

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
21-436s018

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-436

SUPPL # 018

HFD # 130

Trade Name Abilify

Generic Name Aripiprazole

Applicant Name Otsuka Pharmaceutical Company, Ltd.

Approval Date, If Known

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

SE1

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?

Three

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# 21866

NDA# 21713

NDA# 21436

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:

CN138139 and Cn138163

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:

21-436

- 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:

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: CDR William H. Bender
Title: Senior Regulatory Project Manager
Date: 11/13/2007

Name of Office/Division Director signing form: ODE1/DPP/Thomas Laughren, MD
Title: Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Thomas Laughren
11/16/2007 05:50:02 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-436 Supplement Type (e.g. SE5): SE1 Supplement Number: 018

Stamp Date: May 16, 2007 PDUFA Goal Date: November 16, 2007

HFD-130 _____ Trade and generic names/dosage form: Abilify (aripiprazole) 2mg, 5mg, 10mg, 15mg, 20mg and 30mg

Applicant: Otsuka Pharmaceutical Development & Commercialization, Inc.
Therapeutic Class: Adjunctive Treatment in Major Depressive Disorder

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): one

Indication #1: Adjunctive Treatment in Major Depressive Disorder

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA #-###

Page 3

This page was completed by:

{See appended electronic signature page}

William H. Bender
Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.**
- No. Please proceed to the next question.**

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.**
- No: Please check all that apply: ___Partial Waiver ___Deferred ___Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population**
- Disease/condition does not exist in children**
- Too few children with disease to study**
- There are safety concerns**
- Other: _____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population**
- Disease/condition does not exist in children**
- Too few children with disease to study**
- There are safety concerns**
- Adult studies ready for approval**
- Formulation needed**
- Other: _____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

William Bender
11/19/2007 08:49:11 AM

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-436	BLA STN# NDA Supplement # 018	If NDA, Efficacy Supplement Type SE1
Proprietary Name: Abilify Established Name: Aripiprazole Dosage Form: 2mg, 5mg, 10mg, 15mg, 20mg and 30mg tablets		Applicant: Otsuka Pharmaceutical Company, Ltd.
RPM: CDR Bill Bender		Division: HFD-130, DPP Phone # 301-796-2145
<p>NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: x 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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>	<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p>X Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>	
❖ User Fee Goal Date		November 16, 2007
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation 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 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 NDAs and NDA Supplements: <input type="checkbox"/> OTC drug Other: Other comments: Priority Review for the Adjunctive Treatment in Major Depressive Disorder.	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

(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 to the next section below (Summary Reviews).

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).

- (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?

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 written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)</p>	<p>Director’s Memo – 11/16/2007</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)</p>	
Labeling	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	<p>11/16/2007</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	<p>11/16/2007</p>
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
<p>❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)</p>	<p><input type="checkbox"/> DMETS <input type="checkbox"/> DSRCs <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs</p>

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	Filing Review – 11/05/2007
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	N/A
❖ Pediatric Page (all actions)	X 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>)	X Verified, statement is acceptable
❖ Postmarketing Commitment Studies <ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	X None
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings <ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg 12/14/2006 <input type="checkbox"/> No mtg 02.2004 Developmental Mtg.
❖ Advisory Committee Meeting <ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	X No AC meeting
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	10/16/2007
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) <ul style="list-style-type: none"> X Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) <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>) 	10/16/2007
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
❖ Facilities Review/Inspection <ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: 09/10/2007 X Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"> ❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	N/A / Requested / <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested X Not needed
Nonclinical Information	
<ul style="list-style-type: none"> ❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>) 	None
<ul style="list-style-type: none"> ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>) 	X None
<ul style="list-style-type: none"> ❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>) 	X No carc
<ul style="list-style-type: none"> ❖ ECAC/CAC report/memo of meeting 	
<ul style="list-style-type: none"> ❖ Nonclinical inspection review Summary (DSI) 	X None requested
Clinical Information	
<ul style="list-style-type: none"> ❖ Clinical review(s) (<i>indicate date for each review</i>) 	10/23/2007
<ul style="list-style-type: none"> ❖ Financial Disclosure reviews(s) or location/date if addressed in another review 	10/05/2007
<ul style="list-style-type: none"> ❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>) 	X None
<ul style="list-style-type: none"> ❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>) 	X Not needed
<ul style="list-style-type: none"> ❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>) 	None
<ul style="list-style-type: none"> ❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>) 	None
<ul style="list-style-type: none"> ❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>) 	X Not needed
<ul style="list-style-type: none"> ❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>) 	<input type="checkbox"/> None requested
<ul style="list-style-type: none"> • Clinical Studies 	09/10/2007
<ul style="list-style-type: none"> • Bioequivalence Studies 	
<ul style="list-style-type: none"> • Clin Pharm Studies 	
<ul style="list-style-type: none"> ❖ Statistical Review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 10/05/2007
<ul style="list-style-type: none"> ❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 10/19/2007

Appendix A 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 Office of Regulatory Policy representative.

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

/s/

William Bender

11/19/2007 11:31:55 AM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-436 Supplement # 018 Efficacy Supplement Type SE-

Proprietary Name: Abilify
Established Name: Aripiprazole
Strengths: 2mg, 5mg, 10mg, 15mg, 20mg, and 30mg

Applicant: Otsuka Pharmaceutical Company, Ltd.
Agent for Applicant (if applicable): Kusuma Mallikaarjun, Ph.D.

Date of Application: May 16, 2007

Date of Receipt: May 16, 2007

Date clock started after UN:

Date of Filing Meeting: June 28, 2007

Filing Date: July 27, 2007

Action Goal Date (optional):

User Fee Goal Date: November 16, 2007

Indication(s) requested: Adjunctive treatment of Major Depressive Disorder.

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)

Type of Supplement: (b)(1) X (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P X
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid X Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: N/A

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments: N/A

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES X NO
- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] 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.” Applicant may not use wording such as “To the best of my knowledge . . .”
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
[Referred to in a pre-SNDA correspondence of December 14, 2006](#)
YES X NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES X NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO X
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES N/A
- PDUFA and Action Goal dates correct in tracking system? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 42,776; 76,132
- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) December 14, 2006 NO

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO X
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO X
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A X YES NO
- Risk Management Plan consulted to OSE/IO? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO X
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 2, 2007

NDA #: 21-436

DRUG NAMES: Abilify (Aripiprazole)

APPLICANT: Otsuka Pharmaceutical Company, Ltd.

BACKGROUND: This "Prior Approval" supplement (018) is for the treatment of Major Depressive Disorder as an adjunct to antidepressant therapy in major depressive disorder (MDD).

ATTENDEES: Thomas Laughren, M.D., Division Director
Mitchell Mathis, M.D., Deputy Division Director
Ni Khin, M.D., Clinical Team Leader
Peiling Yang, Ph.D., Statistician Team Leader
Karen Brugge, M.D., Medical Reviewer
Thomas Oliver, Ph.D., Chemistry Team Leader
Nallaperum Chidambaram, Ph.D., Chemistry Reviewer
Sonia Tabacova, Ph.D., Pharm/Tox Reviewer
Jialu Zhang, Ph.D., Statistician Reviewer
Kofi Kumi, Ph.D., OCPB Reviewer
Dianne Tesch, Pharmacologist, Site Reviewer
Bill Bender, R.Ph., Senior Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Karen Brugge
Secondary Medical:	
Statistical:	Jialu Zhang
Pharmacology:	
Statistical Pharmacology:	
Chemistry:	Nallaperum Chidambaram
Environmental Assessment (if needed):	
Biopharmaceutical:	Kofi Kumi
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Dianne Tesch
OPS:	
Regulatory Project Management:	Bill Bender
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO

If no, explain:

CLINICAL		FILE	X		REFUSE TO FILE	<input type="checkbox"/>
• Clinical site audit(s) needed?		YES	X		NO	<input type="checkbox"/>
If no, explain:						
• Advisory Committee Meeting needed?		YES, date if known	_____		NO	X
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?		N/A	X		YES	<input type="checkbox"/>
					NO	<input type="checkbox"/>
CLINICAL MICROBIOLOGY	N/A	X		FILE	<input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
STATISTICS	N/A	<input type="checkbox"/>		FILE	X	REFUSE TO FILE <input type="checkbox"/>
BIOPHARMACEUTICS				FILE	X <input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• Biopharm. study site audits(s) needed?					<input type="checkbox"/>	NO X
YES						
PHARMACOLOGY/TOX	N/A			FILE	<input type="checkbox"/>	REFUSE TO FILE <input type="checkbox"/>
• GLP audit needed?				YES	<input type="checkbox"/>	NO X
CHEMISTRY				FILE	X	REFUSE TO FILE <input type="checkbox"/>
• Establishment(s) ready for inspection?				YES	<input type="checkbox"/>	NO <input type="checkbox"/>
• Sterile product?				YES	<input type="checkbox"/>	NO X
If yes, was microbiology consulted for validation of sterilization?				YES	<input type="checkbox"/>	NO <input type="checkbox"/>

