

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-713

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA #21-713

Trade Name: Abilify Oral Solution Generic Name: aripiprazole

Applicant Name: Otsuka HFD # 120

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 question 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

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.

Sponsor relied on 3 ~~to~~ pharmacokinetic studies to extrapolate safety + efficacy to ~~Abilify~~ Abilify tablets.

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?

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# 21-436

~~Abilify~~ Abilify tablets

NDA# _____

NDA# _____

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 / / N/A

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

NDA# _____

NDA# _____

NDA# _____

N/A

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 NDA'S 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:

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

essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

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 # _____ YES /___/ ! NO /___/ Explain: _____
!
!

Investigation #2 !
IND # _____ 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 /___/ Explain _____ ! NO /___/ Explain _____
!
!
_____ !
_____ !

Investigation #2 !
!

YES /___/ Explain _____ ! NO /___/ 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: _____

Signature *John D. Hardum* Date *11/30/04*
Title: *Senior Regulatory Project Manager*

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NA/BLA # : 21-713 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 11-20-03 Action Date: _____

HFD 120 Trade and generic names/dosage form: Abilify (aripiprazole) Oral Solution

Applicant: Otsuka Therapeutic Class: antipsychotic

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: schizophrenia

Is there a full waiver for this indication?

- Yes: Please proceed to Section A.

Indication #2: mania

Is there a full waiver for this indication?

- Yes: Please proceed to Section A.

Section A: Fully Waived Studies

Reason for full waivers:

- Too few children with disease to study

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

DATE: December 10, 2004

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Approval Action for Aripipazole Oral Solution (1 mg/mL)

TO: File for NDA 21-713
[Note: Should be filed with 11-18-04 response to approvable letter.]

Background

Abilify (aripiprazole) is currently available in oral tablet strengths (5, 10, 15, and 30 mg) for the treatment of schizophrenia and for mania. This application provides data in support of an oral aripiprazole solution (1 mg/mL). We issued an approvable letter for this application on 9-20-04. By the time of issuing the approvable letter, all of the pharm/tox, biopharm, and clinical issues had been resolved, leaving only CMC issues for the approvable letter (See my 9-18-04 memo for a summary of the issues leading up to the approvable letter.) Thus, the approvable letter focused on the 6 CMC issues and labeling. The sponsor has responded adequately to all 6 CMC issues, and has essentially accepted our proposed labeling (the exception being a statement added to Information for Patients that is no longer needed because the sponsor is now proposing only the cup for dispensing).

Summary of Responses to CMC Issues

1. Unacceptable Drug Product Facility

The Mt. Vernon, IN facility was found to be unacceptable at the first inspection. However, that site has now been re-inspected and is acceptable.

2. Unacceptable Identification Specifications for Drug Product

The sponsor has updated the Identification Specifications and they are now acceptable.

3. Inadequate Drug Product Release Specifications

The sponsor has adequately addressed how they will control for pH in the drug product.

4. Inadequate Drug Product Specifications with Regard to Refrigerated Storage Conditions

These specifications have now been adequately updated.

5. Inadequate Patient Instructions for Dosing Devices Planned for the Drug Product

The sponsor has decided to use only the cup for dispensing, thus eliminating the need for patient instruction sheets.

6. Identification of Structure for 2 Impurities

The sponsor has identified the structures for the 2 impurities in question.

Conclusions/Recommendations

I agree that this application can now be approved, and I recommend that we issue the attached approval letter with agreed upon final labeling.

cc:

Orig NDA 21-713/Aripiprazole Oral Solution

HFD-120/DivFile

HFD-120/TLaughren/RKatz/GDubitsky/SHardeman

DOC: Memo Aripiprazole Oral Solution AP1.doc

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/s/

Thomas Laughren
12/10/04 07:30:44 AM
MEDICAL OFFICER

Laughren, Thomas P

From: Yasuda, Sally
Sent: Monday, December 06, 2004 2:54 PM
To: Kumi, Kofi A; Laughren, Thomas P
Subject: FW: Abilify solution 21-713

-----Original Message-----

From: Hardeman, Steven D
Sent: Monday, December 06, 2004 2:50 PM
To: Yasuda, Sally
Subject: RE: Abilify solution 21-713

None that I know of.

