CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-866

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06
See OMB Statement on Page 3.

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
21,866

NAME OF APPLICANT / NDA HOLDER
Otsuka Pharmaceutical Co., Ltd.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
ABILIFY

ACTIVE INGREDIENT(S)
ARIPIPRAZOLE

STRENGTH(S)
7.5mg/ml

DOSAGE FORM
Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number
5,006,528

b. Issue Date of Patent
4/09/1991

c. Expiration Date of Patent
10/20/2014

d. Name of Patent Owner
Otsuka Pharmaceutical Co., Ltd.

Address *(of Patent Owner)*
2-9 Kanda Tsukasa-cho, Chiyoda-ku

City/State
Tokyo, Japan

ZIP Code
101-8535

FAX Number *(if available)*

Telephone Number
81-3-3292-0021

E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address *(of agent or representative named in 1.e.)*
Otsuka America Pharmaceutical, Inc.

City/State
2440 Research Boulevard
Rockville, MD

ZIP Code
20850

FAX Number *(if available)*
(301) 212-8643

Telephone Number
(240) 683-3049

E-Mail Address *(if available)*
sheilac@otsuka.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☒ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☒ Yes ☐ No

FORM FDA 3542a (7/03)

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
4.2	Patent Claim Number *(as listed in the patent)*	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☐ Yes ☐ No	
4.2a	If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes	

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Sheila A. Cleary	11/14/2005

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Sheila A. Cleary	
Address Otsuka America Pharmaceutical, Inc.	City/State Rockville, MD
ZIP Code 20850	Telephone Number (240) 683-3049
FAX Number *(if available)* (301) 212-8643	E-Mail Address *(if available)* sheilac@otsuka.com

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INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://forms.psc.gov/forms/fdahtm/fdahtm.html*.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

PSC Media Arts (301) 443-1090 EF

Search results from the "OB_Rx" table for query on "021436."

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	10MG
Application Number:	021436
Product Number:	001
Approval Date:	Nov 15, 2002
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	15MG
Application Number:	021436
Product Number:	002
Approval Date:	Nov 15, 2002
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	20MG
Application Number:	021436
Product Number:	003
Approval Date:	Nov 15, 2002
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: View

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	30MG
Application Number:	021436

Product Number:	004
Approval Date:	Nov 15, 2002
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	TABLET; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	5MG
Application Number:	021436
Product Number:	005
Approval Date:	Nov 15, 2002
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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Division of Labeling and Program Support
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Orange Book Data Updated Through December, 2005

Patent and Generic Drug Product Data Last Updated: February 02, 2006

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Patent and Exclusivity Search Results from query on Appl No 021436 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021436	001	5006528	OCT 20,2014	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021436	001	NCE	NOV 15,2007
021436	001	I-437	SEP 29,2007
021436	001	I-401	AUG 28,2006

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
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Patent and Exclusivity Search Results from query on Appl No 021436 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021436	002	5006528	OCT 20,2014	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021436	002	I-401	AUG 28,2006
021436	002	I-437	SEP 29,2007
021436	002	NCE	NOV 15,2007

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Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021436	003	5006528	OCT 20,2014	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021436	003	NCE	NOV 15,2007
021436	003	I-401	AUG 28,2006
021436	003	I-437	SEP 29,2007

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Patent and Exclusivity Search Results from query on Appl No 021436 Product 004 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021436	004	5006528	OCT 20,2014	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021436	004	NCE	NOV 15,2007
021436	004	I-437	SEP 29,2007
021436	004	I-401	AUG 28,2006

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Patent and Exclusivity Search Results from query on Appl No 021436 Product 005 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021436	005	5006528	OCT 20,2014	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021436	005	I-401	AUG 28,2006
021436	005	I-437	SEP 29,2007
021436	005	NCE	NOV 15,2007

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Search results from the "OB_Rx" table for query on "021713."

Active Ingredient:	ARIPIPRAZOLE
Dosage Form;Route:	SOLUTION; ORAL
Proprietary Name:	ABILIFY
Applicant:	OTSUKA
Strength:	1MG/ML
Application Number:	021713
Product Number:	001
Approval Date:	Dec 10, 2004
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

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Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021713	001	5006528	OCT 20,2014	Y	Y	
021713	001	6977257	APR 24,2022	Y	Y	

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021713	001	NCE	NOV 15,2007
021713	001	I-401	AUG 28,2006
021713	001	I-437	SEP 29,2007

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EXCLUSIVITY SUMMARY

NDA # 21-866 SUPPL # not applicable HFD # 130

Trade Name ABILIFY

Generic Name aripiprazole

Applicant Name Otsuka Maryland Research Institute, Inc.

Approval Date, If Known See AP Letter Date

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(1)

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 (3)

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# 21436 Aripiprazole Tablets

NDA# 21713 Aripiprazole Oral Solution

NDA# 21729 Aripiprazole DISCMELT

2. Combination product. **NOT APPLICABLE**

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:

Agitation related to schizophrenia: Two Studies: CN138050 [#1] and CN138012 [#2].

Agitation related to bipolar disorder: One Study: CN138013. [#3]

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 - schizophrenia related agitation	YES ☐	NO ☒
Investigation #2 - schizophrenia related agitation	YES ☐	NO ☒
Investigation #3 - bipolar related agitation	YES ☐	NO ☒

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒
Investigation #3	YES ☐	NO ☒

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

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

Agitation related to schizophrenia: Two Studies: CN138050 [#1] and CN138012 [#2].

Agitation related to bipolar disorder: One Study: CN138013. [#3]

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 #60158	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #60158	YES ☒	! NO ☐
		! Explain:
Investigation #3		!
		!
IND #60158	YES ☒	! NO ☐
		! Explain:

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(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?

NOT APPLICABLE

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

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

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

YES ☐ NO ☒

If yes, explain:

Name of person completing form: Doris J. Bates, Ph.D
Title: Regulatory Project Manager
Date: See DFS Signature Page

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products
Date: See DFS Signature Page

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

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/s/

Doris Bates
9/19/2006 02:56:57 PM

Thomas Laughren
9/20/2006 04:23:58 PM

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-866 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: 30NOV2005 **Action Date:** 30SEP2006

HFD 130 **Trade and generic names/dosage form:** ABILIFY (aripiprazole) Injection

Applicant: Otsuka Maryland Research Institute

Therapeutic Class: agitation associated with schizophrenia or bipolar mania

Indication(s) previously approved: Schizophrenia, Bipolar Disorder (mania)

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

Number of indications for this application: 2

Indication #1: agitation associated with schizophrenia

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: Waiver requested in teleconference on December 29, 2005**
☐ **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:

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:

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:

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.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA ##-####
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

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

Indication #2: agitation associated with bipolar mania

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: Waiver requested in teleconference on December 29, 2005.**
- ☐ **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:

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:

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:

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

cc: **NDA ##-###**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Doris Bates
8/4/2006 04:10:13 PM
Pediatric waiver requested by firm on December 29, 2005.
Waiver granted as noted in FDA letter of
January 4, 2006.

Bates, Doris J

From: Bates, Doris J
Sent: Friday, August 04, 2006 4:10 PM
To: Bates, Doris J
Subject: FW: RE: NDA 21-866: Pediatric Waiver Request

This email message from BMS was followed by a telephone call in which it was confirmed that the company wished to pursue a full waiver. The waiver was granted on the basis of the company's concern regarding study power, for both the schizophrenia and bipolar agitation indications. T he FDA letter of January 4, 2006 documents the granting of this waiver.

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

-----Original Message-----
From: Susan H Behling [mailto:Susan.Behling@bms.com]
Sent: Thursday, December 29, 2005 3:35 PM
To: Bates, Doris J
Cc: 'Mallikaarjun, Kusuma'
Subject: Re: RE: NDA 21-866

Thanks for your response Doris. We need to meet to discuss this on our end and have a meeting scheduled Jan 10 if it can wait until then.

I noticed that other sponsors have committed to such studies but we have some concern that the numbers of pediatric patients may be so small that completing the studies would be difficult and hence a waiver might be more appropriate than a deferral. Do you know if the Division has a position on this for these indications (agitation in schizophrenia and bipolar mania)?

Sue

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/s/

Doris Bates
8/4/2006 04:19:13 PM
CSO
Waiver request received December 29, 2005.

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NDA NO. 21-866

ABILIFY® (ARIPIPRAZOLE) INJECTION

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred as of the Date of Debarment List Debarment List under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.

Susan H Behling

November 21, 2005

Susan H. Behling
Director, Global Regulatory Science
Bristol-Myers Squibb Company
5 Research Parkway, Dept 718
Signature 91 Building
Wallingford, CT 06492
(203) 677-3810

Certification Date

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA **21-866**	Efficacy Supplement Type ***Original NDA***	Supplement Number --Not applicable--	
Drug: ABILIFY (aripiprazole) Injection		Applicant: Otsuka Pharmaceutical Company Ltd.	
RPM: Bates		HFD-130	Phone # 6-2260
Application Type: **(X)** 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.)		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	not applicable
❖ User Fee Goal Dates	30SEP2006
❖ Special programs (indicate all that apply)	**(X)** 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	**(X)** Paid UF ID number 3006289
• 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 **(X)** No
• This application is on the AIP	**( )** Yes **(X)** No
• Exception for review (Center Director's memo)	not applicable
• OC clearance for approval	not applicable
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	

• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X)** Verified
• 505(b)(2) status?	**Not a 505(b)(2) application.**
❖ Exclusivity (approvals only)	
• 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.)	Summary: Tab F not applicable
• 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 #_____ **(X)** No
❖ Administrative Reviews (Project Manager, ADRA)	not applicable
[redacted]	
❖ Actions	
• Proposed action	**(X)** AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	none, first cycle
• Status of advertising (approvals only)	**(X)** Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X)** Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter **(X) Press Office Decision**
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	See Tab D and AP letter
• Most recent applicant-proposed labeling	See Tab D
• Original applicant-proposed labeling	See Tab D
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings	See Tab M and clinical, pharmtox, biopharm, CMC reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	not applicable
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	not applicable
• Applicant proposed	See Tab D
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See Tab R
• Documentation of discussions and/or agreements relating to post-marketing commitments	See Tab R
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See Tab R
❖ Memoranda and Telecons	See Tab S
❖ Minutes of Meetings --- See Tab S	

• EOP2 meeting	unspecified meeting type, held on 8 July 2004: no apparent pre-NDA meeting minutes on file
• Pre-NDA meeting	
• Pre-Approval Safety Conference	not applicable
• Other	filing meeting 03FEB2006
❖ Advisory Committee Meeting	
• Date of Meeting	Not applicable
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Not applicable
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	Tab J, Tab K
❖ Clinical review(s)	Tab L
❖ Microbiology (efficacy) review(s)	Not applicable
❖ Safety Update review(s)	Tab L
❖ Risk Management Plan review(s)	Not applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Tab G
❖ Demographic Worksheet	Not applicable
❖ Statistical review(s)	Tab N
❖ Biopharmaceutical review(s)	Tab O
❖ Controlled Substance Staff review(s) and recommendation for scheduling	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Tab I
• Bioequivalence studies	Not applicable
❖ CMC review(s)	Tab Q
❖ Environmental Assessment	
• