). The sponsor discussed the advantages of Staccato Loxapine over available products. The sponsor was advised to provide an argument to that effect in the resubmission. The sponsor plans to submit relevant existing data. The study group should be large enough to satisfy basic epidemiology principles.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Alexza Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, R.Ph., M.S.  
Senior Regulatory Project Manager

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/s/  
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THOMAS P LAUGHREN  
05/18/2011

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Friday, March 18, 2011 4:21 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Comments regarding human factors study

Dear Christine,

Please refer to your New Drug Application (NDA 022549) for Adasuve (loxapine) Inhalation Powder and your submission dated February 4, 2011, received February 7, 2011, containing a revised protocol for the human factors validation study.

The Center for Devices and Radiological Health (CDRH) along with the Division of Medication Error Prevention and Analysis (DMEPA) have reviewed your submission and have the following comments/recommendations:



Please let me know if you have any questions.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

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KIMBERLY S UPDEGRAFF  
03/18/2011

**For Internal Use Only**

Meeting Request Granted Form

Application Type	NDA								
Application Number	022549								
<b>DATE Meeting Granted</b>	02/15/2011								
Sponsor was informed of: <ul style="list-style-type: none"><li>• date/time &amp; meeting location</li><li>• expected FDA attendees</li><li>• meeting briefing package due date</li><li>• number of copies</li></ul>	<table style="width: 100%;"><tr><td style="width: 60%;">Yes XX</td><td style="width: 40%;">No</td></tr><tr><td>Yes XX</td><td>No</td></tr><tr><td>Yes XX (date:3/24/2011)</td><td>No</td></tr><tr><td>Yes 3 official, 20 desk</td><td>No</td></tr></table>	Yes XX	No	Yes XX	No	Yes XX (date:3/24/2011)	No	Yes 3 official, 20 desk	No
Yes XX	No								
Yes XX	No								
Yes XX (date:3/24/2011)	No								
Yes 3 official, 20 desk	No								
Project Manager	Kim Updegraff								

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Wednesday, February 23, 2011 2:36 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Type C Meeting Request: Adasuve (loxapine) inhalation powder  
**Attachments:** FOREIGN VISITOR DATA REQUEST FORM.doc

Dear Christine,

Your Type C meeting request, dated and received on February 9, 2011, has been granted.

A face-to-face meeting has been arranged for April 29, 2011 from 1:00 - 2:30 pm EST at the following location:

10903 New Hampshire Avenue / White Oak Building 22/ Conference Room 1313 / Silver Spring, MD 20903

Please have all attendees bring photo identification and allow 30 minutes to complete security clearance. If there are additional attendees, email the information to me at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov) so that I can give security staff time to prepare temporary badges in advance. Upon arrival the FDA, give the guard either of the following numbers to request an escort to the conference room:

Kimberly Updegraff, Project Manager, X2201  
Dave Berman, Division Secretary, X1044

**For Foreign Nationals and Foreign Visitors (See attachment):** Any individual who is not a US citizen will need to complete a "Foreign Visitor Data Request Form". The data request form must be filled out completely for each visitor and the form(s) must be submitted to the FDA Office of Security Operations at least 14 calendar days prior to the visit. Incomplete forms will not be accepted and will be returned to the originator. Please let me know as soon as possible if you have an individual or individuals who will need to complete the form as you are encouraged to submit the form(s) to me as quickly as possible to prevent any potential delays.

Please provide the background information for this meeting (three copies of the meeting briefing package or one electronic copy to the application and 20 desk copies prior to the meeting). If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by March 24, 2011, we may cancel or reschedule the meeting.

Please send the desk copies to me at the following address:

Kim Updegraff, Regulatory Project Manager  
Division of Psychiatry Products  
Food and Drug Administration  
White Oak CDER Building #22, Office 4241  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

If you have any questions or need to reschedule, please let me know.

Best regards,

*Kim*

Reference ID: 2909225

2/23/2011

*Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov*

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/s/  
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KIMBERLY S UPDEGRAFF  
02/23/2011



NDA 022549

**MEETING MINUTES**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Adasuve (Loxapine) Inhalation Powder.

We also refer to the meeting between representatives of your firm and the FDA on December 17, 2010. The purpose of the meeting was to discuss key issues described in the Complete Response Letter issued by the Agency on October 8, 2010.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING**  
NDA 022549; Adasuve™ (loxapine) Inhalation Powder  
Alexza Pharmaceuticals  
Type B Meeting (End of Review)  
December 17, 2010

**Objective:** To discuss the key issues described in the Complete Response Action Letter issued by the Agency on October 8, 2010.

Participants –

**FDA**

Robert Temple, M.D.	Office of Drug Evaluation I Director
Thomas Laughren, M.D.	Division of Psychiatry Products Director
Robert Levin, M.D.	Medical Team Leader
Frank Becker, M.D.	Medical Reviewer
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor
Darren Fegley, Ph.D.	Pharmacology/Toxicology Reviewer
Ramesh Sood, Ph.D.	Office of New Drugs Quality Assessment (ONDQA) Branch Chief
David Claffey, Ph.D.	Chemistry, Manufacturing and Controls Reviewer
Theresa Michele, M.D.	Division of Pulmonary, Allergy and Rheumatology (DPARP) Team Leader
Anya Harry, M.D., Ph.D.	DPARP Reviewer
Lex Schultheis, M.D., Ph.D.	Chief, Center for Devices and Radiological Health (CDRH), Anesthesiology and Respiratory Device Branch (ARDB)
Sugato De	Biomedical Engineer (ARDB)
Quynh Nhu Nguyen	Biomedical Engineer (ARDB)
Carlos Mena-Grillasca, R.Ph.	Division of Medication Error Prevention and Analysis (DMEPA) Team Leader
Kimberly Updegraff, M.S.	Senior Regulatory Project Manager
Sharon Sagoo, PharmD	Regulatory Project Manager

**Sponsor**

Thomas King	President and CEO
James Cassella, Ph.D.	Sr. Vice President, Research and Development
Robert Fishman, M.D.	Vice President, Clinical Development
Darl Moreland	Vice President, Quality
Peter Noymer, Ph.D.	Vice President, Product Research and Development
Edwin Kamemoto, Ph.D.	Executive Director, Regulatory Affairs
Christine Welch, M.S.	Senior Director, Regulatory Affairs
Lily Gong	Senior Regulatory Operations Associate

## **Background:**

Adasuve™ (loxapine) inhalation powder is a single-use, hand-held, drug-delivery combination product submitted by Alexza Pharmaceuticals, Inc. on 12-11-09. NDA 022549 was submitted as a 505(b)(2) marketing application which referenced Loxitane oral tablets, oral solution, and intramuscular injection (Lederle Labs). Alexza developed Adasuve™ (loxapine) inhalation powder for the treatment of agitation associated with schizophrenia or bipolar disorder. The drug-device combination product utilizes the *Staccato* delivery system developed by Alexza Pharmaceuticals.

Loxapine inhalation powder is a new dosage form of loxapine, an approved first generation antipsychotic drug that has been available in the U.S. since 1975 for the treatment of schizophrenia. Loxapine is a dibenzoxazepine compound. It binds with high affinity to the dopamine D2 receptor and acts as an antagonist at this receptor. Loxapine also binds at the serotonin 5-HT2a receptor. Although no longer marketed, an intramuscular formulation of loxapine had been available for the treatment of acute agitation.

The studies in support of this application were conducted under IND 73248. An EOP2 meeting was held with the sponsor on 9-13-07. A meeting to discuss PK comparability data was held on 12-3-08. Additional advice on the pulmonary safety studies was conveyed to the sponsor in a 4- 17-09 communication. A preNDA meeting was held on 7-14-09.

The NDA was submitted on December 11, 2009. The application was reviewed by various disciplines including: clinical, CDRH, DPARP, CMC, pharmacology toxicology, statistics and OCP. On October 8, 2010, the Division issued a CR letter to Alexza Pharmaceuticals citing Pulmonary Toxicity as the primary concern.

In the 3 pulmonary safety studies, pulmonary function testing revealed clinically significant decreases in FEV1 that were greater than 10%, 15%, and 20% for individual subjects. A decrease in FEV1 of greater than 10% is considered clinically significant. To place these findings in perspective, one should note that the standard bronchoprovocation tests cause a decrease in FEV1 of 10-20%. In healthy subjects, 27% of the loxapine group and 27% of the placebo group had a decrease in FEV1 of >10%. Approximately 19% of healthy subjects treated with loxapine and 4% treated with placebo had decreases in FEV1 >15%. In addition, 4% of healthy subjects treated with loxapine had decreases in FEV1 >20%. The decreases in FEV1 observed above occurred in the 8 hours after either dosing.

In subjects with asthma or COPD, the FEV1 findings were marked. In asthma subjects, 85%, 62%, and 42% had decreases in FEV1 >10%, >15%, and >20%, respectively. In COPD subjects, 80%, 56%, and 40% had decreases in FEV1 >10%, >15%, and >20%, respectively. Furthermore, a high proportion (58-69%) of asthmatic and COPD subjects had significant respiratory signs/symptoms or required rescue treatment with

bronchodilator medication. Respiratory signs and symptoms included bronchospasm, dyspnea, wheezing, chest discomfort, and cough.

Pulmonary toxicity was dose-related in the safety studies. Subjects treated with a second dose of loxapine inhalation powder had greater decreases in FEV1 (compared to their first dose), which did not return to baseline at 24 hours post-dose. A significant proportion of asthmatic and COPD subjects discontinued from the study before receiving the second dose, due to a decreased FEV1 and/or the need for rescue treatment of respiratory signs and symptoms. As a result, one cannot determine the true nadir of the FEV1 following treatment with loxapine inhalation powder in the pulmonary safety studies.

Additional factors could contribute to an unacceptable risk of pulmonary toxicity in the intended population. Patients with schizophrenia and bipolar disorder have a high prevalence of tobacco smoking. Thus, many of these patients will have some degree of respiratory disease burden at baseline.

In addition to the pulmonary safety concerns, there are multiple CMC and CDRH concerns that need to be addressed as well. The CMC issues include the following:

DMF <sup>(b) (4)</sup> is unacceptable; (b) (4)

. In addition, CDRH, has requested a complete human factors validation study as well as valid worst-case simulation testing.

**Questions:**

**Pulmonary Toxicity**

**Question 1:** Does the Agency agree that the Phase 2 and Phase 3 studies presented in NDA 022549 show a favorable pulmonary safety profile in the intended patient population?

***Preliminary Comments:*** *No, we do not agree. The pulmonary safety profile in the intended patient population has not been adequately characterized. In the Phase 2 and 3 study protocols, subjects with clinically significant acute or chronic pulmonary disease were excluded. Furthermore, no patients were recruited from medical or psychiatric emergency rooms; yet, medical and psychiatric emergency rooms would likely be common settings for use of Staccato Loxapine if it is approved. It is possible that by excluding patients with clinically significant pulmonary disease and by not enrolling patients at emergency rooms, treatment with Staccato Loxapine resulted in a more*

*favorable pulmonary safety profile in the study population than would be expected in the intended population.*

***Additional FDA Comment:*** *We remain concerned about whether you have demonstrated efficacy in the intended population, particularly in acutely agitated patients who would present to an emergency room or an acute inpatient setting. It appears that the majority of patients were recruited and studied as outpatients. It is not clear whether the efficacy results would be fully generalizable.*

***Discussion at Meeting:*** *Alexza argued that the NDA studies did include patients who were representative of the intended population. Alexza provided clarification about the recruitment, selection, and treatment of subjects during the pivotal studies. Patients were referred by outpatient healthcare providers who had experience in identifying and referring agitated subjects in similarly designed studies. Subjects were not managed as outpatients; they were managed in a clinical research unit, typically during a 2-3 night stay. Furthermore, subjects did not receive training using a complete device with working parts; they had training using a shell of the device. Thus, they did not experience the sensory phenomena of the light flash or the sound of activation of the device. None of the subjects failed to inhale a full dose due to a startle response.*

*The Division requested that the sponsor provide detailed information in the resubmission to make the case that the phase 3 pivotal studies included patients representative of the intended population and were, in fact, naïve to the device. In addition, the division asked the sponsor to provide documentation that it is standard practice to obtain the relevant medical and psychiatric history and brief physical examination on the typical patient for whom this device would be intended.*

**Question 2:** In Study 004-104, a detailed case review of the healthy subjects administered *Staccato* Loxapine who had FEV<sub>1</sub> decreases >10%, including blinded expert examination of flow-volume loops, revealed no evidence of treatment-related bronchospasm. Given this finding, the rare occurrence of airway adverse events across the clinical development program, and other information related to sedation effects in healthy subjects, does the Agency agree that this analysis provides reassurance that *Staccato* Loxapine is safe for use in patients without active airway disease?

***Preliminary Comments:*** *Variations in testing effort and the sedating effects of Staccato Loxapine theoretically could have affected the interpretation of FEV<sub>1</sub> decreases in this study. Whether or not the analysis provides reassurance that Staccato loxapine is safe for use in the intended population is a separate issue, and one that we do not feel has been adequately addressed.*

***Discussion at Meeting:*** *See discussion at meeting for question 1.*

**Question 3:** In Study 004-104, a detailed case review of the healthy subjects administered *Staccato* Placebo who had FEV<sub>1</sub> decreases  $\geq$ 10%, including blinded expert examination of flow-volume loops, revealed no evidence of treatment-related

bronchospasm. Given this finding, the rare occurrence of airway adverse events across the development program in subjects who received placebo, and the plausible explanation that variation in testing effort accounts for the observed decreases in FEV<sub>1</sub>, does the Agency agree the device itself does not present a meaningful risk of bronchospasm?

***Preliminary Comments:*** *It is noteworthy that 11.5% of placebo-treated subjects in the asthma population (Study 004-105) and 11.1% of placebo-treated subjects in the COPD population (Study 004-108) experienced treatment-emergent airway-related adverse events. Thus, it appears that some patients may be susceptible to device-induced respiratory adverse events.*

***Discussion at Meeting:*** *The sponsor stated that they are confident that the placebo device was safe. A blinded expert reviewed the flow loops and determined that there was no consistent pattern suggestive of airway obstruction. Importantly, there was no temporal relationship between placebo administration and decreases in FEV<sub>1</sub>, suggesting that the changes seen were likely background events in the population studied, given the repeated and extensive testing. Alexza stated that they do not plan additional studies to characterize the device in terms of toxic effects of the placebo device. They feel that the briefing package included a thorough discussion of data from the phase I safety studies. Additionally, the aerosol characterization did not demonstrate any results of concern. The sponsor agreed to reiterate these arguments in their response.*

**Question 4:** Decreases in FEV<sub>1</sub> and respiratory signs and symptoms were seen after treatment with *Staccato* Loxapine in asthma and COPD subjects who had clinically active disease and whose quick-relief agents were withheld. However, each event was readily managed with a standard bronchodilator. No subject showed evidence of respiratory distress, required a course of steroids, required a prolonged stay in the clinic or an ER visit, or had any *sequelae* suggesting a sustained adverse effect. Does the Agency agree that the effects of *Staccato* Loxapine in subjects with clinically active airway disease can be effectively managed with standard bronchodilator therapy?

***Preliminary Comments:*** *No, we do not agree. It would not be possible to adequately screen out all patients with asthma or COPD who are at risk for an acute exacerbation of respiratory illness secondary to treatment with *Staccato* Loxapine treatment. It does not seem reasonably safe to rely on bronchodilator rescue treatment as a management strategy for the use of the product.*

*The incidence of airway adverse events was high in subjects with asthma or COPD who were treated with *Staccato* loxapine, compared to placebo. Since rescue albuterol was immediately given per protocol to any subject who had respiratory symptoms or a decrease of  $\geq 20\%$  in FEV<sub>1</sub>, the true nadir of FEV<sub>1</sub> following *Staccato* Loxapine treatment is unknown. We remain concerned that in an acute, uncontrolled setting where doses may be given every 2 hours and the severity of respiratory illness at baseline may not be easily evaluated, there may be a risk of respiratory decompensation following administration of *Staccato* Loxapine. Furthermore, patients who are sedated may be unable to report respiratory symptoms following dosing. Patients could develop*

bronchospasm and prolonged sedation, which could require intubation, mechanical ventilation, and intensive care management.

**Discussion at Meeting:** Refer to the discussion at meeting for Question 5.

a) The data in COPD subjects showed a lower incidence of airway adverse events compared to asthma subjects, and a high incidence of background FEV<sub>1</sub> changes in the placebo group. Does the Agency agree that the risk of bronchospasm after *Staccato* Loxapine treatment is less in COPD subjects than asthma subjects?