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- X No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent

classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Bill Bender
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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 Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES N/A
NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)
- Not applicable (e.g., solely based on published literature. See question # 7)
 - 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
 - 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):
- NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
 - Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
 - 21 CFR 314.50(i)(1)(ii): No relevant patents.
 - 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

William Bender
11/5/2007 10:02:45 AM
CSO

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 3, 2007

TO: William Bender, Pharm. D., Regulatory Project Manager
Karen Brugge, M.D., Clinical Reviewer
Division of Psychiatry Products, HFD-130

THROUGH: Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-436 SE#-018

NME: No

APPLICANT: Otsuka Pharmaceutical Company, Ltd. / Bristol-Myers Squibb

DRUG: Abilify (aripiprazole)

THERAPEUTIC CLASSIFICATION: 3S

INDICATION: Treatment (b) (4)

CONSULTATION REQUEST DATE: June 29, 2007

DIVISION ACTION GOAL DATE: September 28, 2007

PDUFA DATE: November 16, 2007

I. BACKGROUND:

Despite numerous treatment options, major depression remains a widespread, debilitating illness. Two thirds of patients who are initially prescribed medications do not experience a timely remission, as conventionally defined by achieving an absolute depression rating score below a specified cut-off level. Forty to 50% of patients do not experience a timely response, as conventionally defined by achieving a minimal 50% reduction in symptom severity. Furthermore, 10 to 20% of care-seeking depressed patients remain significantly symptomatic after 2 years.

There were two protocol numbers, CN138-139 and CN138-163. The two protocols had identical designs. CN138-163 had more centers involved than CN138-139.

The current studies assessed the utility of aripiprazole, as an adjunctive agent, in patients who have not achieved a complete response after at least 2 adequate antidepressant trials (1 or more historically and 1 prospectively defined).

The primary objective of these studies was to compare the efficacy of aripiprazole to placebo as adjunctive treatment to an assigned open-label marketed antidepressant therapy (ADT) in patients who demonstrated an incomplete response to a prospective 8-week trial of the same assigned open-label ADT.

The primary efficacy endpoint for both studies was the change from the end of Phase B (Week 8 Visit) to the end of Phase C (Week 14 Visit) in the Montgomery Asberg Depression Rating Scale (MADRS) Total Score.

Dr. Khan's site was chosen because he had the highest enrollment for Protocol #CN138-139 and because there was a sub-investigator at his site who left the practice without filing a financial disclosure statement.

For Protocol #CN138-163 Dr. Joseph's and Dr. Simon's sites were chosen because they had significant primary efficacy results and because they had significant treatment differences between groups.

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #	City, State	Protocol #	Insp. Date	EIR Received Date	Final Classification
Arifulla Khan, M.D. site 008	Bellevue, WA	CN138-139	8/20/07-8/29/07	9/28/2007	NAI
Jeffrey S. Simon, M.D. site 010	Brown Deer, WI 53223	CN138-163	8/8/2007-8/15/2007	8/28/2007	NAI
George Joseph, M.D. site 016	Jacksonville, FL 32216	CN138-163	8/13/2007-8/28-2007	pending	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) from regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #CN138-139

1. Arifulla Khan, M.D., site 008, Bellevue, WA:

- a. Ninety-four subjects were screened and forty two subjects were randomized. All subjects' records were reviewed in depth for the data audit inspection.
- b. There were no limitations to the inspection.
- c. No regulatory deficiencies were identified.

- d. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

B. Protocol #CN138-163

1. Jeffrey S. Simon, M.D., site 010, Brown Deer, WI:

- a. Fifty-three subjects were screened, twenty were randomized, and nineteen completed the study. For the data inspection audit fourteen subjects' records were reviewed in depth.
- b. There were no limitations to the inspection
- c. No regulatory deficiencies were identified.
- d. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. George Joseph, M.D., site 016, Jacksonville, FL

- a. Twenty-nine subjects were randomized. Twenty-three subjects' records were reviewed in depth for the inspection.
- b. There were no limitations to the inspection.
- c. There were some problems with drug accountability records at the site. Specifically, various forms used to track supplies were not always in agreement as to how much of each supply (active drug and placebo) were returned to the sponsor. There was also a problem with five subjects not signing the most current version of the informed consent document (ICD), or not signing it in a timely manner. The regulatory deficiencies at the site were clerical in nature and did not have an effect on data integrity.
- d. The data generated by this site appear acceptable in support of the respective indication. However, observations noted above are based on the Form FDA 483 and communications from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The studies appear to have been well conducted at all the sites. No follow up other than routine surveillance is recommended.