-----Original Message-----

From: Yasuda, Sally
Sent: Monday, December 06, 2004 12:05 PM
To: Hardeman, Steven D
Cc: Kumi, Kofi A
Subject: Abilify solution 21-713

Hi Steve,

Did you have any labeling that we need to look at? The response did not come back to us.

Thanks,

Sally



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-713

Otsuka America Pharmaceutical, Inc.
Attention: Kusuma Mallikaarjun, Ph. D.
Director, Regulatory Affairs/Abilify
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your new drug application (NDA) dated November 20, 2003, received November 21, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) 1 mg/mL Oral Solution.

Refer also to your submission of November 18, 2004.

We consider your submission of November 18, 2004, a complete, class 1 response to our September 20, 2004 action letter. Therefore, the user fee goal date is December 19, 2004.

If you have any question, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Robbin Nighswander, R.Ph.
Supervisory Regulatory Project Manager
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Steve Hardeman
11/16/04 01:50:18 PM
signed for Robbin Nighswander, R.Ph.

The sponsor's proposed dosing for this new formulation is mg per mg for the tablet to oral solution switch, except at the highest tablet dose of 30 mg, where the proposed solution dose is 25 mg (i.e., 25 mL). The theory is that the Cmax exposures for these doses for these formulations are very close, and that the slight difference in overall exposure (AUC) resulting from this practice is of no clinical consequence. Since the dose response for efficacy is essentially flat beyond roughly 10 to 15 mg/day up to 30 mg/day, this seems to me a reasonable assumption.

Pharmacokinetic Findings

The sponsor first recognized a potential bio-inequivalence problem for the aripiprazole solution vs tablet with an early pilot study (CN138019) done under IND 42,776. Study CN138063 comparing aripiprazole at doses of 5, 10, and 15 mg of solution with the same doses of aripiprazole tablets confirmed this bio-inequivalence for Cmax, but equivalence criteria were met for AUC. We suggested in a 10-30-02 meeting that they attempt to estimate the solution dose that would best achieve a comparable Cmax to that seen with the maximum 30 mg tablet dose. A final study (CN138108) comparing solutions of 20 and 30 mg with a 30 mg tablet accomplished this goal and established 25 mg of oral solution as the solution dose that achieved a comparable Cmax and AUC to that observed with a 30 mg oral tablet.

Pharmacology/Toxicology Findings and Issues

At our filing meeting on 1-12-04, it was noted that stability testing had revealed 3 degradants [redacted] that were observed to increase over time. The main degradant was [redacted] the known active metabolite of aripiprazole, and thus, not a concern. However, the other 2 degradants were present at [redacted], and the sponsor conducted 3 toxicology studies to qualify these two (13-week tox; Ames; mouse micronucleus). We issued a letter to the sponsor on 4-8-04 noting our potential concern about these 2 degradants and asking they they conduct and submit results of either in-vitro or mouse chromab assays for these 2 substances. We further indicated that, depending on the results of these assays, repro studies may also be needed.

However, the sponsor has subsequently changed the storage conditions for this product, and stability testing at the lower temperature proposed for this product results in much lower levels of the 2 degradants in question [redacted] thus, removing these degradants as a concern, providing the new storage temperature is adopted.

CMC Issues

There are several CMC issues that would need to be addressed prior to final approval of this product, and these are detailed in the approvable letter:

- It was not possible to inspect one of the two manufacturing sites, and the sponsor has been asked to withdraw this site if it cannot be made available for inspection.
- Other deficiencies pertain to drug product specifications, methods description, labeling enhancements, and structural identity of impurities.

PREA Requirements

We are recommending waiving these requirements since a pediatric program is already underway for the tablets.

Clinical Review

There were no safety findings from the 3 clinical studies that would suggest any added risk from this new formulation. There was no need for efficacy data since efficacy was extrapolated from existing data.

Labeling

OCPB has recommended some very modest changes to labeling regarding dosing, but the basic message is still to substitute mg per mg when moving from tablet to oral solution, up to 25 mg, but then not go beyond 25 mg of oral solution for patients taking a 30 mg tablet dose. I agree with these modest changes.

Conclusions/Recommendations

I agree that this application is approvable, and I recommend that we issue the attached approvable letter with draft labeling, in anticipation of final approval.

cc:

Orig NDA 21-713/Aripiprazole Oral Solution

HFD-120/DivFile

HFD-120/TLaughren/RKatz/GDubitsky/SHardeman

DOC: Memo Aripiprazole Oral Solution AE1.doc

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/s/

Thomas Laughren
9/18/04 01:46:22 PM
MEDICAL OFFICER

Hardeman, Steven D

From: Dubitsky, Gregory M
Sent: Thursday, September 02, 2004 10:32 AM
To: Hardeman, Steven D
Subject: RE: aripip oral soln biopharm review

I'm not crazy about the wording. I would say "solution doses can be substituted for the tablet doses on a mg-per-mg basis up to 25mg of the tablet. Patients receiving 30mg tablets should receive 25mg of the solution."

-----Original Message-----

From: Hardeman, Steven D
Sent: Thursday, September 02, 2004 10:27 AM
To: Dubitsky, Gregory M
Subject: aripip oral soln biopharm review

You got any grief with biopharm's proposed labeling changes (pg 15 of the review)? I have already asked the sponsor to clarify what the "other natural flavorings" consist of.

Steve

<< File: CDataMy1.pdf >>

Biopharm AE
CMC AE
Chw AE

Hardeman, Steven D

From: Angelina M Verna [Angelina.Verna@bms.com]
Date: Thursday, September 02, 2004 4:58 PM
To: Angelina M Verna
Cc: hardemans@cder.fda.gov; Susan H Behling; Mallikaarjun, Kusuma; Marian E Young
Subject: Re: [Fwd: Aripip Oral Soln] CORRECTED LETTER

Dear Steve,

I apologize for referencing the wrong drug product. The product in question is the "oral solution" and I wrote "IM injection." Below is a corrected letter.

Angie

To: CAPT Steven D. Hardeman, R.Ph.

Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

Dear Steve,

This is in response to your request (below) to Sue Behling for information on the flavors used in Abilify Oral Solution NDA 21-713, and whether food allergens are present.

The composition of the flavor is proprietary information and is contained in DMF [redacted] from [redacted] DMF# [redacted] has been reviewed by the Agency. The Abilify Oral Solution NDA 21-713, Section 3.2.P.4.3, presented the Letter of Authorization allowing the Agency to refer to the information for this ingredient ([redacted] Natural Orange Flavor, [redacted] Type) in DMF [redacted] on behalf of Bristol-Myers Squibb Company.

In response to your question, I contacted [redacted] and was provided the attached list comparing common food allergens to the ingredients in the flavor ([redacted] Natural Orange Flavor, [redacted] Type) used in Abilify Oral Solution. None of the common food allergens are contained in the flavor.

If you have any further questions, please feel free to contact me either by email or phone at 609-818-4063, or my supervisor Ms. Marian Young, Group Director GRS-CMC at 609-818-4685.

Thank you,
Angie Verna

Angelina M Verna wrote:

To: CAPT Steven D. Hardeman, R.Ph.

Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

Dear Steve,

This is in response to your request (below) to Sue Behling for information on the flavors used in Abilify [REDACTED] and whether food allergens are present.

The composition of the flavor is proprietary information and is contained in DMF [REDACTED] from [REDACTED] DMF# [REDACTED] has been reviewed by the Agency. The Abilify [REDACTED] NDA, Section 3.2.P.4.3, presented the Letter of Authorization allowing the Agency to refer to the information for this ingredient [REDACTED] Natural Orange Flavor ([REDACTED] Type) in DMF [REDACTED] on behalf of Bristol-Myers Squibb Company.

In response to your question, I contacted [REDACTED] and was provided the attached list comparing common food allergens to the ingredients in the flavor [REDACTED] Natural Orange Flavor ([REDACTED] Type) used in Abilify [REDACTED]. None of the common food allergens are contained in the flavor.

If you have any further questions, please feel free to contact me either by email or phone at 609-818-4063, or my supervisor Ms. Marian Young, Group Director GRS-CMC at 609-818-4685.

Thank you,
Angie Verna

Susan H Behling wrote:

Subject: Aripip Oral Soln
From: "Hardeman, Steven D" <HARDEMANS@cder.fda.gov>
Date: Thu, 02 Sep 2004 09:48:38 -0400
To: 'Susan H Behling' <Susan.Behling@bms.com>
To: 'Susan H Behling' <Susan.Behling@bms.com>

Sue,

One of the other reviewers may have already asked this, but I can't find any reference. The label states that the product composition includes "other natural flavors." Could you clarify what those flavors are (whether food allergens are present). Just trying to cover all of the bases. I have the biopharm review now and all looks well. They do have some labeling changes. I'll work on them and get you an email.

Thanks,
Steve

CAPT Steven D. Hardeman, R.Ph.
Senior Regulatory Project Manager
Division of Neuropharmacological Drug Products / HFD-120
Food and Drug Administration
Rockville, Maryland 20857

Phone: 301-594-5525

Fax: 301-594-2859

Email: hardemans@cdcr.fda.gov

"MMS <cdcr.fda.gov>" made the following annotations.

This message was sent from Bristol-Myers Squibb, Co. across the Internet in encrypted format and was successfully decrypted, unless otherwise noted. Bristol-Myers Squibb
=====

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/s/

Steve Hardeman
9/3/04 09:26:19 AM
CSO

David, Paul A

From: David, Paul A
Sent: Tuesday, May 04, 2004 1:45 PM
To: 'Susan.Behling@bms.com'
Cc: David, Paul A
Subject: FW: [Fwd: NDA 21-713 74 day letter]



NDA 21-713 74
day letter

Hello Susan,

The Pharm/Tox Team Leader, Dr. Lois Freed, forwarded your e-mail to me since I am covering for Steve. Below is the response to your question:

We acknowledge that the specifications for degradants, (C) and (D) are (E) respectively, not (F) as incorrectly specified in the 74-day letter. However, according to ICH-Q3B (Impurities in New Drug Products), the qualification threshold for these degradants is (G). Therefore, the need for either an in vitro chromosomal aberration assay in mammalian cells or an in vitro mouse lymphoma tk assay (with colony sizing) remains.

If you have any questions, please feel free to contact me. Regards, CDR Paul David, R.Ph.
Senior Regulatory Project Manager Division of Neuropharmacological Drug Products, HFD-120
ODE1; CDER; FDA

Telephone: 301-594-5530

Fax: 301-594-2859

avid@cdcr.fda.gov

-----Original Message-----

From: Freed, Lois M
Sent: Monday, May 03, 2004 8:29 AM
To: David, Paul A
Subject: FW: [Fwd: NDA 21-713 74 day letter]

-----Original Message-----

From: Susan H Behling [mailto: Susan.Behling@bms.com]
Sent: Friday, April 30, 2004 5:22 PM
To: FreedL@cdcr.fda.gov
Subject: [Fwd: NDA 21-713 74 day letter]

Dear Dr. Freed: I understand that Steve is on vacation next week and I did not have a chance to discuss this with him before he left. I am hoping that you can consider the question outlined below with respect to the oral solution so that we can proceed with our plans for this.

Thanks very much,

Sue

David, Paul A

From: Susan H Behling [Susan.Behling@bms.com]
Sent: Friday, April 30, 2004 1:25 PM
To: Hardeman, Steven D
Cc: kusuma mallikaarjun
Subject: NDA 21-713 74 day letter

Importance: High

Hi Steve- The BMS team reviewed the letter today and we thought it would be important to ask for clarification from the chemistry and toxicology reviewers.

The letter states:

"The specification you have proposed for degradants [redacted] exceed the threshold for qualification for the drug product." The letter goes on to indicate that based on this assumption, we are requested to submit data from an in vitro chromab or mouse lymphoma study for these degradants.

Please note to the reviewers that the proposed specifications for these two degradants are [redacted] respectively, not [redacted] as indicated in the letter. The NDA indicates that we believe the [redacted] level would be qualified based on the results of the toxicology studies that were completed, but this is not the proposed limit.

Given this information, does the Division's concern and request for the mouse lymphoma data still apply?

Please let me know as soon as possible since the studies requested have not been conducted and we would not want this to impact the timeline for the approval of this formulation.

Best regards,

Sue

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/s/

Paul David
5/4/04 01:43:29 PM
CSO



FILING COMMUNICATION

NDA 21-713

Otsuka Pharmaceutical, Inc.
Attention: Kusuma Mallikaarjun, Ph.D.
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your November 20, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Oral Solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 20, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

- The specification you have proposed for degradants [REDACTED] exceeds the threshold for qualification for the drug product. You have conducted a 13-week oral toxicity study in rats and two genotoxicity studies (Ames test, *in vivo* micronucleus assay in mice). However, you have not tested these degradants in the following: (a) either an *in vitro* chromosomal aberration assay in mammalian cells or an *in vitro* mouse lymphoma assay (with colony sizing) and (b) an embryo-fetal development study in either rat or rabbit (with selection of species justified).

We are providing the above comments to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

- Please submit the results of an in-vitro chromab or mouse lymphoma for degradants [REDACTED]. Based on these results, you may need to conduct a repro study.

Please respond only to the above requests 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.

NDA 21-713

Page 2

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.

Director

Division of Neuropharmacological Drug Products

Office of Drug Evaluation I

Center for Drug Evaluation and Research

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/s/

Russell Katz

4/8/04 11:05:50 AM



Otsuka America Pharmaceutical, Inc.

74 Day letter

2440 Research Boulevard
Rockville, Maryland 20850
Phone: 301.990.0030
Fax: 301.990.0035
www.otsuka.com

November 20, 2003

Russell Katz, M.D., Director
Division of Neuropharmacologic Drug Products-HFD-120
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852
Attention: Document Control Room

**New Drug Application (NDA) for ABILIFY™ (aripiprazole) Oral Solution
NDA #21-713**

Dear Dr. Katz:

Reference is made to NDA # 21-436 for ABILIFY™ (aripiprazole) Tablets, which was approved on November 15, 2002. Further reference is made to our October 30, 2002 meeting and to the correspondence to IND #62, 216 (Sub. No. 031, September 12, 2003) regarding our intent to submit a New Drug Application for ABILIFY Oral Solution. Pursuant to 21 CFR 314.70, Otsuka Pharmaceutical Co. Ltd., (OPC) is hereby submitting the NDA for ABILIFY Oral Solution for the treatment of patients with schizophrenia.

This electronic NDA has been organized using CTD formats. We request a waiver of the requirement for paper copies of the NDA. This NDA cross-refers to NDA #21-436 for ABILIFY (aripiprazole) Tablets for the safety and efficacy, nonclinical, and drug substance data.

As discussed with the Division in October 2002, the initial clinical pharmacokinetic studies conducted with this formulation suggested that the formulation was unlikely to meet the requirements to declare bioequivalence to the approved ABILIFY Tablets, given the more rapid absorption and greater maximum plasma concentrations observed with the solution. Therefore, the registrational program included three clinical pharmacology studies, two of which (Studies CN138063 and CN138108) were designed to estimate the doses of the oral solution that would be expected to deliver equivalent exposures to the approved ABILIFY Tablet formulation. The proposed revisions to the ABILIFY Tablets package insert reflecting the addition of the relevant prescribing information for ABILIFY Oral Solution includes the recommendation to administer the oral solution and tablets on a mg per mg basis at doses below 30 mg. As agreed during the October 2002 meeting, the rationale for this labeling approach is that though the products are not strictly bioequivalent, the small differences in the estimated doses of the oral solution that would provide 'equivalent' exposures to the tablets are unlikely to be clinically relevant within the range of tablet doses that have been systematically evaluated for safety and efficacy. However, given the paucity of safety data for aripiprazole at tablet doses above 30 mg to justify the higher CMAX of the oral solution at this dose, the proposed labeling recommends a 'capped' dose of the oral solution at 25 mg. We believe this proposal is supported by the data provided in this application.

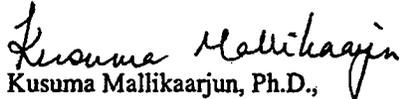
In accordance with PDUFA III, payment in the amount of \$573,500.00 has been sent to the Food and Drug Administration, Philadelphia, Pennsylvania. This NDA has been assigned the User Fee Identification Number 4631.

Aripiprazole was discovered by OPC and developed in collaboration with the Bristol-Myers Squibb Company (BMS). This collaboration extends to the successful approval and commercialization of the product in the U.S. As a result, BMS is delegated to act on behalf of OPC in the negotiation of this NDA with the Agency. The agency was informed of this collaborative agreement and delegation in Submission No. 223 (dated November 16, 1999) and Submission No. 233 (dated January 4, 2000) respectively to IND#42, 776.

Please be advised that OPC considers the information in this NDA to be confidential and proprietary and therefore we request that no portions thereof be disclosed to third parties, other than BMS, under FOI or otherwise, without first obtaining written consent from OPC.

We look forward to working with you to facilitate the review and approval of this application. If there are any questions or concerns regarding this application, please contact Ms. Susan H. Behling, Director, Regulatory Science, Bristol-Myers Squibb Co., at 203-677-3810.

Sincerely,


Kusuma Mallikaarjun, Ph.D.,
Director, Regulatory Affairs/Abilify

Electronic Media Information

November 20, 2003

New Drug Application (NDA) No. 21-713 Abilify™
(Aripiprazole) Oral Solution

Original Application

The archival copy of this submission is a fully compliant electronic submission and is being provided electronically in lieu of paper as per the Guidance for Industry: Providing Regulatory Submissions in Electronic Format - General Considerations, dated January 27, 1999, and the Guidance for Industry: Providing Regulatory Submissions in Electronic Format - NDAs, dated January 27, 1999.

The media for this electronic submission has been prepared as follows:

The total size of the electronic submission is approximately 104 MB and is being provided on 1 CD-ROM disk to the Central Document Room. There are 205 files and 89 folders. The files have been checked for viruses using virus definitions available on November 14, 2003 with McAfee VirusScan Software (Version 4.5.1) and no viruses were detected.

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 30, 2002
TIME: 2:00 PM
LOCATION: WOC II - Conf. Room E
APPLICATION: IND 62,216 -- Aripiprazole Oral Solution
TYPE OF MEETING: End of Phase II
MEETING CHAIR: Russell Katz, M.D.
MEETING RECORDER: Steve Hardeman, R.Ph.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Russell Katz, M.D., Director, DNDP
Tom Laughren, M.D., Psychopharm Team Leader, DNDP
Greg Dubitsky, M.D., Medical Officer, DNDP
Ray Baweja, Ph.D., Team Leader, HFD-860
Steve Hardeman, R.Ph., Regulatory Project Manager, DNDP

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Bristol-Myers Squibb Company

Susan Behling, Director Regulatory Science, Neuroscience
David Kornhauser, M.D., Executive Director, Clinical Discovery
Ronald Marcus, M.D., Group Director, Neuroscience Clinical Design and Evaluation
Elyse Stock, M.D., Vice President, Global Development Champion, Aripiprazole
Charles Wolleben, Ph.D., Director, Regulatory Science, Neuroscience

Otsuka Maryland Research, Inc.

Kusuma Mallikaarjun, Ph.D., Director, Regulatory Affairs

Otsuka Pharmaceutical Co., Ltd.

William Carson, M.D., Vice President, Product Development/Aripiprazole

DISCUSSION POINTS

The meeting was structured around the five FDA questions posed by the sponsor on pages 17-18 of their 9-27-02 Background Document (attached).

Question #1(a): Registration of the oral solution will not require demonstration of safety and efficacy in a clinical trial since the blood levels of aripiprazole after administration of the solution will be bracketed by the levels achieved with approved doses of the soon to be approved tablet product.

Question #1(b): Not applicable since study CN138091 is not required.

Question #2: The safety experience with aripiprazole tablets should be sufficient to support registration of the oral solution up to the solution dose that produces exposure not exceeding that of the 30mg tablet.

Question #3(a): We have no objection to conducting study CN138108 as planned, with oral solution doses of 20 and 30mg. These PK data should provide some basis for estimating, by linear interpolation and extrapolation, equivalent oral solution doses for patients to be switched from the tablet formulation at daily doses above 15mg. Similarly, study CN138063, which examined tablet and solution pharmacokinetics at doses of 5, 10, and 15mg, should provide a basis for switching patients at lower tablet doses.

Question #3(b): We cannot make any commitments regarding labeling at this time. However, we anticipate that dosing recommendations will parallel those for aripiprazole tablets (i.e., a starting dose and a dose range with a cap).

Question 4: A food effect study will not be needed.

Question 5: Cross-referencing most of the oral solution NDA to the tablet NDA is acceptable.

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

/s/

Russell Katz
11/1/02 11:02:36 AM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Applicant Information		
NDA 21-713	Efficacy Supplement Type SE-	Supplement Number
Drug: Abilify (aripiprazole) oral solution		Applicant: Otsuka
RPM: Steven D. Hardeman, R.Ph.		HFD-120 Phone # 301-594-5525
<p>Application Type: (*) 505(b)(1) () 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		(*) Standard () Priority
		3
❖ User Fee Goal Dates		
		Approval: 12-19-04
❖ Special programs (indicate all that apply)		
		(*) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		(*) Paid UF ID number 4631
		() Small business () Public health () Barrier-to-Innovation () Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP • This application is on the AIP 		() Yes (*) No
		() Yes (*) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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 box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the 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 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).

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 box below (Exclusivity).

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.

❖ Exclusivity (approvals only)		
<ul style="list-style-type: none"> Exclusivity summary Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	done	
<ul style="list-style-type: none"> Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? 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. 	<input type="checkbox"/> Yes, Application # _____ <input type="checkbox"/> No	
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	NA	

General Information	
Actions	
• Proposed action	(*) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	Approvable: 9-20-04
• Status of advertising (approvals only)	(*) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (*) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(*) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	In package
• Most recent applicant-proposed labeling	In package
• Original applicant-proposed labeling	In package
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	None
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	10/30/02
• Pre-NDA meeting (indicate date)	none
• Pre-Approval Safety Conference (indicate date; approvals only)	none
• Other	none
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	None
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	None
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	None
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	None
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	In package
❖ Demographic Worksheet (NME approvals only)	None
❖ Statistical review(s) (indicate date for each review)	None
❖ Biopharmaceutical review(s) (indicate date for each review)	In package
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Na
• Bioequivalence studies	Na
CMC Information	
❖ CMC review(s) (indicate date for each review)	In package
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	In CMC review
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Na
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable (*) Withhold recommendation
❖ Methods validation	() Completed () Requested (*) Not yet requested
Pharm/tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	None
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	None
❖ CAC/ECAC report	None
❖	

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-713	Efficacy Supplement Type SE-	Supplement Number
Drug: Abilify (aripiprazole) oral solution		Applicant: Otsuka
RPM: Steven D. Hardeman, R.Ph.		HFD-120 Phone # 301-594-5525
<p>Application Type: (*) 505(b)(1) () 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		(*) Standard () Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
User Fee Goal Dates		For Approvable 9-21-04
❖ Special programs (indicate all that apply)		
		(*) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
• User Fee		(*) Paid UF ID number 4631
• User Fee waiver		() Small business () Public health () Barrier-to-Innovation () Other (specify)
• User Fee exception		() Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		() Yes (*) No
• This application is on the AIP		() Yes (*) No

received a written notice from the 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 box below (Exclusivity).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the 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 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).

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 box below (Exclusivity).

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❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? 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. 	() Yes, Application # _____ () No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	NA

General Information	
❖ Actions	
• Proposed action	<input type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	<input type="checkbox"/> Materials requested in AP letter <input type="checkbox"/> Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	<input type="checkbox"/> Yes <input type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> Press Release <input type="checkbox"/> Talk Paper <input type="checkbox"/> Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
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• Original applicant-proposed labeling	In package
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (<i>indicate dates of reviews and meetings</i>)	NA
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	NA
• Applicant proposed	NA
• Reviews	NA
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	NA
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	None
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	10/30/02
• Pre-NDA meeting (indicate date)	none
• Pre-Approval Safety Conference (indicate date; approvals only)	none
• Other	none
❖ Advisory Committee Meeting	
• Date of Meeting	None
• 48-hour alert	None
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	None

Summary Application Review

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	9-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	None
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	None
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	None
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	In package
❖ Demographic Worksheet (NME approvals only)	None
❖ Statistical review(s) (indicate date for each review)	None
❖ Biopharmaceutical review(s) (indicate date for each review)	In package
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Na
• Bioequivalence studies	Na
CMC Information	
❖ CMC review(s) (indicate date for each review)	In package
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	Na
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable (*) Withhold recommendation
❖ Methods validation	() Completed () Requested (*) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	None
❖ Nonclinical inspection review summary	None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	None
❖ CAC/ECAC report	None
❖	

Appendix A to NDA/Efficacy Supplement Action Package Checklist

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

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (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.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).