**Preliminary Comments:** *It is not surprising that smaller decreases in FEV1 were observed in the COPD population compared to the asthma population, since by definition COPD patients have some degree of fixed rather than reversible airway obstruction. In addition, starting from a lower baseline FEV1, a smaller impairment may be sufficient to cause respiratory compromise in COPD. Since many patients with schizophrenia and bipolar disease smoke, it is likely that a large proportion of patients receiving this drug will have some degree of respiratory disease at baseline. Thus, we remain concerned that a significant risk of respiratory decompensation exists in COPD patients and the intended population who receive Staccato Loxapine.*

**Discussion at Meeting:** Refer to the discussion at meeting under Question 5.

**Question 5:** The pulmonary safety program has identified patients who may be susceptible to bronchospasm, the nature of this event, and how it can be managed. Considering the intended healthcare settings for *Staccato* Loxapine and the well characterized risk, does the Agency agree that the risk of bronchospasm in susceptible patients in the intended population can be managed through appropriate labeling and a risk mitigation strategy?

**Preliminary Comments:** *We do not agree that the risk of pulmonary toxicity with Staccato Loxapine can be managed through labeling and a risk mitigation strategy. You have not presented new data that change the unfavorable risk/benefit profile for Staccato Loxapine. The pulmonary safety trials demonstrated that both the device and the drug contribute to pulmonary toxicity in all types of subjects in the pulmonary safety studies, particularly in patients with underlying lung disease. Your Phase 2/3 data are insufficient to demonstrate pulmonary safety in your proposed patient population.*

**Discussion at Meeting:** *The sponsor again argued that the risks associated with Staccato Loxapine treatment could be mitigated through appropriate labeling and a comprehensive REMS program, including both a communication plan and a medguide. Alexza discussed the settings in which it envisions the product being used. Initially, patients with agitation would likely be treated in the ER; then they would likely be admitted to a psychiatric unit for approximately 7-14 days. Alexza estimates that 50% of patients with acute agitation would present to an ER; another 50% would present to a clinic, psychiatric unit, or clinician's office. Alexza pointed out that the standard of care in an emergency room is to obtain a medical history and perform a physical exam, during*

*which pulmonary risk factors can be identified. The sponsor believes that most patients presenting with acute agitation will have a known medical history or will have a family member available from whom a medical history can be obtained. In addition, medical records would be available. The sponsor stated that patients treated with bronchodilators or inhaled corticosteroids as well as patients for whom a medical history is not known should not be treated with Staccato Loxapine.*

*The Division expressed concern that the risk of pulmonary toxicity in the intended population remains. The basic question is whether one can identify patients at risk of developing pulmonary toxicity with Staccato Loxapine treatment. Alexza must address the problem of defining the patient populations who should and should not be treated with Staccato Loxapine. In addition, Alexza must address the concern about the potential negative outcomes of treatment and how the treatment can be used safely.*

*The Division stated that it would be reasonable to propose a REMS program for the use of Staccato Loxapine. The Division requested that the sponsor provide a detailed proposal including labeling, a medication guide, a communication plan, and postapproval studies to manage the risks.*

*The Division also requested that the sponsor provide information about what percentage of agitated patients in the intended population would be ineligible to receive treatment with Staccato Loxapine. In addition, we requested that the sponsor consider a phase 4 study of real-world use of Staccato Loxapine in a cohort of typical agitated patients, in order to provide information about the use of the product.*

*The Division informed the sponsor that we would likely present the application to an Advisory Committee.*

### **Aerosol Characterization**

**Question 6:** As summarized in the Information Package, studies have characterized the total mass of drug deposited in the lung, the amounts of impurities and leachables emitted from the device, and demonstrated an absence of (b) (4) in the airstream. Does the Agency agree that no further studies are needed to characterize the total mass of drug or other potential products that could be deposited in the lung?

**Preliminary Comments:** *You indicated that that further studies are not needed to characterize the total mass of drug and other potential products that could be deposited in the lungs. However, CDRH is interested in evaluating the fraction of the respirable mass likely to be deposited in the airways that may be most susceptible to broncho-reactivity. Deposition of specific particle sizes may be related to the cross-sectional dimension of airways responsible for airway reactivity. For our review, we prefer to analyze sample data for each (b) (4) using the two specified doses (5mg and 10mg) from your characterization studies, as you have agreed to provide from our telephone discussion on 12/13/2010.*

**Discussion at Meeting:** *The Division agreed that no additional studies are necessary.*

**Human Factors Assessment**

**Question 7:** Does the Agency agree that the design and methodology for the proposed human factors validation study is adequate to validate that the product can be used effectively in the proposed clinical setting? In particular, does the Agency agree that the directed task scenarios, the evaluation methodologies, and the enrollment criteria for representative healthcare providers and representative patients are adequate for this study?

**Preliminary Comments:** *We do not agree. Refer to the following detailed comments on the proposed human factors validation study design and methodology. Please note that comments provided to specific sections of the protocol may require revisions to other sections of the protocol.*

*However, please see the following comments from CDRH and DMEPA:*



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**Discussion at Meeting:** Alexza agreed to modify the human factors study as per recommendations #2 through #10. To address comment #1, Alexza proposed to include patients with bipolar disorder or schizophrenia who are not agitated. We agreed that the studies should not include agitated patients. We requested that the sponsor revise and formally submit the protocol for review and comments.

### **Heat Package – Worst Case Simulation Testing**

**Question 8:** Does the Agency agree with the proposed test configurations and measurement parameters to simulate a worst-case manufacturing scenario for heat packages in order to characterize the safety risk?

**Preliminary Comments:** In the response, you proposed to conduct a worse case testing using heat packages that have (b) (4). This was not significantly different than the study that you conducted by (b) (4) to the heat package.

Upon further discussion with CDRH, you have now provided a summary test report for the heat package (b) (4) (the scenario you suggested during our discussion). We acknowledge that this new information was sufficient to address our concern associated with either a catastrophic failure or a worst case manufacturing defect.

**Discussion at Meeting:** The sponsor agreed to formally submit the summary test report to the NDA.

## **Container Closure System**

**Question 9:** Does the Agency agree that the data summarized in the Information Package provide substantive evidence that (b) (4) do not adversely impact package integrity and strength?

**Preliminary Comments:** *This will be a review matter; however, the data provided do appear to demonstrate that the (b) (4) on the (b) (4) do not adversely impact package integrity and strength. On resubmission, we request that the individual data points be provided in the application, rather than just their average and standard deviation.*

**Discussion at Meeting:** *The sponsor agreed to our request.*

**Question 10:** Does the Agency agree that Alexza's proposed control plan will control for (b) (4) on the commercial drug product to acceptable levels?

**Preliminary Comments:** *We encourage you to continue to work with your supplier to resolve this issue; otherwise the proposed control plan for (b) (4) appears reasonable. We recommend that the control for (b) (4) be included in the drug product stability protocol.*

**Discussion at Meeting:** *The sponsor agreed to submit data on (b) (4) as requested.*

**Question 11:** Does the Agency agree that the data summarized in the Information Package demonstrate the suitability of the (b) (4) as the container closure system for the commercial drug product?

**Preliminary Comments:** *We expect that the stability data will provide conclusive evidence of the suitability of (b) (4) as the container closure system. (b) (4)*

*we recommend that a limit be set for this parameter and that it be part of the stability protocol.*

**Discussion at Meeting:** *The sponsor agreed to our request.*

## **Stability**

**Question 12:** Does the Agency agree on the proposed stability protocol for the Primary Stability Lots?

**Preliminary Comments:** *The proposed stability protocol appears reasonable. We request that you ensure that the appearance test includes a test/limit for (b) (4)*

(b) (4) We recommend that a (b) (4) test be included as the results to date show significant decreases. We recommend that the device functionality test be reinstated.

**Discussion at Meeting:** There was no further discussion.

**Question 13:** Will the Agency accept at resubmission of the NDA, 3 month data from the Primary Stability Lots, with the commitment of providing 6 months data (minimum) during the review?

**Preliminary Comments:** This will be a review matter, however, we recommend that 12 months of long-term and six months of accelerated stability data be provided at time of NDA submission.

**Discussion at Meeting:** The sponsor proposed to submit 6 months of stability data with the complete response along with a rationale. The Agency recommended that 12 months of long-term data be provided and cautioned that the use of data from supportive stability lots to support an extrapolation from primary stability lot data to establish a commercially viable expiry period would be a review matter.

**Question 14:** Does the Agency agree that real-time data on the Primary Stability Lots (in conjunction with 24 months data from the Registration Stability Lots and other supportive stability lots) supports an expiry period of (b) (4), as outlined in the schedule provided in Table 32? Does the Agency agree that post-approval stability updates can be submitted as a Supplement – Changes Being Effectuated?

**Preliminary Comments:** The determination of the expiry period will be a review matter, however, we recommend that 12 months of long-term and six months of accelerated stability data be provided at time of NDA submission. Postapproval stability updates can be submitted as a CBE supplement, or possibly in an Annual Report (Draft Guidance for Industry. CMC Postapproval Manufacturing Changes Reportable in Annual Reports.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM217043.pdf>).

**Discussion at Meeting:** We reiterated that determining an expiry would be a matter of review and stated our preference for a complete package upon submission.

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Alexza Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, R.Ph., M.S.  
Senior Regulatory Project Manager

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
01/13/2011

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, October 28, 2010 4:01 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Adasuve (loxapine) Inhalation Powder : End of Cycle Meeting Request  
**Attachments:** FOREIGN VISITOR DATA REQUEST FORM.doc

Dear Christine,

Your request for a meeting received on October 21, 2010 has been granted. A face-to-face meeting has been arranged for December 17, 2010 from 1:00 - 2:30 pm EST at the following location:

White Oak Building 22, Room 1415  
10903 New Hampshire Avenue  
Silver Spring, MD 20903

Please have all attendees bring photo identification and allow 15 - 30 minutes to complete security clearance. If there are additional attendees, email the information to me at [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov) so that I can give security staff time to prepare temporary badges in advance. Upon arrival the FDA, give the guard either of the following numbers to request an escort to the conference room:

Kimberly Updegraff, Project Manager, X2201  
Dave Berman, Division Secretary, X1044

**For Foreign Nationals and Foreign Visitors (See attachment):** Any individual who is not a US citizen will need to complete a "Foreign Visitor Data Request Form". The data request form must be filled out completely for each visitor and the form(s) must be submitted to the FDA Office of Security Operations at least 10 calendar days prior to the visit. Incomplete forms will not be accepted and will be returned to the originator. Please let me know as soon as possible if you have an individual or individuals who will need to complete the form as you are encouraged to submit the form(s) to me as quickly as possible to prevent any potential delays.

Please provide the background information for this meeting (three copies of the meeting briefing package and 20 desk copies) prior to the meeting. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by November 22, 2010, we may cancel or reschedule the meeting.

Please send the desk copies to the following address:

Kim Updegraff  
Division of Psychiatry Products  
Food and Drug Administration  
White Oak CDER Building #22, Office 4241  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

If you have any questions/concerns, please let me know.

Best regards,

10/28/2010

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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Meeting Request Granted Form

Application Type	NDA												
Application Number	022549												
Type of Meeting	A												
Letter Date	10/21/2010												
Date Sponsor Informed of Meeting Granted	10/28/2010												
Date of FDA Premeeting	12/10/2010												
Date of Meeting	12/17/2010												
Sponsor was informed of: <ul style="list-style-type: none"> <li>• date/time &amp; meeting location</li> <li>• expected FDA attendees</li> <li>• meeting briefing package due date</li> <li>• number of copies</li> </ul>	<table style="width: 100%; border: none;"> <tr> <td style="width: 150px;">Yes</td> <td style="width: 50px;">✓</td> <td style="width: 150px;">No</td> </tr> <tr> <td>Yes</td> <td>✓</td> <td>No</td> </tr> <tr> <td>Yes</td> <td>✓</td> <td>No</td> </tr> <tr> <td>Yes</td> <td>✓</td> <td>No</td> </tr> </table> <p>Other: Sponsor agreed to the December 17, 2010 meeting date and time.</p>	Yes	✓	No									
Yes	✓	No											
Yes	✓	No											
Yes	✓	No											
Yes	✓	No											
Project Manager	Kim Updegraff												

\*\*Any follow-up letter must be checked into DFS as an advice letter, **NOT** as a meeting request granted letter.

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/s/

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KIMBERLY S UPDEGRAFF  
10/28/2010

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Friday, April 23, 2010 3:50 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** Alexza, Staccato Loxapine NDA 022549 - Information request

**Importance:** High

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We request that you provide a response to the following the questions:

1. Your correspondence, dated February 2, 2010, includes the foil pouch stock qualification test results, Table 5. There appear to be no acceptance criteria for microbial limits, as the table marks it "Report only". Please justify this discrepancy. Please also provide sample size data and justification for the qualifications performed.
2. You provided **m3.2.P.2.5 Microbiological Attributes** as the microbiological testing summary for the Staccato® Loxapine, a (b) (4) drug product. However it is unclear whether the verification was performed after the supplier change. Please provide clarification on this point.
3. You provided **m3.2.P.7 Container Closure System – Heat Package**, dated November 11, 2009, to meet the requirements of 21 CFR 820.50. However, this procedure is not adequate because it fails to establish provisions for supplier controls and balancing the purchasing assessment with the receiving acceptance protocols. Please provide revised procedures that address the following:
  - a. The method of determination of the type of and extent of control that is exercised over suppliers.
  - b. Maintenance of records of acceptable suppliers and the method of addressing the purchasing data approval process.
  - c. Balancing of purchasing assessment and receiving acceptance protocols to ensure that products and services are acceptable for their intended use.
4. You provided **m3.2.P.7 Container Closure System – Heat Package**, dated November 11, 2009, to meet the requirements of 21 CFR 820.72. However, this document is not adequate, because it does not provide a summary of inspection, measuring, and test equipment procedure specific to the manufacturing of the *Staccato* Loxapine. Please provide a sample of the most relevant procedures, specific to the production of this device, which explain how inspection, measuring, and test equipment is routinely calibrated, inspected, checked, and maintained. If no test equipment is utilized in the manufacturing of the device, please provide an explanation as to how the manufacturing equipment is qualified.
5. You have not provided a copy of the process validation master plan, or an equivalent, to meet the requirements of 21 CFR 820.75. This is not adequate. Please provide the following:
  - a. Validations of software used as part of the production or quality system.
  - b. A list of processes for the device under review that will not be validated but will be verified by inspection and test.
6. You provided **m3.2.P.3.5 Process Validation and/or Evaluation**, to meet the requirements of 21 CFR 820.75(a). This is not adequate. Please provide a validation procedure or individual validation plan for

each process that will be validated for the device under review with the following components:

- a. The validation procedure(s) or plan(s) should describe how appropriate statistical methods for data collection and analysis are used, including that specific statistical metrics that will be utilized to determine and assess both intra- and inter-batch performance.
- b. The validation procedure(s) or plan(s) should define the criteria for re-validation.

Please respond by COB on Tuesday, April 27, 2010. If you have any questions, please let me know.

Thank you,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Monday, August 09, 2010 10:41 AM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly; Edwin Kamemoto  
**Subject:** NDA 022549: Staccato loxapine - clinical info request

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We are currently reviewing your submission and we have the following request(s):

1. For Trials AMDC-004-201, AMDC-004-301, and AMDC-0040-302, you note that 3 types of patients could be enrolled: 1) patients admitted to a hospital or research unit for the purpose of the trial, 2) patients already hospitalized for treatment of Schizophrenia who had acute agitation, and 3) patients treated at a psychiatric emergency room setting that allowed extended patient stays in a secluded observation room for the period of the trial. We request that you provide a list of enrolled subjects according to the three sources. In addition, we request that you perform subgroup efficacy analyses for each of the three sources of subjects.
2. For Trials AMDC-004-201, AMDC-004-301, and AMDC-0040-302, we request that you provide a detailed description of the screening process in each study. How were subjects identified who were suitable for enrollment? In Trial AMDC-004-301, where the screening period could be 2 weeks, how were subjects selected who were already hospitalized for treatment of schizophrenia? What was the actual duration of time between screening and study drug treatment for each subject? How did this compare to subjects screened from the other 2 types of subjects?
3. We request that you provide a detailed description of the subject training process for the use of the device in each of the 3 studies. How were subjects evaluated for "their ability to properly perform the inhalation maneuver required to use *Staccato* Loxapine/ *Staccato* Placebo"? For the 3 studies, was the training process identical? Within the 3 studies, was the training process the same for the 3 types of patients screened? Was the actual device to be studied used in the training process?

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Monday, August 02, 2010 3:01 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Staccato loxapine CMC-Pulmonology request

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We are currently reviewing your submission and we have the following request:

*Please provide an agreement that you will revise the stability protocol for the process validation lots to also include an assessment of some units of the product without (b) (4) for all storage conditions (25°C/60%RH, 40°C/75%RH and 30°C/65%RH, as necessary). Provide these data to the Agency as they become available (annual reports). These additional systematic stability data have been recommended as part of the drug product characterization for similar inhalation products (metered dose inhalers and dry powder inhalers) and help gauge the importance of the (b) (4) to the drug product stability, and any additional controls that may be needed for the acceptance and application of the (b) (4) as part of the drug product.*

Please let us know as soon as possible if you agree to our request or if you have any questions.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

8/4/2010

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

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/s/

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KIMBERLY S UPDEGRAFF  
09/01/2010

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, July 15, 2010 2:36 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 : Staccato loxapine: ONDQA comment

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We also refer to our May 17, 2010 information request letter. The Office of New Drug Quality (ONDQA) would like to relay the following comment:

"With regard to ONDQA Question 2 of the May 17, 2010 information request letter and your response in the June 7, 2010, amendment, we would like to inform you that it is no longer considered necessary for you to develop a more sensitive method for the detection of (b) (4) with the emitted dose of the drug product. Our pharmacology/toxicology team has been able to locate supportive qualification data such that the current detection limit of your (b) (4) for (b) (4) is considered acceptable."

Best regards,

Kim Updegraff, MS, RAC

Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation

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

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/s/

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KIMBERLY S UPDEGRAFF  
07/15/2010

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Tuesday, April 27, 2010 11:31 AM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 22549 / Staccato Loxapine: FDA Request for Information

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We request that you respond to the following the questions:

1. **Trial AMDC-004-103:** How was it determined that Subject 008 did not receive a full dose of loxapine from the clinical device? Was there a device malfunction reported in association with this particular dose administration? Please provide detailed information regarding the pharmacokinetic assessments and device evaluations for this subject (or direct us to the relevant information in the NDA).
2. **Trials AMDC-004-301 & AMDC-004-302:** There were numerous cases of concomitant use of antipsychotics, antidepressants, benzodiazepines, hypnotics, and other psychotropic medications during the trials or recently before the trials. The protocols prohibited use of specific concomitant medications from 4 hours prior to administration of study drug until the end of the 24-hour post-treatment evaluation period. Please discuss the following: 1) what were the procedures for discontinuing prohibited medications within the specified time frames before an episode of acute agitation; 2) was the failure to discontinue prohibited medications before study drug administration considered a protocol violation; and 3) were efficacy data excluded for subjects later found to have been treated with concomitant psychotropic medication during the prohibited time period? In general, we would like to have a detailed understanding of the actual use of concomitant psychotropic medications and how this was managed in relation to the efficacy assessments and efficacy analyses.
3. **Trial AMDC-004-302:** Subjects 03-044 and 14-280 were discontinued from the trial due to adverse events of anxiety. What was the timing of anxiety in relation to dosing with loxapine? Did these subjects have akathisia, restlessness, or any other psychiatric or medical adverse events? Did these subjects have efficacy assessments after their dose? Were their data included in the efficacy analysis? Please provide all available information on these 2 subjects in the form of narratives.
4. **For subject 19-038,** please provide all study information including follow-up and autopsy results in the form of a narrative.
5. **Trial 104-202:** Please provide follow-up information regarding the subject who became pregnant (Subject 012-293). What was the outcome of the pregnancy?
6. **Trial 004-102:** For subject 01-030, what type of tachycardia was observed? Was an ECG performed to evaluate this adverse event?

We request a response by Wednesday, May 5, 2010. Please let me know if you have any questions.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, May 27, 2010 12:15 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 : Staccato loxapine : Information request

Dear Christine,

You provided **SLP0007 Validation Program**, Rev. 03, dated April 27, 2010, to meet the requirements of 21 CFR 820.75(a). This procedure is not adequate as it fails to define specific criteria for revalidation, stating that failures to meet the requirements of the protocol are subject to requalification and subsequent revalidation. Please explain the criteria used to determine whether a failure necessitates a revalidation. The procedure also states that revalidation of a system may be required whenever changes are made to the equipment or system. Please define the changes that qualify for such a revalidation.

Additionally, you did not provide a validation procedure or individual validation plan for each process that will be validated for the *Staccato* Loxapine. Please provide a validation procedure or individual validation plan for each process that will be validated for the device under review with the following components:

- a. The validation procedure(s) or plan(s) should describe how appropriate statistical methods for data collection and analysis are used, including that specific statistical metrics that will be utilized to determine and assess both intra- and inter-batch performance.
- b. The validation procedure(s) or plan(s) should define the criteria for re-validation.

Please provide a response by June 2, 2010.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

7/15/2010

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

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/s/

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KIMBERLY S UPDEGRAFF  
07/15/2010

**Updegraff, Kimberly**

**From:** Christine Welch [cwelch@alexza.com]  
**Sent:** Tuesday, July 13, 2010 8:25 PM  
**To:** Updegraff, Kimberly  
**Cc:** Christine Welch  
**Subject:** RE: NDA 022549: Staccato loxapine : Information request (CDRH)  
**Attachments:** 1-11-1-resp-to-info-req-qlty-07jul2010-13jul2010.pdf; 022549-cover-resp-info-req-cdrh-13jul2010.pdf

Dear Kim,

In response to the Information Request (CDRH) received July 7, 2010, please find attached a response document (and cover letter) that provides responses to the list of questions.

As requested we have sent by Fedex today (for delivery on Wednesday morning) both a desk copy and a CD to the CDRH reviewer.

The eCTD sequence (0014) will be submitted through the ESG at the latest on Thu July 15. Please let me know if you have any questions related to this submission and if we can be of any further assistance.

With best regards,  
Chris

.....  
Christine Welch, MS, RAC  
Senior Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: 650 944-7030  
Fax: 650 944-7983  
cwelch@alexza.com

**From:** Updegraff, Kimberly [mailto:Kimberly.Updegraff@fda.hhs.gov]  
**Sent:** Wednesday, July 07, 2010 9:32 AM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Staccato loxapine : Information request (CDRH)

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We request that you respond to the following:



(b) (4)

**Changes to the Heat Package**

(b) (4)

**Changes to Pouch**

(b) (4)

**Human Factors**

5. In your response our previous deficiency regarding human factors, you clarified that Study 004-R1 was not by itself intended to support a usability and human factors evaluation of the final product. An evaluation of usability and human factors was based on clinical experience with Staccato Loxapine and formal risk analysis. You reported that studies have shown that a naïve user is capable of reliably actuating the device without extensive training and with minimal instruction. While you have referred to the clinical experience, and indicated that there were no usability-related issues identified in various clinical trials, please note that human factors validation is an independent validation, and it is different than that of a clinical validation. Human factors validation has its own objective in determining that that device is safe in the hands of representative users; data and results in demonstrating that potential use errors and inadequate user performance have been successfully mitigated. Please provide a discussion of what you have defined as potential use errors and inadequate user performance, how you have successfully mitigated potential use errors and inadequate user performance, and that you have incorporated representative user population in your evaluation. Provide objective and subjective (if possible) data to demonstrate that such untrained users will reliably take a “steady deep breath” during administration. Furthermore, conclusions that the device can be safely used in the hands of representative users need to be clearly delineated in your response.

We request that, in addition to the official submission, you provide a desk copy as well as a CD to the CDRH reviewer at the following address:  
US Food & Drug Administration

Center for Devices and Radiological Health  
QuynhNhu Nguyen (DAGID/ARDB)  
10903 New Hampshire Ave  
WO66 Room 2531  
Silver Spring, MD 20993

Please let me know if you have any questions.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: [Kimberly.Updegraff@fda.hhs.gov](mailto:Kimberly.Updegraff@fda.hhs.gov)

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Wednesday, July 07, 2010 1:13 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549/Staccato Loxapine: Planned Amendments/request for telecon

Dear Christine,

In response to the email below dated May 11, 2010 regarding your planned CMC amendment containing specification updates, we have the following comment:

(b) (4)

Please let me know if you have additional questions.

Best regards,

Kim

---

**From:** Christine Welch  
**Sent:** Tuesday, May 11, 2010 12:13 PM  
**To:** Updegraff, Kimberly  
**Cc:** Christine Welch  
**Subject:** NDA 022549/Staccato Loxapine: Amendments

Dear Kim,

With reference to NDA 022549 (*Staccato Loxapine*), the purpose of this message is to provide an update on several amendments that we plan to submit during May and June. The amendments are as follows:

- 1. CMC Amendment: 12 month stability data:** The original NDA included 6 month stability data on registration lots. At the Pre-NDA Meeting (Official Meeting Minutes, 27 July 2009), we agreed with the Division to provide stability updates when available; the first update comprising 12 month data (registration lots) is scheduled to be submitted on **Friday 21 May**.
- 2. Submission of pediatric plan:** In our request for a deferral of pediatric studies for children/adolescents aged 10-17 years (IND 73,248, Serial Submission No. 0065, dated September 30 2009), we committed to providing synopses of the proposed pediatric studies within a pediatric plan during the first half of 2010. The pediatric plan is scheduled to be submitted **Friday 16 June**.
- 3. Submission of updated labeling:** We would like to submit an update to the *draft carton and container labels* ( [m1.14.1.1](#)) to include revised content in accordance with applicable regulations. Additionally, we would like to provide an update to the *draft labeling text* ([m1.14.1.3](#)) to include organizational changes in accordance with 21 CFR Part 201.56.(d)(1). These labeling updates will be ready to submit within the next two weeks. However, the proposed Trade name is currently under review and if this was approved during May, the Trade name could be included in the labeling update. Considering this, I would appreciate your advice on the best timing of this submission.

7/7/2010

**4. CMC Amendment: Specification Updates.** Alexza plans to submit a CMC Amendment containing two specification updates. A brief description is provided below. It would be productive to be able to discuss these changes with the respective Chemistry reviewers at CDER and CDRH. Please could you advise as to the possibility of scheduling a teleconference for this purpose.

(b) (4)

**(ii) Drug Substance Specification**

Per the harmonization of USP chapters <61> and <62>, acceptance criteria for Microbial Limits (NDA 022549, Sequence 0000, m3.2.S.4.1) have been updated. The list of specified organisms has been updated to include gram negative bile tolerant organisms, and acceptance criteria for Aerobic Count and Yeast/Molds have been clarified.

Please let me know if you have any questions or comments on these proposals. I look forward to hearing feedback regarding the timing of the labeling update (#3) and the possibility of a teleconference to discuss #4.

Best regards,

Chris

.....  
Christine Welch, MS  
Senior Director, Regulatory Affairs  
Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court, Mountain View, CA 94043  
Phone: 650 944-7030  
Fax: 650 944-7983  
cwelch@alexza.com

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22549

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ORIG-1

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ALEXZA  
PHARMACEUTICA  
LS INC

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Staccato (loxapine) for Oral  
Inhalation

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KIMBERLY S UPDEGRAFF

07/07/2010

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Saturday, June 26, 2010 10:01 AM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549: Information request for Staccato loxapine (inhalation)

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for *Staccato* loxapine for inhalation. We request that you provide responses to the following:

- 1)
- 2)
- 3)
- 4)
- 5)
- 6)
- 7)
- 8)
- 9)
- 10
- 11

(b) (4)

(b) (4)

12)

(b) (4)

13)

14)

15)

16)

17)

18)

19)

20)

Please let us know when you expect to submit a response. We request that you respond as soon as possible.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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

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KIMBERLY S UPDEGRAFF  
06/28/2010

# Mid-Cycle Meeting Description and Agenda Template

## Mid-Cycle Meeting Agenda Template

### Staccato Loxapine for inhalation

May 3, 2010 (2:00 - 3:30 PM)

#### 1. Important Goal Dates

*Review Completion Goal Date according to GRMP:*

Review due to Team Leader: September 6, 2010

Review due to CDTL: September 13, 2010

Action Package due to Division Director: September 20, 2010

*PDUFA Goal Date:* October 11, 2010

#### 2. Discipline Specific Reviews of Application

##### a. CMC – David Claffey (2:00 – 2:15 PM)

\* Review progressing, first draft will be complete in a few weeks

\* Consulted CMC-pulmonology, review is complete – requests for information need to be sent to sponsor

\* LNC/DMEPA: dosage form should be “loxapine inhalation powder”- info needs to be sent to sponsor

\* CDER/OC inspection of drug product site scheduled for June, CMC will attend. Question surrounding the inspection since FDA can only inspect the NDA holder itself.

##### b. CDRH (Consult) – Quynh Nhu Nguyen (2:15 – 2:30 PM)

\* Will prepare a list of requests to be sent to the sponsor. Reviewer needs a consolidated document of clinical and commercial versions of the device as well as listings of in vitro performance testing and actuation reliability testing.

##### c. P/T – Darren Fegley (2:30 – 2:35 PM)

\* Review almost complete, currently reviewing two additional impurities mentioned in the CMC-pulmology review. No issues expected.

##### d. Clin Pharm/Biopharm – Andre Jackson (2:35 – 2:45 PM)

\* Single dose and multiple dose study basically linear; Smoker vs. Non-Smoker basically linear.

Clin Pharm Stat (Consult) – Donald Schuirmann

\* BE Study: Does not pass if subject 8 is included/passes if not included.

##### e. DPAP (consult) – Anya Harry & Team Leader, Theresa Michele (2:45 – 3:10 PM)

\* Preliminary review: found a significant drop in FEV1 in asthmatics as well as in healthy subjects.

\* Will be finishing review within the next few weeks.

\* May recommend a Complete Response.

##### f. Clinical – Frank Becker (3:10 – 3:20 PM)

## Mid-Cycle Meeting Description and Agenda Template

- \* Review approximately 50% complete, efficacy demonstrated at 10mg
- g. Statistical – Yeh-Fong Chen (3:20 – 3:25 PM)
  - \* Even though the sponsor-proposed procedure for dealing with multiple comparison due to two doses and the multiple efficacy endpoints was not valid for controlling the type I error rate, the efficacy of treatment effect was demonstrated as a result of extremely p-values
  - \* Both efficacy results based on EPC scores for Staccato Loxapine 5 mg and 10 mg at individual time points were described in the labeling, but the reviewer noted that only the comparison for 10 mg was prospectively planned in the protocol.
  - \*It was noted that the sponsor also described in the labeling the Staccato Loxapine’s efficacy findings at (b) (4) which was not a prospectively planned analysis.
- h. DMEPA – Judy Park (3:25 – 3:30 PM)
  - \* Tradename review complete, OSE will issue letter soon.
  - \* In agreement with dosage form recommendation.
- 3. Pending Consults – Kim Updegraff, RPM (3:30 – 3:35 PM)
  - a. DSI Inspection
    - \* Site 8: Completed and OK based on preliminary communication with field office.
    - \* Site 17: Scheduled for late May 2010.
  - b. DSI-OCP Inspection – Scheduled for June/July 2010.
  - c. QT consult complete and in DARRTS – labeling recommendations.
  - d. DDMAC consulted 3/11/2010.
- 4. Issues Requiring Resolution - Kim Updegraff, RPM
  - \* Information request letter will need to be sent to sponsor ASAP.
  - \*CDRH/CMC to provide language for requests.
- 5. Labeling Issues – Will discuss at status meeting scheduled for 6/29/2010.
- 6. PMC and Risk Management Plan Issues – Will discuss at next status meeting scheduled for 6/29/2010.
  - \* REMS Needed / Need for Pre-Approval Safety Conference?
- 7. Scheduled Meetings – Kim Updegraff, RPM (3:35 – 3:40 PM)
  - \* Status meetings: 6/29/2010; 7/19/2010
  - \* PeRC: Prep meeting scheduled for 7/13/2010; PeRC date is 8/4/2010
  - \* Wrap-Up: 8/24/2010
  - \* Labeling: #1 scheduled for 9/8/2010 ; #2 scheduled for 9/17/2010

Application  
Type/Number

Submission  
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Submitter Name

Product Name

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NDA-22549

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ORIG-1

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ALEXZA  
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Staccato (loxapine) for Oral  
Inhalation

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KIMBERLY S UPDEGRAFF

06/21/2010



NDA 022549

**INFORMATION REQUEST**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Sterlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your new drug application (NDA) dated and received on December 11, 2009, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Staccato® Loxapine for Inhalation 5mg and 10mg units.

We are reviewing your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA. Please note that complete and concise responses to our requests are necessary for us to adequately evaluate your submission.

**The Center for Devices and Radiological Health:**

**Evolutionary Changes during Product Development**

1. There are numerous inconsistencies found in January 27, 2010 response, February 3, 2010 response, and the NDA application regarding the changes that were made during the development of the product. For example, you provided table 5 on pages 16-17 of the January 27, 2010 response, which outlines a list of device versions and changes without specifying specific Commercial Versions. In addition, this January 27, 2010 response had a table on page 109 that lists the details of the Phase 2 device design and manufacturing changes. In the February 3, 2010 response, you provided narrative description of the changes on pages 6-7 between the commercial versions. Furthermore, throughout the submission, you provided various tables and descriptions outlining the changes. These changes can be found in Tables 22 (Page 90), Table 23 (page 91), various descriptions on page 41, and various other sections throughout the submission. To complete our review, please provide a single consolidated document that focuses on the evolutionary changes of the device from Clinical Version 1 to Commercial Version 2.1 (manufacturing, design, component, etc.).

**For each change, please provide the following information**

- a. detailed description of the change
- b. statement of where in the development the change took place
- c. schematics and labeled engineering diagrams of the specific change

- d. discussions of how the change may affect in-vitro aerosol properties, and/or delivery mechanism; and/or in-vivo studies
- e. functional analysis and comparison between the change and its prior design,
- f. discussion of how the was implemented, and tested both in-vitro and in-vivo studies
- g. clarifications if the change was a result of either use or device-related risks

For each of the changes from Clinical Version 2 to Commercial Version 1, please provide a detailed analytical discussion from design change to design requirement/specification to hazard/risk analysis, to verification and validation testing (in-vitro and in-vivo) including comparative analyses to demonstrate that operation of the device is not adversely affected by the change, and continue to perform equivalently and not inferior to the prior design.

**In Vitro Aerosol Performance Test Reports**

- 2. In 32p22-004, you provided numerous comparisons in terms of aerosol performances between Clinical Version 2 and Commercial Version 1 (pages 90 to 100); and in 32p54, you also provided batch analyses across different device versions. Please provide a consolidated and complete test reports including test protocols, acceptance criteria, results, and conclusions for Emitted Dose and Emitted Dose Content Uniformity, Aerosol Size Distribution, Aerosol Impurities for both versions.

**Electrical and Electromagnetic Compatibility Tests**

- 3. In accordance with IEC 60601-1: Medical Electrical Equipment – Part 1: General Requirements for Safety and IEC 60601-1-2: 2001, Medical Electrical Equipment – Electromagnetic Compatibility, please provide the following information for each test that is conducted:
  - a. a summary of the testing that was done;
  - b. the requirements of the standard that were met (including immunity test levels);
  - c. the pass/fail criteria used;
  - d. the functions of the device that were considered to be essential performance;
  - e. the performance of the device during each immunity test (i.e., degradation observed);
  - f. identification of and justification for any of the standard's allowances that were used;
  - g. a description of and justification for any deviations from the requirements of the standard;
  - h. evidence of compliance with the standard's labeling (identification, marking and documents) requirements; and
  - i. if any device modifications were needed in order to pass any of the EMC testing, a description of these modifications and a statement that they will all be incorporated into the production units
- 4. In addition, it was noted that the electrical safety testing was conducted on Commercial Version 1. Please provide a justification as to why the electrical safety and EMC test results for Commercial Version 1 can be used for Commercial Version 2.

- 5.  (b) (4)

**Summary of Testing Conducted**

6. Please provide in a tabular format summarizing all of the tests specifically relating to in-vitro device performance, electrical safety, mechanical safety, EMC, biocompatibility that were conducted for each device version from Clinical version 1 to Commercial Version 2.1. Please include all relevant test reports in this response.

**Actuation Reliability Study and Human Factors Validation**

7. You provided summarized results of an Actuation Reliability Study on Commercial Version 2. You stated that this study was primarily used to evaluate user experience with device actuation. While the results of this study demonstrated a high success rate, it is not clear how the test was administered (test protocols), what user tasks and use or device-related risks were evaluated. Please provide additional information for the above concerns.
8. Further, it is not clear if this study is intended to support a usability and human factors (HF) evaluation of the final product (Commercial Version 2.1). Please direct your submission to discuss how you have characterized the use of the device, and evaluated use-related risks in a systematic approach. In doing so, please provide the following:
  - a. A description of the anticipated user population, user interfaces, anticipated user interaction with the device, and use environments.

- b. A comprehensive analysis of use-related hazards and associated risks that are based on the user interactions with the device. It should be noted that use-related hazards and associated risks can occur for a number of reasons. For example, the device is being used in ways that were not anticipated; device use requires physical, perceptual, or cognitive abilities that exceed those of the users; device use environment affects device operation and this effect is not understood by the user; etc. It is critical that the risk analysis for use-related risks is conducted appropriately and that these risks are evaluated in the human factors validation process.
- c. Meaningful evaluation of user performance (with at least 15 representative users) on the critical tasks associated with the use of the device in simulated high risk use scenarios and in realistic use environments; and evaluation of device use by representative test participants which focuses on their impression of how well they are able to perform those tasks including any instances of specific difficulty or confusions they may have experience.
- d. A description of the test materials including instructions for use, training, etc.

**Risk Analysis**

- 9. Information about risk evaluation for the proposed device could not be located in your submission. Generally, an FDA recognized standards such as ISO 14971:2007, Medical devices - Application of risk management to medical devices, or a recognized approach is applicable. Please provide your risk evaluation documentation.

**Reliability Evaluation**

- 10. The reliability assessment is based upon a series of device actuation studies. Your submission also refers to characterization studies and four reliability observations. It is not clear that these studies have been provided for our evaluation. The description of the reliability work is not complete and does not allow FDA to determine that the specified reliability level has been met. The analysis should include a description of your system's reliability specification and the reliability activities completed to verify and validate that the specification has been met (e.g., design analysis, test plans, and test reports).
- 11. Additionally, given that the device is a single-use, on demand system, an assessment of reliability should include an accelerated or real-time aging model to evaluate the reliability of the device in time. If an accelerated model is implemented, justification to validate the accelerated method for your device should be provided.

**The Office of New Drugs Quality Assessment:**

- 1. We request that you provide the pertinent method validation data (specificity, linearity, range, accuracy, precision, limit of detection, and limit of quantitation) that support the ability of the various methods to quantify the leachables that have been observed in the aerosol emitted from the drug product, i.e., (b) (4) (b) (4).
- 2. (b) (4) of the potential leachables, (b) (4), (b) (4) which are structural alerts for mutagenicity. The current (b) (4) is

said to be able to detect these (b) (4) potential leachables between (b) (4) (b) (4) respectively. As the safety concern threshold (PQRI recommendation) for leachables is 0.05 mcg/device, you are required to either modify the current method or develop a new method(s) to demonstrate that these compounds are routinely below this threshold, or provide the necessary qualification data and risk assessment for review by our pharmacology/toxicology team.

3. Additional comments may be forthcoming regarding your control strategy for extractables/leachables pending review of the risk assessment information and data and biological reactivity test results by our pharmacology/toxicology team.
4. Provide a commitment to finalize and put into practice, controls (extractables testing with acceptance criteria) for the various components of the device and packaging to assure that the levels of volatile compounds (e.g., (b) (4) (b) (4)) that may be emitted during use of the drug product, will always be at levels that are lower than what you have qualified from a toxicological perspective with your risk assessments presented in module 4 of the application. These controls will be implemented within 6 months of the date of approval of the application.
5. You have indicated that the foil pouch is used to (b) (4) (b) (4). We acknowledge that you have assessed the impact on dosing performance and impurities, with respect to the removal of the foil pouch for a period of up to 24 hours. However, no data could be found in the application that would provide any indication of how the product performance would be affected if there were a failure of the foil pouch seal of a released product for periods longer than 24 hours. The Agency generally recommends that, for products that include a protective package that is to be removed prior to patient use, formal stability studies include some samples of unprotected product (i.e., without foil pouches). We request that you provide data from such stability studies so that the impact of a failed pouch can be assessed in terms of the performance of the product and its ability to meet the specification.
6. With regard to the two Commercial Version-2 devices that had out-of-specification (OOS) flow switches, we request that you provide details about the specification in question, the percentage of these OOS parts found in the population that was dimensionally inspected, and details regarding the corrective action that has taken place at the component vendor's manufacturing site.
7. We request that you revise the method for collection of the delivered dose uniformity (QTP002016) such that a fixed collection time is specified, as the delivery of the drug aerosol from the device is mainly driven by the inhalation breath of patients. The Agency recommends that the total volume be limited to about (b) (4).
8. We request that you revise the specification for each strength to clearly indicate the number of devices that are tested for aerodynamic particle size distribution (APSD) and how the acceptance criteria for the stage groupings are applied (e.g., individually or for an average of results of separate APSD determinations).

9. We request that you revise the mass balance (recovery) requirement section (10.2.4) of the APSD method QTP002018 to clearly indicate what components of the apparatus are included in the mass balance determination.
10. We request that you revise the mass balance (recovery) run qualification requirement for the (b) (4) recovery of the aerodynamic particle size distribution method QTP002018 such that it is consistent with Agency recommendations, i.e., that the total mass of the drug collected on all stages and accessories be held to between (b) (4) of the label claim emitted dose (b) (4) 9.1 mg). In addition, the discarding of data collected with mass balance outside of the acceptable range should be limited, as a repeated failure not attributed to analyst, environmental, or instrumental errors may be a result of product not delivering doses that are on target. Revise the method to include instructions that outline a limit on the number of retests and the investigational steps taken in the event of a mass balance run qualification failure.
11. We request that you revise the method for determination of the APSD (QTP002018) such that a fixed collection time is specified in 9.2.7, as the delivery of the drug aerosol from the device is mainly driven by the inhalation breath of patients. The Agency recommends that the total volume be limited to not more than (b) (4).
12. An examination of the APSD stability data provided for the Clinical Version 2 batches (M0293 and M0294 (b) (4) and the Commercial Version 1 and 2 batches (M0583, M0584 and M0626-A, M0633- A, M0636-A, M0624-A, M0629-A, M0634-A (b) (4) revealed differences. (b) (4)

**Additional Chemistry, Manufacturing and Controls Questions:**

1. Provide updated drug product stability data.
2. Provide details of the experimental design and statistical analysis you employed for the drug deposition process (3.2.P.2.3.3).
3. We acknowledge your data from studies where the heat package was intentionally compromised with 1 mm holes (3.2.P.2.2.1.5.3.7). Has the impact of a more catastrophic failure of the heat package been studied, i.e. the possible impact of the loss of integrity of one or more of the heat package seams prior to or during actuation? If so, provide full details of such studies and results (e.g. emitted particulate levels, ICP-MS, mass balance data, etc).

In addition, the Division of Medication Error Prevention and Analysis along with Chemistry, Manufacturing and Controls, request that the current dosage form designation of “loxapine for inhalation” be changed to “loxapine inhalation powder” upon recommendation by the Labeling and Nomenclature Committee.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

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/s/

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THOMAS P LAUGHREN  
05/17/2010



NDA 022549

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Alexza Pharmaceuticals, Inc.  
2091 Stierlin Court  
Mountain View, California 94043

ATTENTION: Christine Welch, M.S.,  
Director, Regulatory Affairs

Dear Ms. Welch:

Please refer to your New Drug Application (NDA) dated December 11, 2009, received December 11, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Loxapine for Inhalation, 5 mg and 10 mg.

We also refer to your February 8, 2010 correspondence, received February 8, 2010, requesting review of your proposed proprietary name, Adasuve.

We have completed our review of Adasuve and have concluded that it is acceptable. The proposed proprietary name, Adasuve, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your February 8, 2010 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sandra Griffith, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-2445. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kimberly Updegraff at 301-796-2201.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, R.Ph.  
Director  
Division of Medication Error Prevention and Analysis  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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

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/s/

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CAROL A HOLQUIST  
05/06/2010

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Friday, April 23, 2010 3:50 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** Alexza, Staccato Loxapine NDA 022549 - Information request

**Importance:** High

Dear Christine,

Please refer to your new drug application (NDA) submitted and received on December 11, 2009 for Staccato loxapine for inhalation. We request that you provide a response to the following the questions:

1. Your correspondence, dated February 2, 2010, includes the foil pouch stock qualification test results, Table 5. There appear to be no acceptance criteria for microbial limits, as the table marks it "Report only". Please justify this discrepancy. Please also provide sample size data and justification for the qualifications performed.
2. You provided **m3.2.P.2.5 Microbiological Attributes** as the microbiological testing summary for the Staccato® Loxapine, a (b) (4) drug product. However it is unclear whether the verification was performed after the supplier change. Please provide clarification on this point.
3. You provided **m3.2.P.7 Container Closure System – Heat Package**, dated November 11, 2009, to meet the requirements of 21 CFR 820.50. However, this procedure is not adequate because it fails to establish provisions for supplier controls and balancing the purchasing assessment with the receiving acceptance protocols. Please provide revised procedures that address the following:
  - a. The method of determination of the type of and extent of control that is exercised over suppliers.
  - b. Maintenance of records of acceptable suppliers and the method of addressing the purchasing data approval process.
  - c. Balancing of purchasing assessment and receiving acceptance protocols to ensure that products and services are acceptable for their intended use.
4. You provided **m3.2.P.7 Container Closure System – Heat Package**, dated November 11, 2009, to meet the requirements of 21 CFR 820.72. However, this document is not adequate, because it does not provide a summary of inspection, measuring, and test equipment procedure specific to the manufacturing of the *Staccato* Loxapine. Please provide a sample of the most relevant procedures, specific to the production of this device, which explain how inspection, measuring, and test equipment is routinely calibrated, inspected, checked, and maintained. If no test equipment is utilized in the manufacturing of the device, please provide an explanation as to how the manufacturing equipment is qualified.
5. You have not provided a copy of the process validation master plan, or an equivalent, to meet the requirements of 21 CFR 820.75. This is not adequate. Please provide the following:
  - a. Validations of software used as part of the production or quality system.
  - b. A list of processes for the device under review that will not be validated but will be verified by inspection and test.
6. You provided **m3.2.P.3.5 Process Validation and/or Evaluation**, to meet the requirements of 21 CFR 820.75(a). This is not adequate. Please provide a validation procedure or individual validation plan for

each process that will be validated for the device under review with the following components:

- a. The validation procedure(s) or plan(s) should describe how appropriate statistical methods for data collection and analysis are used, including that specific statistical metrics that will be utilized to determine and assess both intra- and inter-batch performance.
- b. The validation procedure(s) or plan(s) should define the criteria for re-validation.

Please respond by COB on Tuesday, April 27, 2010. If you have any questions, please let me know.

Thank you,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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

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/s/

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KIMBERLY S UPDEGRAFF  
04/23/2010

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Monday, March 15, 2010 10:10 AM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 Staccato loxapine : Request

Dear Christine,

We have a request regarding NDA 022549, Staccato loxapine for inhalation. The review team is requesting samples of the drug product used in the Phase 3 clinical studies and of the final commercial version (two of each). We would like to see both the fully-assembled and un-assembled versions.

Please let us know when you expect to provide the samples. We request that you respond as soon as possible.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

## Updegraff, Kimberly

---

**From:** Updegraff, Kimberly  
**Sent:** Monday, March 22, 2010 2:09 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 Staccato loxapine : Request

Dear Christine,

Thank you for providing samples of the drug product used in the Phase 3 clinical studies and the final commercial version.

We feel that it would be helpful to see un-assembled versions of the entire product line. Please provide two copies of **each version** of the device, with the exception of the ones we have already received.

Please let us know when you expect to provide the samples.

Best regards,

*Kim*

Kimberly Updegraff, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22549

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ORIG-1

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ALEXZA  
PHARMACEUTICA  
LS INC

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Staccato (loxapine) for Oral  
Inhalation

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/s/  
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KIMBERLY S UPDEGRAFF

03/29/2010

## Updegraff, Kimberly

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**From:** Updegraff, Kimberly  
**Sent:** Thursday, February 04, 2010 5:24 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 : Staccato Loxapine for Inhalation : Request

Dear Christine,

Please refer to your submission dated and received on December 11, 2009 for Staccato Loxapine for Inhalation. I am currently working on the filing review for your application and have not been able to locate the Debarment Certification.

If the statement is already present in your submission, please direct me to the location, if not, please provide the document by COB on Friday, February 5, 2010.

Sincerely,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

**Updegraff, Kimberly**

---

**From:** Updegraff, Kimberly  
**Sent:** Tuesday, February 02, 2010 3:44 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 Staccato Loxapine for inhalation: Telcon follow up QUESTIONS

Dear Christine,

Please refer to your new drug application (NDA 022549) for Staccato loxapine for inhalation and the teleconference between representatives of your firm and the FDA on Friday, January 29, 2010. As discussed during the teleconference, we are currently conducting our filing review of your application and need additional information to complete our initial review.

You stated that the to-be-marketed commercial version has not been studied in humans. It will be very important that you provide responses to the questions below to help us better understand the various commercial versions developed and how each has been studied.

- 1) Provide in tabular form, a list of the various versions of the "commercial" drug product. Clearly identify each commercial version (e.g. Commercial Version #1, etc) including detailed narrative descriptions of the changes, the number of batches produced per version, and indicate which studies (e.g., clinical, stability, verification/validation) were conducted for each version. Please also clearly specify in the table, performance validation measures conducted for each version, summary results of those measures and where complete test reports pertaining to those validation measures can be located in you submission. It should be very clear how each commercial device differs from the previous version.
- 2) Provide performance validation data on the changes to the heat package shields and stainless steel.
- 3) Please include the performance validation standards used (i.e., numerical limits, confidence intervals, etc).

As discussed during the teleconference, please provide the information by COB on Wednesday, February 3, 2010.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

2/8/2010

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

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/s/

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KIMBERLY S UPDEGRAFF  
03/29/2010

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Tuesday, February 09, 2010 4:38 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 : Staccato Loxapine for Inhalation: Filing

Dear Christine,

Please refer to your new drug application (NDA) dated and received on December 11, 2009, for Staccato® Loxapine for Inhalation. We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed. The review classification for this application is **standard** and the user fee goal date is October 11, 2010. A letter with our comments and requests will arrive within the next few weeks.

Please let me know if you have any additional questions or concerns.

Sincerely,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22549

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ORIG-1

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ALEXZA  
PHARMACEUTICA  
LS INC

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Staccato (loxapine) for Oral  
Inhalation

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/s/  
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KIMBERLY S UPDEGRAFF

03/29/2010



NDA 022549

**FILING COMMUNICATION**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Sterlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your new drug application (NDA) dated and received on December 11, 2009, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Staccato® Loxapine for Inhalation 5mg and 10mg units.

We also refer to your submissions dated February 2, 2010, February 4, 2010 and February 5, 2010.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 11, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 21, 2010.

Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may arise as we review the application.

We request that you provide reviewer notes denoting which commercial version you are referencing throughout the submission.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver and deferral of pediatric studies for this application. Once we have reviewed your request, we will notify you if the request is denied.

If you have any questions, call Kimberly Updegraff, M.S., Senior Regulatory Project Manager, at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.

Director

Division of Psychiatry Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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

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/s/  
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THOMAS P LAUGHREN  
02/22/2010

**Updegraff, Kimberly**

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**From:** Updegraff, Kimberly  
**Sent:** Monday, January 25, 2010 8:26 PM  
**To:** Christine Welch  
**Cc:** Updegraff, Kimberly  
**Subject:** NDA 022549 : Staccato Loxapine Information Request

Dear Christine,

We are currently conducting our filing review of your NDA submission 022549 dated and received on December 11, 2009 for Staccato Loxapine for Inhalation. You have stated in the NDA submission that there have been a number of modifications to the commercial device. We would like to clarify which specific versions of the device were used in each individual study and whether any modifications to the commercial device have taken place between or after completion of the recent clinical studies. In addition, we would like to obtain detailed information regarding each version of the device. It would be helpful to provide the information in tabular form whenever possible, including corresponding study numbers and lot numbers for each device version. Please provide the following information:

- Tabular listing of each clinical study and corresponding device versions, lot numbers, and dates of study and manufacture. Please include data regarding excipient and technological parameters for each device. A timeline of device development and clinical studies would be helpful.
- A consolidated list of all manufacturing, testing, and packaging sites, including name, address, and CFN# of each facility.
- Detailed descriptions of each of device version, highlighting the differences among versions. Please provide clearly labeled engineering diagrams of each version. Indicate whether modifications were performed all at once or step-wise.
- Comparative analysis regarding similarities and differences between device versions and a discussion of the incremental changes during product development. Please include an evaluation of the potential for the device changes to impact clinical safety, efficacy, and overall performance of the product.
- Results of performance testing for the final product to be marketed.
- Clarify whether the device to be marketed is identical to that studied in the bioequivalence study and the special safety studies. Please provide details about any modifications to the device between these studies or since the completion of these studies.
- Clearly label (i.e., lot number, etc.) each clinical and commercial device and provide a tabular listing of the devices used in the Bioequivalence study 004-103. Please identify the devices used for studies 004-107, 004-106, 004-102 and 004-101.

- During our July 14, 2009 meeting, the Office of Clinical Pharmacology requested that you provide a rationale for deleting Subject #8 in from the analysis of Bioequivalence Study 004-103. We request that you provide a detailed discussion regarding the proposal to delete this subject's data from the bioequivalence analysis. You should take into consideration the possibility that there are individuals like Subject #8 in the relevant patient population who might have significantly different loxapine exposures than others. If the analysis excludes subject #8, one needs to consider the following questions: a) How many patients like subject #8 might have similar PK findings? And b) What are the implications of such findings for the safety and efficacy of the commercial product?

Please note that we have a teleconference scheduled for Friday, January 29, 2010 from 11:00 AM to 12:00 PM. We will discuss the issues listed above, so please respond as soon as possible to allow ample time for preparation. Feel free to contact me if you have any questions regarding our requests.

Best regards,

*Kim*

Kimberly Updegraff, RPh, MS, RAC  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Center for Drug Evaluation and Research, FDA  
Office of Drug Evaluation  
Phone: (301)796-2201  
Email: Kimberly.Updegraff@fda.hhs.gov

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

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/s/

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KIMBERLY S UPDEGRAFF  
01/26/2010



NDA 022549

**NDA ACKNOWLEDGMENT**

Alexza Pharmaceuticals, Inc.  
Attention: Christine Welch, M.S.  
2091 Sterlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Staccato® Loxapine for Inhalation

Date of Application: December 11, 2009

Date of Receipt: December 11, 2009

Our Reference Number: NDA 022549

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 9, 2010 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size.

Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>

If you have any questions, please contact me at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Kimberly Updegraff, R.Ph., M.S.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

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/s/

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KIMBERLY S UPDEGRAFF  
12/23/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 73,248

Alexza Pharmaceuticals  
Attention: Christine Welch, M.S.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Staccato® Loxapine for Inhalation.

We also refer to the meeting between representatives of your firm and the FDA on July 14, 2009. The purpose of the meeting was to obtain agreement on the content and format of the NDA.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Senior Regulatory Project Manager at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

**MEMORANDUM OF MEETING**  
IND 73,248; Staccato® Loxapine for Inhalation  
Alexza Pharmaceuticals  
Type B meeting (PreNDA)  
Meeting with Sponsor: July 14, 2009

**Objective:** To obtain agreement on the content and format of the NDA, including the scope and presentation of the each of the technical sections, the electronic submission requirements, and other regulatory considerations.

**Participants –**

**FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Robert Levin, MD	Medical Team Leader
Frank Becker, MD	Medical Reviewer
Jenn Sellers, MD	Medical Reviewer (observer)
Barry Rosloff, PhD	Pharmacology/Toxicology Supervisor
Darren Fegley, PhD	Pharmacology/Toxicology Reviewer
Thomas Oliver, PhD	Pharmaceutical Assessment Lead
Chhagan Tele, PhD	Chemistry, Manufacturing, Controls Reviewer
Andre Jackson, PhD	Clinical Pharmacology/Biopharmaceutics Reviewer
Bei Yu, PhD	Clinical Pharmacology/Biopharmaceutics Reviewer
Donald Schuirmann, MS	Statistics Reviewer
Peiling Yang, PhD	Statistics Team Leader
George Kordzakhia, PhD	Statistics Reviewer
Lester Schultheis, MD, PhD	Acting Branch Chief, CDRH (Center for Devices and Radiological Health)
Sugato De	Biomedical Engineer Reviewer, CDRH (Center for Devices and Radiological Health)
Anthony Durmowicz, MD	Medical Reviewer, DPAP (Division of Pulmonology and Allergy Products)
Kimberly Updegraff, MS	Regulatory Project Manager

**Sponsor**

James Cassella, PhD	Sr. Vice President, Research and Development
Robert Fishman, MD	Vice President, Clinical Development
 (b) (4)	 (b) (4)
 (b) (4)	 (b) (4)
Mike Simms, MBA	Sr. Vice President, Operations and Manufacturing
Peter Noymer, PhD	Vice President, Product Research & Development
Barbara Stewart, PhD	Senior Director, Toxicology
Edwin Kamemoto, PhD	Senior Director, Regulatory Affairs
Christine Welch, MS	Director, Regulatory Affairs
Alexis Palefsky, BS	Manager, Clinical Development

**Background:**

Staccato<sup>®</sup> Loxapine for Inhalation (*Staccato* Loxapine) is under development for the treatment of acute agitation associated with Schizophrenia and Bipolar Disorder. Staccato Loxapine is a hand-held drug-device product for rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine (an antipsychotic drug). Oral inhalation through the device initiates the controlled rapid heating of a thin film of excipient-free loxapine to form a highly pure drug vapor. The vapor condenses into aerosol particles with an appropriate particle size distribution for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after treatment administration.

During the clinical development program and manufacturing scale-up activities, the sponsor has made several changes to the current *Staccato* Loxapine product, (b) (4)

The main features of the device are the heat package, airway, and breath sensor. A thin film of loxapine is coated on the heat package at a dose of 5 mg (single-sided coating) or 10 mg (2-sided coating). The sponsor states that the fundamental operating principles of the current and updated versions of the device are the same, with comparable performance (aerosol) attributes and user interface characteristics (including the inhalation effort to use the device).

At the End-of-Phase 2 Meeting with the Division (September 13, 2007), Alexza obtained the Division's concurrence on the general aspects of the proposed CMC, nonclinical, and clinical development plans to support registration of the current *Staccato* Loxapine product. On December 3, 2008, Alexza met with the Division for a Type C meeting to discuss the design updates to the *Staccato* Loxapine product, summarize the data package that demonstrates the comparability of the updated and current versions of the device and to obtain agreement on the proposed studies using the update version of the device to support product registration.

The sponsor has conducted several studies in patients, using the original formulation of the device. Study AMDC-004-201 was a Phase 2, multicenter, inpatient, randomized, double-blind, placebo-controlled, single-dose, efficacy and safety study of *Staccato* Loxapine (5 and 10 mg doses) in 129 schizophrenic patients with acute agitation. The primary endpoint was the change in PEC scores 2 hours after first dose. Study AMDC-004-301 was a Phase 3, multicenter, inpatient, randomized, double-blind, placebo-controlled, multiple-dose, efficacy and safety study of *Staccato* Loxapine (5 and 10 mg doses) in 344 schizophrenic patients with acute agitation. Study AMDC-004-302 is a Phase 3, multicenter, in-patient, randomized, double-blind, placebo-controlled, multiple-dose, efficacy and safety study of *Staccato* Loxapine (5 and 10 mg doses) in 314 patients with bipolar I disorder and acute agitation.

**Questions:**

**Regulatory Questions**

**Question 1**

Does the Agency agree with the proposal to submit the NDA to support the marketing approval of *Staccato* Loxapine for the treatment of agitation as a 505(b)(2) application with cross-reference to approved NDAs for loxapine and the published literature?

**Preliminary Comments:** *On face, the proposal appears to be acceptable for review of the NDA for agitation associated with Schizophrenia or Bipolar Disorder. However, the decision about filing of an NDA would be made upon submission.*

**Discussion at Meeting:** *No further discussion.*

**Question 2**

Does the Agency agree that pending its review, the content of the NDA as outlined in the Meeting Information Package and supported by cross-reference to approved NDAs and the published literature, is adequate to support approval of *Staccato* Loxapine for the indication of *treatment of agitation associated with schizophrenia or bipolar disorder*?

**Preliminary Comments:** *On face, the proposed content appears acceptable for filing of the NDA.*

**Discussion at Meeting:** *No further discussion.*

**Question 3**

Does the Agency anticipate that presentation to an Advisory Committee will be required?

**Preliminary Comments:** *The decision regarding whether or not presentation to an Advisory Committee will be required cannot be made at this time and will be made during review of the NDA.*

**Discussion at Meeting:** *We noted that, it seemed unlikely that an Advisory Committee meeting would be necessary; however, the decision would be made early in the review cycle.*

#### Question 4

Does the Agency agree that the concepts described within the draft Target Product Profile provide an appropriate basis for development of the annotated draft labeling?

***Preliminary Comments:*** *On face, the concepts appear to be acceptable. We will discuss the components with you in more detail after the proposed labeling has been submitted in the PLR format (Physician's Labeling Rule) and reviewed.*

***Discussion at Meeting:*** *We reiterated that it is premature at this point in the application process to be discussing labeling.*

#### Clinical Questions

##### Question 5

Does the Agency agree that the comparability data from Study AMDC-004-103 are adequate to support the registration of the commercial version of *Staccato* Loxapine?

***Preliminary Comments:*** *On face, the comparability data from Study AMDC-004-103 is adequate for filing an NDA. Approvability of the commercial version of Staccato Loxapine will be based on review of all data submitted in the NDA including all bioequivalence and comparability data.*

***Additional Comment:*** *The Office of Clinical Pharmacology has looked at the data you submitted regarding Study AMDC-004-103 for the new metric AUC (0-2) which was presented to compare the current and updated formulations. The data are suitable for review; however, the determination of the bioequivalence of the current and updated formulations based upon this metric will remain a question for review.*

##### ***Discussion at Meeting:***

*The sponsor had three specific questions they wanted to address for this topic:*

**1.** *Will AUC(0-2) be the primary BE metric with AUC(0-inf) as a secondary metric?*

*It has been determined that AUC(0-2) will be the primary metric and AUC(0-inf) will be a secondary metric.*

**2.** *Will the pooling of the 5mg and 10 mg doses be acceptable to Clinical Pharmacology?*

*We indicated that we will explore the data both by individual dose and pooled, and requested that they make an argument for why the data should be pooled.*

**3.** *Does Clinical Pharmacology agree with subject 8 being designated as an outlier?*

*We indicated that, if this study had been submitted to the Office of Generic Drugs, it would not have been acceptable to consider subject # 8 as an outlier. Nevertheless, we indicated that we would explore the study results with and without the data for this subject. We noted that the question for the agency was whether subject #8 should be considered unique, or are there other persons in the population who might have different drug levels with the two formulations, and what the implications of such differences might be. The sponsor was asked to provide a rationale regarding the possible impact of subjects such as # 8 in the general population who might have different exposures when switched from the clinical to the proposed commercial formulation.*

*In addition, it was pointed out to the sponsor that they had conducted a replicate design study and that the FDA had previously posted SAS code in a 2001 statistical guidance to industry (Statistical Approaches to Establishing Bioequivalence - the PDF link is still active) to analyze this type of study. The sponsor has chosen to use a different set of SAS program statements. Although the FDA does not generally tell the sponsors what type of analysis to use, a justification should be provided to the Agency if one chooses to conduct an analysis different from what is suggested in the guidance.*

#### **Question 6**

Does the Agency concur with the methodology applied to the statistical analysis of the Phase 3 clinical studies?

**Preliminary Comments:** *Your recent submission (June 1, 2009) is under review. We will convey our comments to you as soon as the review is completed. Please also refer to our comments on your previous submissions pertaining to these two phase 3 studies (AMDC-004-301 and AMDC-004-302).*

**Discussion at Meeting:** *The sponsor explained their statistical testing methodology. We told the sponsor that this is a complex subject, and it would be best to communicate in written format. We reiterated that we would convey our written comments to the sponsor, and we agreed to have a teleconference afterwards if needed.*

#### **Post-meeting Statistics Comments**

*For your multiplicity testing procedure, using the F-test as a “gate keeper” does not help resolve the issue. In a scenario in which one of the loxapine arms is infinitely effective versus placebo on the primary endpoint, and the other loxapine dose arm is infinitely effective versus placebo on the key secondary endpoint, both F-tests will be statistically significant, which allows proceeding to the Dunnett’s tests on both the primary and key secondary endpoints. Based on computer simulations, in the case where test statistics associated with primary endpoint are independent from test statistics associated with the key secondary endpoint, the overall type I error rate is strictly greater than 0.05.*

*There have been two categories of gate keeping procedures in the literature; one is referred to as “serial” gate keeping, and the other is “parallel” gate keeping (see A. Dmitrienko, A. Tamhane “Gatekeeping procedures with clinical trial applications” Pharmaceutical Statistics 2007; X. Chen, X. Luo, T. Capizzi “The application of enhanced parallel gatekeeping strategies” Statistics in Medicine 2005; A. Dmitrienko, W. Offen, P. Westfall “Gatekeeping strategies for clinical trials that do not require all primary effects to be significant” Statistics in Medicine 2003). The parallel gate keeping was proposed because, using the serial gate keeping procedure, one would not be able to proceed with testing the key secondary endpoint unless a statistically significant difference with respect to the primary endpoint is demonstrated for each dose. In summary, your multiple testing procedure does not fall in either aforementioned category, and it is not a closed testing procedure. If you believe that your procedure controls the overall type I error rate at the 0.05 level under any circumstance, please provide a reference to the corresponding literature/paper, or provide a proof of the strong control of the overall type I error rate.*

### **Question 7**

Does the Agency agree that the organization and content of the proposed clinical section of the NDA is adequate to support the NDA for *Staccato* Loxapine?

**Preliminary Comments:** *On face, the proposed organization and content appear acceptable for review. Reference is made to the Type C meeting of December 3, 2008. You are reminded that you agreed at that time to continue to evaluate failed medical devices, determine causality, and incorporate corrective actions to your device. All such data should be included in your NDA.*

**Discussion at Meeting:** *The proposed submission of clinical data appears to be acceptable.*

*We clarified that our request for information regarding failed devices is a generic issue for any product that has the potential for failure.*

### **Question 8**

Does the Agency agree with the categories of study subjects for which individual Case Report Forms will be provided in the NDA?

**Preliminary Comments:** *The proposed categories (Deaths, SAE, discontinuations due to AE, and respiratory AE) are acceptable.*

**Discussion at Meeting:** *There was no further discussion on this point.*

## Question 9

Does the Agency agree that subject profiles and analysis programs are not required as components of the clinical datasets?

**Preliminary Comments:** *We agree that subject profiles are not routinely necessary. However, we might request profiles or a similar presentation of safety data for particular subjects of interest.*

*Please define “analysis programs.” To what types of analysis programs are you referring?*

**Discussion at Meeting:** *The Division clarified that we would not require the sponsor to submit any subject profiles for the original submission. It is possible that we would request profiles for particular subjects of interest during the review.*

## Question 10

Does the Agency agree with the planned analysis to support the Integrated Summary of Efficacy and the Integrated Summary of Safety?

**Preliminary Comments:** *On face it appears acceptable. Please note that the efficacy of Staccato Loxapine will be evaluated based on the results of the individual studies. To assist you in developing an informative integrated analysis of efficacy, we encourage you to refer to the draft guidance “Integrated Summary of Effectiveness” available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf>.*

**Additional Comment:** *For the controlled efficacy trials, please include in your NDA submission: a) all raw as well as derived variables in .xpt format; b) SAS programs that produced all efficacy results; c) SAS programs by which the derived variables were produced from the raw variables; d) a list of INDs, serial submission numbers, submission dates of all protocols, amendments, SAPs, and related meetings; and e) results of exploratory subgroup analysis by country/region, for international studies.*

### **Discussion at Meeting:**

**Statistics comments:** *We agree with the sponsor's proposal to provide the SAS codes for selected efficacy endpoints in the three efficacy studies.*

**Clinical comments:** *The proposals for the ISS safety populations, groupings, and subgroup analyses are acceptable. There will be two main pooled safety populations: 1) pooled controlled trials in patients with agitation and Schizophrenia or Bipolar Disorder; and 2) pooled studies in healthy volunteers. Subjects with compromised lung*

function (asthma and COPD) will each be examined as separate populations within the ISS, based on individual safety data.

## Nonclinical Questions

### Question 11

Does the Agency agree that the organization and content of the proposed nonclinical section of the NDA is adequate to support the NDA for *Staccato* Loxapine?

**Preliminary Comments:** *Based on the provided Table of Contents (page 75), the proposed organization appears to be adequate for NDA filing. We have asked that you conduct gene mutation assays with Loxapine aerosol condensate if possible (End of Phase II meeting minutes 2007); you agreed. To date you have tested Loxapine free base alone, (b) (4) alone, and the metabolite 8-OH-Loxapine alone in gene mutation assays; please provide an explanation as to why you have not tested the condensate.*

**Discussion at Meeting:** *The sponsor provided an adequate explanation as to why (b) (4) alone, and not the aerosol condensate, was tested in the gene mutation assays. The sponsor stated that obtaining an adequate amount of condensate was a technical barrier to its utilization. The sponsor stated that the only impurity detected at levels above 0.1% in the aerosol condensate was the compound (b) (4). The sponsor stated that they have identified several of the impurities at levels below 0.1%. None of these impurities have structural alerts for genotoxicity following Derek analysis. As a result the sponsor chose to test (b) (4) alone instead of spiking it into loxapine freebase. The sponsor stated that they will provide impurity data for the aerosol condensate. If no impurities other than (b) (4) are above 0.1 % then the current genetic toxicity battery is adequate.*

## Quality Questions

### Question 12

Does the Agency agree with the proposed stage groupings for controlling particle size distribution in the drug product specification?

**Preliminary Comments:** *It is premature to provide an agreement on stage groupings for control of aerodynamic particle size distribution (APSD) prior to full review of the NDA.*

(b) (4)  
*This information may influence our evaluation of the stage groupings.*

**Discussion at Meeting:** (b) (4)

(b) (4). We recommended that the sponsor continue to collect data and propose their stage groupings (with justification) in the NDA. (b) (4)

### Question 13

Does the Agency agree with the approach to correlate and include the data obtained from both cascade impactor methods in the determination of particle size distribution specifications?

**Preliminary Comments:** We do not agree. Proposed APSD acceptance criteria and specifications for the commercial drug product should be based on representative data from the (b) (4) alone, in view of the differences between the (b) (4) and the (b) (4).

**Discussion at Meeting:** The sponsor agreed to use only data from (b) (4) for the proposed acceptance criteria for commercial drug product and indicated they will use (b) (4) data as part of supportive stability studies.

### Question 14

Does the Agency agree that, in addition to 24 months supportive stability data, inclusion of 6 months accelerated and real time registration stability data in the initial NDA submission and the commitment to provide 12 month real time stability data during the review period will adequately support establishment of an initial 24 month expiration date?

**Preliminary Comments:** Your ultimate expiry will be determined as part of the NDA review based on the quality and quantity of your stability data. We recommend submitting an NDA amendment that will include an additional 6 months of long-term data by midway through the review cycle which will allow sufficient time for the review.

**Discussion at Meeting:** The sponsor agreed to submit the additional data “by midway through the review cycle” and stated that the target submission date for the 12 month data is May 2010.

### Question 15

Does the Agency agree that the organization and content of the proposed quality section of the NDA is adequate to support the NDA for *Staccato* Loxapine?

Specifically does the Agency agree with:

- (i) referencing drug substance information to the (b) (4) DMF Letter of Authorization in Module 1?
- (ii) presenting information on the control of device components in individual files in Section 3.2.P.7 Container Closure System?

**Preliminary Comments:** *Yes, your plan seems reasonable for referencing drug substance information to the (b) (4) DMF Letter of Authorization in Module 1 and presenting information on the control of device components in individual files in Section 3.2.P.7 Container Closure System. Include drug substance manufacturing site information, batch analysis of clinical batches, and analytical methods with validation used to test incoming drug substance batches.*

**Discussion at Meeting:** *The sponsor agreed to include the drug substance manufacturing site information, batch analysis of clinical batches, and analytical methods with validation used to test incoming drug substance batches.*

### Question 16

The Sponsor is considering filing a separate Drug Master File (DMF) for the Drug Product concurrent with the NDA. In this case, does the Agency concur with the approach of cross-referencing Modules 2.3.P and 3.2.P to the DMF submission?

**Preliminary Comments:** *Our recommendation would be to submit the drug product information directly in the NDA.*

**Discussion at Meeting:** *The sponsor agreed to submit drug product information directly in the NDA.*

### **Additional Comments:**

#### **Center for Devices and Radiological Health (CDRH):**

*In your upcoming NDA, please include the test reports for mechanical safety, electrical safety or electromagnetic compatibility. Because the changes implemented in the updated design of your device include (b) (4)*

*, this testing is necessary in order to demonstrate the safety of your device. It is recommended that this testing be performed in accordance with IEC 60601-1: Medical Electrical Equipment General*

*Requirements for Safety and with IEC 60601-1-2: Electromagnetic Compatibility Requirements and Tests.*

*Please clarify that the genotoxicity tests discussed in the internal meeting included consideration of impurities generated by leachable device components, [REDACTED] (b) (4) [REDACTED]. As discussed, please specifically indicate which recorded impurities were generated by the materials used in the construction of the delivery device.*

*In addition, please record any specific device modifications made during clinical development. Your SAS transport files for clinical data should include a column that indicates the model of the device being studied for each patient.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Alexza Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, RPh, MS  
Senior Regulatory Project Manager

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 73248

-----  
ALEXZA  
PHARMACEUTICALS  
INC

-----  
STACCATO (LOXAPINE)INHALATION

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
07/22/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

IND 73,248

Alexza Pharmaceuticals  
Attention: Christine Welch, M.S.  
2091 Stierlin Court  
Mountain View, CA 94043

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Staccato® Loxapine for Inhalation.

We also refer to the meeting between representatives of your firm and the FDA on December 3, 2008. The purpose of the meeting was to discuss the design updates to the Staccato Loxapine product, to summarize the data package, and to discuss the studies proposed to support product registration.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager at (301)796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

## MEMORANDUM OF MEETING

IND 73,248; Staccato® Loxapine for Inhalation  
Alexza Pharmaceuticals  
Type C meeting (CMC meeting)  
December 3, 2008

The objective of this meeting was to discuss the design updates to the *Staccato* Loxapine product, to summarize the data package that demonstrates the comparability of the updated and current versions of the device, and to obtain agreement on the proposed studies using the updated version of the device to support product registration.

### Participants –

#### **FDA**

Thomas Laughren, MD	Division of Psychiatry Products Director
Mitchell Mathis, MD	Deputy Director
Robert Levin, MD	Medical Team Leader
Frank Becker, MD	Medical Reviewer
Aisar Atrakchi, PhD	Pharmacology/Toxicology Team Leader
Darren Fegley, PhD	Pharmacology/Toxicology Reviewer
Imran Khan, PhD	Pharmacology/Toxicology Reviewer (observer)
Tom Oliver, PhD	Pharmaceutical Assessment Lead
Chhagan Tele, PhD	Chemistry, Manufacturing, Controls Reviewer
Raman Baweja, PhD	Clinical Pharmacology Team Leader
Andre Jackson, PhD	Clinical Pharmacology/Biopharmaceutics Reviewer
Kimberly Updegraff, MS	Regulatory Project Manager

#### **Sponsor**

James Cassella, PhD	Sr. Vice President, Research and Development
Robert Fishman, MD	Vice President, Clinical Development

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

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

Carlos Parra	Vice President, Quality
Daniel Myers, PhD	Director, Product R&D
Edwin Kamemoto, PhD	Senior Director, Regulatory Affairs
Christine Welch, MS	Director, Regulatory Affairs

#### **Background:**

Staccato® Loxapine for Inhalation (*Staccato* Loxapine) is under development for the treatment of acute agitation associated with schizophrenia and bipolar disorder. Staccato Loxapine is a hand-held drug-device product for rapid systemic delivery by inhalation of a thermally-generated aerosol of loxapine (an antipsychotic drug). Oral inhalation through the device initiates the controlled rapid heating of a thin film of excipient-free

loxapine to form a highly pure drug vapor. The vapor condenses into aerosol particles with an appropriate particle size distribution for efficient delivery to the deep lung. The rapid absorption of the drug provides peak plasma levels in the systemic circulation within minutes after treatment administration.

During the clinical development program and manufacturing scale-up activities, the sponsor has made several changes to the current *Staccato* Loxapine product, (b) (4)

The main features of the device are the heat package, airway, and breath sensor. A thin film of loxapine is coated on the heat package at a dose of 5 mg (single-sided coating) or 10 mg (2-sided coating). The sponsor states that the fundamental operating principles of the current and updated versions of the device are the same, with comparable performance (aerosol) attributes and user interface characteristics (including the inhalation effort to use the device).

At the End-of-Phase 2 Meeting with the Division (September 13, 2007), Alexza obtained the Division's concurrence on the general aspects of the proposed CMC, nonclinical, and clinical development plans to support registration of the current *Staccato* Loxapine product. The trials completed to date, all with the original device formulation, include: 1) a single-dose pharmacokinetic study in healthy volunteers (AMDC-004-101), 2) a multiple-dose PK study in non-agitated subjects with schizophrenia treated on stable antipsychotic regimens (AMDC-004-102), 3) a Phase 2A study in schizophrenic subjects with acute agitation (AMDC-004-201), and 4) a Phase 3 study in schizophrenic subjects with acute agitation (AMDC-004-301). A Phase 3 study in subjects with bipolar disorder has completed enrollment (AMDC-004-302).

The sponsor states that *Staccato* Loxapine demonstrated efficacy in the Phase 3 study in schizophrenic subjects with acute agitation (AMDC-004-301). The primary endpoint was the change from baseline in the Positive and Negative Symptom Scale-Excited Component (PANSS-PEC) score measured 2 hours after the first dose of *Staccato* Loxapine. Reportedly, the 5 mg and 10 mg doses demonstrated statistically significant efficacy, compared to placebo.

Since the clinical studies conducted to date employed the original version of the device, a clinical bioequivalence study was conducted to demonstrate the bioequivalence of the updated version of *Staccato* Loxapine with the original version. The study was a single-center, randomized, open-label, 4-period, 2-treatment, dose-stratified, replicate crossover pharmacokinetic study of *Staccato* Loxapine in healthy volunteers (conducted in Australia). The sponsor states that bioequivalence was established as measured by the primary PK parameter,  $AUC_{inf}$ . The sponsor states that  $C_{max}$  was designated as the secondary PK parameter. It appears that  $C_{max}$  was not bioequivalent between the two versions of the device.

The sponsor's objectives of this meeting are to discuss the design updates to the *Staccato* Loxapine product, to summarize the data package that demonstrates the comparability of the updated and current versions of the device, and to obtain agreement on the proposed studies using the updated version of the device to support product registration.

**Questions:**

**Question 1**

Does the Division agree that the proposed pharmaceutical development studies to be conducted on the updated version of the device and the registration stability program are adequate to support registration of the updated *Staccato* Loxapine product?

**Preliminary Comments:**

**A. Clinical Comments**

One of the critical issues to discuss is whether or not you have demonstrated bioequivalence between the original and new devices. In addition, we will need to consider the safety findings and user experience to date, in order to decide on whether additional studies would be required.

We note that you plan to conduct 3 studies using the updated device: 1) a thorough QT study in healthy volunteers; 2) a pulmonary safety study (in subjects with asthma or COPD); and (3) a PK study in smokers and non-smokers.

**Discussion at Meeting:** *We noted that, on face, the proposed studies appear adequate. However, as noted, it will be critical to establish bioequivalence between the original and the updated device (see discussion, under question 2B).*

**B. CMC Comments**

Yes, your approach seems reasonable. However, we have the following comments about the updated version of your device:

(b) (4)  
[Redacted]  
We recommend that you continue to evaluate failed devices (FMEA), determine causality, and incorporate corrective actions to your device. All of this information should be included as part of your upcoming NDA. New materials should be evaluated for the possible introduction of new impurities (b) (4) into the emitted aerosol.

**Discussion at Meeting:** The sponsor agreed to evaluate failed devices (updated), delineate causes of failure and corrective actions taken.

(b) (4)  
[Redacted]  
We request that you provide data on the battery life as a function of the drug product shelf life. Assignment of the product expiry will take into account battery functionality.

Please provide data evaluating [REDACTED] (b) (4) as a function of time and temperature in the updated Staccato Loxapine device.

**Discussion at Meeting:** The sponsor agreed to provide data on the battery life and data evaluating [REDACTED] (b) (4) as a function of time and temperature in the updated device.

[REDACTED] (b) (4)

**Discussion at Meeting:** The sponsor agreed to provide information requested above.

[REDACTED] (b) (4)

**Discussion at Meeting:** The sponsor agreed to provide information requested above.

**Additional CMC Comments:**

1. We refer you to our previous CMC comments during the EOP2 meeting to support your registration of the updated *Staccato* Loxapine product.

**Discussion at Meeting:** No further discussion.

2. Regarding your registration stability program, we refer you to ICH guidance Q1A(R2). We recommend that you provide stability data on at least three primary batches of each strength manufactured using different batches of the drug substance. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified.

**Discussion at Meeting:** The sponsor agreed to provide stability data for three batches each of the 5 mg and 10 mg strengths manufactured using two drug substance batches.

- Information about any (b) (4) should be included in your NDA submission (along with a justification for the use of any (b) (4)).

**Discussion at Meeting:** The sponsor agreed to provide information about any (b) (4) used in the manufacture of the drug product.

- Indicate any material or manufacturing differences between the 5 mg strength (one sided coating) and the 10 mg strength (two sided coating). In addition, provide comparative data evaluating the physical and chemical properties of the aerosols from the two dosage strengths.

**Discussion at Meeting:** The sponsor agreed to provide information about any material or manufacturing differences between the 5 mg strength (one sided coating) and the 10 mg strength (two sided coating) including comparative data evaluating the physical and chemical properties of the aerosols from the two dosage strengths.

- You have stated that you will test for foreign particulates in your updated device. It is recommended that your study include a variety of aged devices (new and stored devices) to determine if the presence of foreign particulates increases over time. You will need to provide data from this study and a rationale for not including this test as part of your stability program. The acceptability of not including foreign particulate testing in your stability program will be a review decision.

**Discussion at Meeting:** The sponsor 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.

(b) (4)

## **Question 2**

Does the Division agree that the completed *in vitro* comparability testing and clinical bioequivalence study support the switch from the current to the updated version of the device in the ongoing clinical development program for registration of the updated *Staccato* Loxapine product?

### **Preliminary Comments:**

#### **A. Center for Devices and Radiological Health Comments**

The comparability assessment of aerosol particle size distribution adequately indicates that the updated and current device are substantially equivalent in terms of aerosol

particle size distributions and supports the conclusion that there was no significant impact on particle size distribution as a result of the changes incorporated in the updated device. Assessment of additional user interface parameters (the inspiratory resistance of the device and the performance of the breath actuation mechanism) demonstrate the comparability between the two versions of the device.

Additional Comments:

1. Your submission does not include the test reports for mechanical safety, electrical safety or electromagnetic compatibility. (b) (4)  
[REDACTED]  
[REDACTED] this testing is necessary in order to demonstrate the safety of your device. It is recommended that this testing be performed in accordance with IEC 60601-1: Medical Electrical Equipment General Requirements for Safety and with IEC 60601-1-2: Electromagnetic Compatibility Requirements and Tests. If the device was tested by another method, or if the recommended information is omitted, please explain why the method used is acceptable, or how the device can be found substantially equivalent without the omitted information. Please provide complete test reports supporting conformance to the standards specified above, including protocols, acceptance criteria, results and conclusions. Alternatively, you may simply choose to fill out the Standards Data Report for 510(k)s Form for IEC 60601-1 and IEC 60601-1-2. This form is available at <http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3654.pdf>. As instructed in the above form, please clearly indicate which clauses of the standard were satisfied, and whether any deviations were made from the recommended testing protocols, procedures or acceptance criteria in the standard.
2. Please clarify whether the subject device is intended for use in both home and healthcare settings, and whether the device is intended for transport use. If your device is intended for out-of-hospital transport use, please be aware that additional testing is required in order to support this indication. These tests include radiated electromagnetic immunity tests according to IEC 60601-1-2 with the 3 V/m level replaced by 20 V/m, and sinusoidal vibration, random vibration and bump tests in accordance with IEC 60068-2. If your device is not intended for transport use, please include this information in both the package labeling and the Information Manual. Additionally, if the device is intended for use in both home and healthcare settings, please provided draft labeling demonstrating how specific instructions (i.e. cleaning and disposal instructions) may differ based on the user and the environment of use.
3. In your submission, you have noted that the generation of degradants as a result of aerosolization by the subject device has been identified as a significant potential risk. In addition, you have provided a table demonstrating that minimal levels of total impurities were observed in both the updated and current designs of the device. Please provide a complete test report, including protocols, acceptance criteria, results and conclusions, demonstrating how these data were generated, and how the given conclusions are made. You may refer to *ASTM D5466-01: Standard Test Method for*

*Determination of Volatile Organic Chemicals in Atmospheres* for appropriate test methods in this regard.

**Discussion at Meeting:** The sponsor will submit questions separately for review by the Center for Devices and Radiological Health.

**B. Office of Clinical Pharmacology Comments**

We would like to discuss with you the bioequivalence data from Study AMDC-004-103. Currently, we find it difficult to interpret the data, for the following reasons: 1) the replicate statistical model was not presented in detail; 2) the pharmacokinetic data were pooled for the 5 mg and 10 mg doses; and 3) the range for the Tmax values are quite different for the original and updated devices. Please refer to the table below.

	Current 5 mg	Updated 5 mg	Current 10 mg	Updated 10 mg
Tmax fold range, min	(b) (4)			
Ratio( upper limit/lower limit)				

On page 50 of 53 you have stated: “As detailed in Table 14 and based on the results of the bioequivalence study and the in vitro comparability data, Alexza plans to use the updated version of Staccato Loxapine in the ongoing program of clinical safety studies.” However, it is not clear that you have established bioequivalence between the original and the new device. Therefore, the proposed clinical studies should not be conducted with the new device until all issues related to bioequivalence have been resolved.

Additional Comments:

1. The PEC score versus time curve appears to show no clear dose-response relationship. Although there appears to be a considerable degree of overlap for the SEM values, you have stated that the differences are significant.
2. Please discuss the rationale for designating Cmax as a secondary bioequivalence parameter for a device that is intended to provide a rapid onset of drug activity.
3. We would like to discuss with you in more detail the proposed PK/PD model of sedation. It is difficult to interpret the data for the new device, since it appears to be based on simulation from sedation data. The simulated data were compared with actual Stanford Sleepiness Scale score data obtained in Study AMDC-004-101. Furthermore, you have applied 90% CI to the mean Smax comparisons, which assumes that the data are log-normally distributed. You have not presented data to establish that the scale data for the Stanford Sleepiness Scale is log-normally distributed. We would like to discuss the choice of the Stanford Sleepiness Scale as a clinical endpoint for assessing drug exposure.

**Discussion at Meeting:**

The Division inquired about the reason for pooling of data for the 5 mg and 10 mg doses. The sponsor explained that the analysis was not designed to compare doses, but rather to make within-subject comparisons between devices.

There was considerable discussion about the results of analyses for C<sub>max</sub> and T<sub>max</sub> for the two versions of the device. The Division commented on the wide range of T<sub>max</sub> values. (b) (4)

The Division commented that the range for T<sub>max</sub> for the current device still appears to be significantly different from that for the updated device. The sponsor explained that with administration through inhalation (with rapid drug absorption at 0.5 to 10 minutes), it is difficult to measure T<sub>max</sub> and C<sub>max</sub> (as is the case with i.v. boluses). The sponsor further explained that this difficulty resulted in the decision to designate C<sub>max</sub> as a secondary, as opposed to the primary, pharmacokinetic measure of interest. However, the Division pointed out that there are still potentially significant differences between PK results for the versions of the device. The median values appear to be similar, whereas the mean exposure values between devices are different. The Division inquired whether the sponsor could provide an explanation for these differences. The sponsor responded that there is currently no clear explanation. We noted that, if the C<sub>max</sub> is higher for the new product, then bioequivalence has not been established between these two versions of the device, and the new version might be considered a new product. The Division also noted that the C<sub>max</sub> values for the 5 mg dose between devices appear to be relatively similar; but the C<sub>max</sub> values for the 10 mg dose between devices appear to have greater differences.

Dr. Laughren suggested analyzing the data for AUC(0-2 hours), since the primary clinical endpoint would be assessed 2 hours after administration. There was agreement that this would be a useful approach to consider. The Division stated that the plan would be to review the relevant data, in order to decide whether this could be a valid primary analysis of the pharmacokinetic data. Thus, the Division requested that the sponsor provide data and analyses for the 2-hour pharmacokinetic data, with separate analyses for the 5 mg and 10 mg dose (for descriptive analysis). The analysis of the pooled dose data at 2 hours might be used in a statistical analysis. The Division also requested that the sponsor provide plots of concentration over time for individual subjects. The sponsor also agreed to submit all raw plasma data (i.e., 5 mg and 10 mg doses) and derived parameters (i.e., C<sub>max</sub> and AUC) as a SAS transfer file.

The Division suggested that the sponsor analyze and provide clinical adverse events and vital signs data from the bioequivalence data, in order to determine whether the patterns of safety finding might be different between different versions of the devices. The sponsor has performed such an analysis, and there did not appear to be any notable differences. In addition, the sponsor agreed to provide these data.

**Post-Meeting Note to Sponsor:**

- Please submit all raw data and derived parameters, i.e., C<sub>max</sub> and AUC, as a SAS transfer file.
- Please conduct the analysis as two single replicated studies, one for the 5 mg dose and a separate one for the 10 mg dose.

-Please include AUC (0-2 hrs) as a parameter for evaluation.

### **Question 3**

Does the Division agree that the planned patient exposure and user experience with the updated version of the device are adequate to support product registration of the updated *Staccato* Loxapine product?

#### **Preliminary Comments:**

We will need to discuss this with you further in the context of the overall clinical program and specific studies that will be required. As noted in the response to Question 1, issues to consider include:

- 1) whether you have established bioequivalence between the original and new devices;
- 2) a review of the safety data collected to date; and 3) an assessment of the user experience to date and specific patient use assessments that might be required.

#### **Discussion at Meeting:**

The sponsor asked, assuming that bioequivalence between the two versions of the device can be established, if the Division generally agrees with the proposed clinical program. We stated that, on face, the plan appears to be reasonable. The sponsor plans to submit protocols for the remaining safety studies to be conducted using the updated device.

#### **Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Alexza Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, RPh, MS  
Regulatory Project Manager

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 73248

-----  
ALEXZA  
PHARMACEUTICALS  
INC

-----  
STACCATO (LOXAPINE)INHALATION

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
12/19/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 73,248

Alexza Pharmaceuticals, Inc.  
Attention: Edwin Kamemoto  
1020 East Meadow Circle  
Palo Alto, CA 94303

Dear Dr. Kamemoto:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for *Staccato*® Loxapine for Inhalation.

We also refer to the meeting between representatives of your firm and the FDA on September 13, 2007. The purpose of the meeting was to discuss the clinical, nonclinical, and CMC plans to support a New Drug Application (NDA) for *Staccato* Loxapine.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Kimberly Updegraff, Regulatory Project Manager, at (301) 796-2201.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure

**MEMORANDUM OF MEETING**

IND 73,248 Loxapine for Inhalation

Alexza Pharmaceuticals

EOPII / Type B

September 13, 2007

Participants –

**FDA**

Thomas Laughren, MD	Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, MD	Deputy Director
Ni Aye Khin, MD	Medical Team Leader
Michelle Chuen, MD	Medical Reviewer, DPP
Peiling Yang, PhD	Statistics Team Leader
Barry Rosloff, PhD	Pharmacology/Toxicology Supervisor
Aisar Atrakchi, PhD	Pharmacology/Toxicology Reviewer
Thomas Oliver, PhD	Pharmaceutical Assessment Lead
Chhagan Tele, PhD	Chemistry Reviewer
Michael Husband	Biomedical Engineer Reviewer, CDRH (Center for Devices and Radiological Health)
Anthony Durmowicz, MD	Medical Reviewer, DPAP (Division of Pulmonology and Allergy Products)
Kimberly Updegraff, MS	Regulatory Project Manager

**Sponsor**

James Cassella, PhD	Sr. Vice President, Research and Development
Daniel Spyker, PhD, MD (b) (4)	Sr. Director, Drug Safety & Pharmacovigilance (b) (4)
Chiao-Wen Chen, PhD	Sr. Scientist, Toxicology
Barbara Stewart, PhD	Director of Toxicology
Marc Glazer, PhD	Technical Leader
Dan Myers, PhD	Associate Director, Product R&D
Joseph Baker	Vice President, Manufacturing and Global Supply Chain
Ed Kamemoto, PhD (b) (4)	Director, Regulatory Affairs (b) (4)

**Background:**

*Staccato* Loxapine is a hand-held drug product for rapid systemic delivery of loxapine via inhalation of a thermally-generated aerosol. Alexza submitted an IND for *Staccato* Loxapine on 8-31-05. The Phase I (AMDC-004-101, involving single doses up to 10 mg) and Phase 2 (AMDC-004-201, involving single doses of 5 and 10 mg in agitated schizophrenic patients) clinical studies were completed in November, 2005 and March, 2007. Another Phase 1 study (AMDC-004-102), a multiple-dose tolerability and PK study in non-agitated schizophrenic patients, will be completed before Phase 3 is initiated. Alexza is developing *Staccato* Loxapine for inhalation for the acute treatment

of agitation. [REDACTED] (b) (4)

The agitation program will focus on 2 psychiatric populations, i.e., schizophrenia and mania of bipolar disease. The sponsor plans a program similar to that utilized for the development of injectable olanzapine for agitation. Thus, they plan two acute studies to assess the effects of *Staccato* Loxapine at doses of 5 and 10 mg (vs placebo) in each of schizophrenia and mania. These will be randomized, double-blind, placebo-controlled fixed-dose studies (5 and 10 mg) in patients with acute agitation (1 study in schizophrenia [AMDC-004-301] and 1 study in mania [AMDC-004-302]). [REDACTED] (b) (4)

Each study will enroll about 300 patients (i.e., about 100 patients per group). The primary outcome will be the excited component of the PANSS (i.e, PEC), change from baseline to 2 hours for the first dose.

The sponsor is also planning on conducting a thorough QT study [AMDC-004-103]. In addition, they will conduct a study in asthmatics [AMDC-004-104]. They expect to accumulate exposures to *Staccato* Loxapine in approximately 600 patients.

### **Questions:**

#### **CLINICAL QUESTIONS**

1. Does FDA agree that the two pivotal Phase 3 studies, as described in Section 2.4, will support approval for the proposed indication assuming the primary endpoint is met and the secondary endpoints support safety and activity of *Staccato* Loxapine?

***Preliminary Comments:*** *On face, the proposed studies are acceptable. We will likely have additional comments once the full protocols are submitted. We strongly recommend that you limit enrollment in the schizophrenia study to patients with schizophrenia. In any case, we will focus only on patients with this diagnosis.*

*Since the primary objective is to compare overall treatment effects between treatment arms, we recommend that you exclude the treatment center interaction from the primary statistical model. You can explore the interaction in a secondary analysis.*

*Regarding the secondary endpoints, if the goal is ultimately to describe the results on one of these measures in labeling, you will need to pre-specify a key secondary endpoint and a multiple testing procedure that properly controls the familywise type 1 error rate in the setting of multiple doses in combination with multiple endpoints. The results would need to be replicated in a second study. We recommend that you select change from baseline in either CGI-S or BARS at 2 hours, but not both, as a key secondary endpoint.*

**Discussion at Meeting:** *The sponsor stated that they will select one of the key secondary endpoints recommended above for the agitation study for schizophrenia and asked if they propose the same key secondary for the replication study with agitated bipolar patients, would such proposal meet the second study requirement for the possible labeling claim. We responded that their proposal would be acceptable.*

2. Does FDA agree with the primary endpoint of statistically significant superiority on PANSS-EC at 2 hours when *Staccato* Loxapine is compared to *Staccato* Placebo?

**Preliminary Comments:** *The primary endpoint of statistically significant superiority on “mean change from baseline on PANSS-EC at 2 hours” when *Staccato* Loxapine is compared to *Staccato* Placebo is acceptable.*

**Discussion at Meeting:** *No further discussion.*

3. We anticipate having a safety database of > 600 subjects who received at least one dose of *Staccato* Loxapine and > 900 subjects who used *Staccato* Placebo or *Staccato* Loxapine. The safety profile of loxapine has been well characterized since its original marketing approval in 1975. Given that acute agitation in schizophrenia or manic phase bipolar disease is an intermittent condition, *Staccato* Loxapine would not be labeled for chronic use. Does FDA agree that the size of the safety database proposed for *Staccato* Loxapine would be adequate to support this NDA?

**Preliminary Comments:** *Yes, generally this proposal would be acceptable for Loxapine exposure. However, you have not provided information on the extent of your pulmonary safety database. Without this information, we cannot make a definitive judgment on the adequacy of your safety database to support a NDA. Please specify your proposed pulmonary safety database including the number of subjects with pulmonary function test data following single and multiple doses of *Staccato* Loxapine.*

**Discussion at Meeting:** *See “Discussion at Meeting” under question #4.*

4. Does FDA agree that the studies listed in Section 2.5 for the assessment of safety and efficacy of *Staccato* Loxapine are sufficient to support this NDA?

**Preliminary Comments:** *From a pulmonology standpoint, we do not agree. The evaluation for the potential for *Staccato* Loxapine to cause acute bronchospasm is inadequate. Subjects who receive *Staccato* Loxapine should have pulmonary function monitoring serially after treatment beginning 10-15 minutes post-dose.*

*This comment was conveyed in a February 8, 2006, IND letter; however, Study AMDC-004-101 did not include early spirometry assessments. Your pulmonary safety database should adequately characterize the change in pulmonary function (spirometry) following administration of Staccato Loxapine. In addition, if Staccato Loxapine has the potential for multiple dose administration, we recommend your pulmonary safety database address this potential (e.g. characterize the change in pulmonary function following each dose). Because of the potential difficulties of obtaining this information in your planned phase 3 studies with agitated patients, you may assess the change in pulmonary function in healthy subjects, for example, 25 subjects in each treatment arm. However, you should plan to carefully document any respiratory adverse events in your phase 3 studies.*

*The protocol for study AMDC-004-104 for evaluation of Staccato Loxapine in patients with pulmonary disease (asthma, COPD) should also include serial pulmonary function testing to evaluate for acute bronchospasm. We recommend you submit this protocol for comments prior to conducting the study.*

(b) (4)

*The pharmacokinetics of Staccato Loxapine should be evaluated in subjects who smoke cigarettes.*

*Include an outlier analysis (e.g. patients with >10, >15, > 20 decline FEV1) in the study report for each study in which you obtain pulmonary function tests. Correlate any reported respiratory system related SAEs with pulmonary function tests.*

*The above recommendations for pulmonary safety data are based upon the limited information available at this time. If a pulmonary safety signal is noted, additional safety data may be requested.*

*We will likely want a risk management plan for Staccato Loxapine, including pulmonary safety.*

***Discussion at Meeting:*** *The sponsor agreed that they would conduct a study to evaluate the pulmonary functions following a single dose Staccato Loxapine treatment in normal volunteers. As they intend to study the potential use of Staccato Loxapine up to a maximum of 3 doses/24 hrs in the planned phase 3 studies with agitated schizophrenia/bipolar patients, they acknowledged that they would also have the pulmonary function monitoring serially for multiple dose administration. However, they are concerned about tolerability issues in normal volunteers following multiple dose of Staccato Loxapine. We will provide feedback on this topic after we receive consultative input from the Division of Pulmonology and Allergy Products (see post-meeting note).*

*The sponsor stated that they plan to study whether Staccato Loxapine causes acute bronchospasm. In addition, subjects with pulmonary disease and PK in subjects who smoke will also be evaluated. An outlier analysis of spirometry data will also be conducted for the planned studies. DPAP recommended the sponsor submit the protocols for comments prior to conducting the studies.*

## NONCLINICAL QUESTION

1. Does FDA agree that the nonclinical program, including the use of existing data, safety pharmacology, inhalation toxicity studies, and additional genotoxicity evaluation, is sufficient to support this NDA?

### **See Section 3.4 Nonclinical Development Plan in Support of a NDA**

***Preliminary Comments:*** *The bacterial gene mutation assay performed with loxapine did not include S. typhimurium strain TA102 or E.coli WP2 uvrA or E.coli WP2 uvrA(pKM101). Therefore, the bacterial gene mutation assay should be repeated to include one of the above strains as recommended in the ICH S2A (1996) guidance. This is in addition to the proposal by the sponsor to conduct the in vitro chromosomal aberration test in order to complete the genetic toxicology battery for loxapine. If possible, these tests should be conducted using loxapine condensate.*

*The existing nonclinical information on general toxicity and reprotoxicity will be adequate unless new or significantly increased amounts of loxapine metabolites are formed in humans which are not seen with oral dosing; in this case some animal testing of such metabolites might be necessary.*

***Discussion at Meeting:*** *The sponsor agreed to conduct a bacterial gene mutation assay with the appropriate strains as recommended in the ICH S2A guidance and to conduct the in vitro chromosomal aberration assay that will complete the genetic toxicity battery. The sponsor also stated that they will test either loxapine condensate or aerosol as appropriate, in these two assays since these are more representative of the clinical formulation than testing loxapine alone. The sponsor added that no new human metabolites have been identified and no marked quantitative differences in the formed metabolites have been measured after inhalation of Staccato loxapine relative to those observed in the nonclinical studies following oral and other routes of administration. Therefore, previously conducted general toxicity and reprotoxicity studies should be adequate to assess the potential drug toxicity on these parameters.*

## CHEMISTRY, MANUFACTURING, AND CONTROLS QUESTIONS

1. Does FDA agree that the proposed approach for characterization and control of the heat package is adequate to demonstrate heat package seal integrity during product use over the proposed shelf-life of the product?

See Section 4.3.2.2.3 Heat Package Integrity (b) (4)

**Preliminary Comments:** *Yes, your approach seems reasonable. Based upon the data generated, additional release testing may be needed. We recommend continuing the heat package seal integrity test as an in-process control during manufacturing. In addition, your NDA should include a description for the control of housing temperature (from batch to batch) and information about changes in the housing temperature as a function of device storage.*

**Discussion at Meeting:** *The sponsor asked for clarification about the housing temperature information. The sponsor was requested to provide data of device housing temperature from batch to batch at release and as a function of storage. The sponsor agreed to provide information in the NDA.*

2. Does FDA agree that the proposed approach for characterization and control of extractables of individual components and volatile extractables in the aerosol (leachables) is adequate to support this NDA?

See Section 4.3.2.2.4 Extractables and Leachables

**Preliminary Comments:** *Yes, your approach seems reasonable. The acceptability of the results from the various studies outlined will be reviewed upon NDA submission for characterization and control of extractables of individual components and volatile extractables in the aerosol (leachables). In addition, we request you to submit a list of potential extractables/leachables. The generated data and the analytical methods utilized should also be submitted as part of the NDA along with a discussion of how the testing of the chosen device components is representative of the commercial product.*

**Discussion at Meeting:** *The sponsor was asked to provide a safety assessment of the potential extractables/leachables. The sponsor agreed to provide the information in the NDA.*

3. Does FDA agree that the completed and proposed development studies on morphology, uniformity, and mechanical stability of the coated drug film are adequate to support this NDA?

See Section 4.3.2.3.3 Evaluation of the Coated Drug Film

**Preliminary Comments:** *Your NDA submission should include data to support your statement 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 acceptability of the data will be reviewed upon NDA submission.

***Discussion at Meeting:*** The sponsor was asked to provide information about (b) (4) the drug substance in the emitted aerosol. The sponsor agreed to provide the information in the NDA.

4. Does FDA agree that the proposed characterization program is adequate to characterize the product performance for its intended use?

**See Section 4.3.2.4 Product Characterization Studies**

***Preliminary Comments:*** Yes, it appears adequate at this time. In addition, you will need to include the procedure for disposing of the device after use.

***Discussion at Meeting:*** No further discussion.

5. Does FDA agree that the proposed approach is adequate to support switching from the (b) (4) method to measure particle size distribution?

**See Section 4.3.4.2 Justification for Test Parameters, Test Methods, and Acceptance Criteria**

***Preliminary Comments:*** The Agency agrees that the proposed approach is adequate to support switching from the (b) (4) method to measure particle size distribution. You should generate “comparative data” from multiple batches using both the (b) (4). When sufficient data are available, specifications for APSD may be based upon a number of stage groupings to maintain the profile, as appropriate. There should be a specification for mass balance.

***Discussion at Meeting:*** No further discussion.

6. Does FDA agree that the test attributes and test methods listed in the drug product specification are sufficient to control for the drug product? Do you agree with our approach to setting acceptance criteria for the commercial product?

**See Section 4.3.4.2 Justification for Test Parameters, Test Methods, and Acceptance Criteria**

***Preliminary Comments:*** Yes. The identification of the foreign particles should be determined and a safety assessment of these particles should be included as part of your submission. The acceptability of the ultimate specification limits will be subject of the NDA review.

***Discussion at Meeting:*** The sponsor asked for clarification on the foreign particles question. We requested the sponsor to provide data of foreign particles

*in the emitted aerosol (including identification and a safety assessment). The sponsor agreed to provide information in NDA.*

7. Does FDA agree that the proposed registration stability study protocol is adequate to support expiry dating period for the commercial product?

**See Section 4.3.6.1 Registration Stability Study Program**

**Preliminary Comments:** *Yes, at this time.*

**Discussion at Meeting:** *No further discussion.*

8. Does FDA agree that the proposed approach to the manufacture of the registration stability batches is acceptable?

**See Section 4.3.6.2 Manufacturing Scale for the Registration Stability Lots**

**Preliminary Comments:** [REDACTED] (b) (4)

*This issue will be discussed further during the meeting.*

**Discussion at Meeting:** *Since there was very little information provided on the [REDACTED] (b) (4), it was difficult to determine whether the batches manufactured for stability would be representative of commercially prepared product.* [REDACTED] (b) (4)

*Additional information will need to be submitted before a response for this question can be given.*

***Additional CMC Comments:***

1. *The NDA should contain information from your clinical studies about the failure, misuse or any other events (such as burns) during the use of the device. In addition, any information learned upon examination of the device, and corrective actions taken in the manufacture of the device should be delineated in the NDA.*
2. *Your choice of starting material(s) will need to be supported.*

**Discussion at Meeting:** *No further discussion of items 1 and 2.*

*In the preparation of the NDA, we recommend that you include a discussion of the critical quality attributes (e.g., particle size) associated with the drug product and its delivery. In addition, what factors affect these quality attributes and how they are controlled should also be included in the discussion.*

***Additional Comments from the Center for Devices and Radiological Health (CDRH):***

***Section 4.3.2.1***

*You mention the device has undergone several device revisions and that these revisions achieved a high level of reliability. CDRH would like to see the test protocols, set up, and acceptance criteria of the performance testing.*

***Section 4.3.2.2***

*CDRH would like to review the Risk Analysis.*

***Section 4.3.2.2.3***

*CDRH would like to see the test protocol, set up, and acceptance criteria for the testing described in the first three bullet points on page 50.*

***Section 4.3.2.3.1***

*Please provide the following for the IEC 60601-1 and IEC 60601-2 standards:*

- a. Please provide a summary of the testing performed.*
- b. Please provide a summary of the requirements that were met.*
- c. Please provide the pass/fail criteria used for each test, if the criteria are not stated in the standard.*
- d. Please provide a description of the performance of the device during each immunity test (i.e. degradation observed).*
- e. Please provide a summary of any deviations or omissions from the standards*

*Please provide complete software documentation in accordance with a minor level of concern consistent with the guidance cited.*

***Discussion at Meeting: The sponsor asked for clarification on the IEC standards. CDRH clarified the standards as IEC 60601-1 and 60601-1-2.***

***Section 4.3.2.3.2***

*CDRH would like to see the test protocol, set up, and acceptance criteria for the testing described.*

***Post-Meeting Notes from the Division of Pulmonology and Allergy Products (DPAP):***

***Question #3: DPAP recommends that the sponsor provide updated information on the extent of the pulmonary database for Staccato Loxapine at the time of the NDA application.***

***Question #4: DPAP recommends performing the multiple dose pulmonary safety study using the 10 mg loxapine dose and, if required due to excessive sedation, to reduce the study to two doses rather than three. One possible design would be to perform spirometry prior to and serially after both the first and***

*second loxapine doses (separated by 6-12 hours) and then again 24 hours after the second dose. We again, recommend you submit this protocol for comments prior to conducting the study.*

**Conclusions:**

Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. Alexza Pharmaceuticals is responsible for notifying us of any significant differences in understanding they have regarding the meeting outcomes.

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Kimberly Updegraff, R.Ph., M.S.  
Regulatory Project Manager

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this page is the manifestation of the electronic signature.**  
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/s/

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Thomas Laughren  
9/22/2007 03:03:38 PM

**MEMORANDUM OF TELECONFERENCE  
MEETING MINUTES**

**Meeting Date:** December 12, 2006  
**Location:** White Oak  
**Application:** (b) (4)  
**Drug:** (b) (4)  
**Type of Meeting:** EoP2 CMC/ CDRH  
**Meeting Chair:** Eric Bastings, MD  
**Meeting Recorder:** Lana Chen, RPh

**FDA Attendees**

Eric Bastings, MD, Neurology Team Leader, Division of Neurology Products (DNP), CDER  
Martha Heimann, PhD, Chemistry PAL, Division of Neurology Products, CDER  
Michael Husband, MD, CDRH  
Lana Chen, RPh, Project Manager, Division of Neurology Products, CDER

**Sponsor Attendees**

James Cassella, Ph.D.	Alexza Pharmaceuticals
William Houghton, M.D.	Alexza Pharmaceuticals
Pravin Soni, Ph.D.	Alexza Pharmaceuticals
Ed Kamemoto, Ph.D.	Alexza Pharmaceuticals
Joseph Baker	Alexza Pharmaceuticals
Peter Noymer, Ph.D.	Alexza Pharmaceuticals
Sandy Mohan, Ph.D.	Alexza Pharmaceuticals
(b) (4)	(b) (4)

**Purpose**

The Sponsor requested this End of Phase 2 CMC/ CDRH meeting to discuss (b) (4)

**Discussion**

- 1. Does the Division agree with Alexza's approach to the heat package design safety margin and controls to assure safety during use?**

**Response**

From a CMC perspective the approach appears reasonable.  
CDRH would like to see test set up, test protocol, and acceptance criteria for design verification tests on page 15 in addition to demonstrated performance after repeated cleaning of the device. CDRH would also like you to address the electrical and EMC safety of the device through IEC 60601-1 and IEC 60601-1-2.

Meeting Discussion

The sponsor indicated that the test set up, test protocol, and acceptance criteria for design verification tests would be provided in the NDA submission. Since this is a single-use device, performance after repeated cleaning is not an issue. Electrical and EMC safety will be addressed in the NDA through the referenced IEC standards.

2. **Does the Division agree with Alexza's approach to characterizing and controlling the heat content of the inhaled aerosol and the housing of the device?**

Response

From a CMC perspective, the approaches to characterizing and controlling heat content of the aerosol and device housing appear reasonable. (b) (4)

The final decision regarding adequacy of heat content controls will be based on clinical review of information obtained in trials using the proposed commercial device, (b) (4)

CDRH agrees with CDER that the approach seems reasonable; (b) (4)

Meeting Discussion

3. **Does the Division agree with Alexza's approach to design control, risk management and change control to support component or manufacturing process changes that result in a finished device** (b) (4)

Response

CMC: As indicated during our previous meeting on August 17, 2005, we agree with the general approach in principal but will need more details prior to agreement on specifics. (b) (4)

CDRH agrees with CDER that the approach seems reasonable.

Meeting Discussion

The sponsor acknowledged the Agency's comments.

**4. Does the Division agree with Alexza's approach to microbial limits acceptance criteria?**

Response

Yes.

Meeting Discussion

There was no discussion at the meeting.

Minutes Preparer: \_\_\_\_\_

Lana Chen, R.Ph.  
DNP Project Manager

Chair Concurrence: \_\_\_\_\_

Eric Bastings, MD  
DNP Neurology Team Leader  
(designated signatory)

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/s/

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Eric Bastings  
1/31/2007 04:36:50 PM

**MEMORANDUM OF TELECONFERENCE  
MEETING MINUTES**

**Meeting Date:** August 17, 2005  
**Location:** WOCII 4th Floor Conference Room  
**Application:** (b) (4)  
**Drug:** (b) (4)  
**Type of Meeting:** EoP2 CMC  
**Meeting Chair:** Martha Heimann, PhD, Acting Chemistry Team Leader,  
Division of Neurology Products  
**Meeting Recorder:** Lana Chen, RPh

**FDA Attendees**

Martha Heimann, PhD, Acting Chemistry Team Leader, Division of Neurology Products  
Alan Schroder, PhD, Chemistry Reviewer, Division of Pulmonary Drug Products  
Richard Lostritto, PhD, Chemistry Team Leader, Division of Pulmonary Drug Products  
Lana Chen, RPh, Project Manager, Division of Neurology Products

**Sponsor Attendees**

**Alexza**

Dr. James Cassella, Sr. VP, Research and Development, Alexza MDC  
Dr. Pravin Soni, Vice President, Product Research and Development, Alexza MDC  
Mr. David Schmidt, Director, Quality Systems, Alexza MDC  
Mr. Ramesh Damani, Sr. Director, Commercial Manufacturing Development, Alexza MDC

(b) (4)

**Purpose**

The Sponsor requested this End of Phase 2 Chemistry meeting to discuss development of

(b) (4)

**Discussion**

- 1. Does the Division agree with our proposed method for measuring aerosol particle size, and the proposed details to be included in the particle size specification (Section 2.1.1)?*

(b) (4)

The following points were also discussed:

- 

(b) (4)

- [REDACTED] (b) (4)
- Information about flow rates typically achieved by patients should be provided. Air flow rates achieved by compromised patients, e.g., patients with asthma, should also be considered.
- Tentative specifications should be established prior to initiation of Phase 3 studies.

**2. *Does the Division agree with our proposed method for emitted aerosol dose measurement, and the proposed specification for emitted dose (Section 2.2.1)?***

The Division indicated that the proposed method for determination of emitted dose content uniformity appears acceptable pending review of the NDA submission. The proposed acceptance criteria are consistent with Agency guidances and should be acceptable.

**3. *Does the Division agree with our proposed method for measuring foreign particles, and the proposed basis for generating specifications for foreign particles (Section 3.1.1)?***

The approach [REDACTED] (b) (4) may be acceptable.

During drug development, however, efforts should be made to identify the materials comprising the foreign particles in the drug. Acceptance criteria for particles should be based upon representative data. Proposed specifications and identities of the foreign particles will be subject to a pharmacology/toxicology assessment, and the Sponsor was asked to provide such a safety assessment as well for proposed specifications.

The Division noted that the EPA air quality standard referenced in the briefing package is not relevant to this product as the patient will be inhaling deeply through the device rather than breathing normally.

**4. *Does the Division agree with our proposed approach to aerosol impurity qualification and identification (Section 4.1.1)?***

The approach is adequate from a CMC perspective but the Sponsor should verify that animal studies performed are appropriate. [REDACTED] (b) (4)

**5. *Does the Division agree with our proposed approach for volatile organic impurity testing, and our proposed method for setting limits on the volatile organic impurity levels in the components (Section 5.1.1)?***

The Division agreed with the general approach. The Sponsor will need to demonstrate that

exposure temperature adequately demonstrates a "worst case" scenario for each component and provides for an adequate safety margin.

(b) (4) The Division recommended testing samples representative of different heat source and device lots.

6. *Does the Division agree with our proposed approach for (b) (4) used in the product (Section 5.2.1)?*

The approach was generally acceptable to the Division but the Sponsor should assess individual components for ingredients (b) (4) that may migrate when heated.

7. *Does the Division agree with our proposed stability testing plan, and the elements to be included in the stability specification (Section 6.1.1)?*

The Division suggested that the Sponsor address the following during the registration studies:

- (b) (4)

Stability studies should include accelerated (40°C/75% R.H.) and intermediate (30°C/65% R.H.) conditions (b) (4)

The Division noted that the proposed microbial limits acceptance criteria (b) (4) appears to be too high. (b) (4)

The Division and

(b) (4)

End of Phase 2 CMC Meeting Minutes  
Page 4

Sponsor agreed that control of microbial limits in the bulk drug substance might be a better option.

8. ***Does the Division agree with our proposed approach for heat package manufacture, and the elements of the release specification for the heat package (Section 7.2)?***

The Division generally agreed with the proposal but recommended that tests performed during Phase 3 include examination of average surface temperature and uniformity at a number of time points to justify the appropriateness of the chosen set point for quality control testing.

9. ***Does the Division agree with our proposed approach to change control for modifications to heat package design and process (Section 7.2)?***

The Division agreed with the general approach in principal. More specific details would need to be examined prior to agreements on specifics. (b) (4)

10. ***Does the Division agree with our approach to (b) (4), and the proposed method for assessing (b) (4) (Section 8.1)?***

The approach was generally acceptable to the Division; however, (b) (4) was recommended.

### ***Other Issues***

The sponsor was reminded that the temperature of air inhaled through the device may be the subject of additional concern during the NDA review.

The Division recommended that the Sponsor perform a more complete characterization of the effects of heat package leakage.

Minutes Preparer:

\_\_\_\_\_  
Lana Chen, R.Ph.  
Project Manager, DNNDP

Chair Concurrence:

\_\_\_\_\_  
Martha Heimann, PhD  
Acting Chemistry Team Leader  
Division of Neurology Products  
(designated signatory)

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/s/

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Martha Heimann

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