[See appended electronic signature page](#)

Dianne Tesch
Consumer Safety Officer

CONCURRENCE:

Supervisory comments

[{ See appended electronic signature page }](#)

Joseph P. Salewski
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Dianne Tesch
10/3/2007 09:45:42 AM
CSO

Joseph Salewski
10/3/2007 11:15:21 AM
CSO

Bender, William

From: Bender, William
Sent: Thursday, August 30, 2007 12:44 PM
To: 'Susan.Behling@bms.com'
Cc: 'Mallikaarjun, Kusuma'
Subject: NDA 21-436 s-018 adjunct tx in MDD

Good Day Susan,

Please refer to Section 4.3 of CSRs for study cn138139 (-139) and -163 (the 2 pivotal efficacy trials) of NDA21436 N018.

- 1) We note a large number of protocol deviations in each pivotal study regarding
- a) Eligibility criteria (relevant to defining the MDD population) and
 - b) Relevant to substance use (e.g. Positive UDS and using opiates, barbiturates and potentially other drugs typically used by substance abusers). This question includes any other subjects using other substances of abuse (e.g. alcohol).

Please provide the following information regarding subjects included in the efficacy analysis dataset for each study?

- a) Please clarify for each study the nature and number of protocol deviations relevant to defining the MDD population and provide your argument for why these deviations are not clinically relevant.
- b) Please also provide deviations relevant to substance use and identify which subjects had a history of substance abuse or dependence and identify the substance used during the study.

Please include any additional relevant information that may assist us in determining the potential impact of the above deviations on efficacy results.

- 2) Please also provide the following information for each pivotal trial:
- a) Identify any psychiatric comorbidity (showing the incidence for each comorbid diagnosis or condition) for each treatment group of each study.
 - b) It appears from your eligibility criteria for each study that patients with Generalized Anxiety disorder were included in the trial. If such patients were included, would you please provide the incidence of these subjects by treatment group?

Please perform the analyses on the primary and key secondary endpoints on Per Protocol population in both Study 138139 and Study 138163. Please submit the dataset and the SAS program that produce the results.

If the information requested above is already included in your submission, please direct us to it. We would like your response by 4 September 2007.

Thank you,
William H. Bender
CDR, USPHS
Regulatory Health Project Manager, FDA/CDER/DPP
Phone: 301-796-2145
william.bender@fda.hhs.gov

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/s/

William Bender
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CSO



FILING COMMUNICATION

NDA 21-436

Otsuka Pharmaceutical Company, Ltd.
Attention: Susan H. Behling, Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Ms. Behling:

Please refer to your May 16, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (Aripiprazole) 2mg, 5mg, 10mg, 15mg, and 20mg tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. In addition, we grant a priority review to this application. Therefore, this application has been filed under section 505(b) of the Act on June 28, 2007 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call CDR Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145.

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/

Thomas Laughren
7/2/2007 10:44:27 AM



PRIOR APPROVAL SUPPLEMENT

NDA 21-436/S-018

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: Kuzuma Mallikaarjun, Ph.D., Sr. Director, Regulatory Affairs
2440 Research Blvd.,
Rockville, MD 20850

Dear Dr. Mallikaarjun:

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

Name of Drug Product: Abilify (aripiprazole) 2mg, 5mg, 10mg, 15mg, 20mg and 30mg tablets.
NDA Number: 21-436
Supplement number: 018
Date of supplement: May 16, 2007
Date of receipt: May 16, 2007

This "Prior Approval" supplemental application proposes the use of Abilify for the treatment of Major Depressive Disorder as an adjunct to antidepressant therapy. 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 July 15, 2007 in accordance with 21 CFR 314.101(a).

Please cite the application number listed above 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

If you have any question, call me at (301) 796-2145.

Sincerely,

{See appended electronic signature page}

Bill Bender, R.Ph.
Senior Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

William Bender
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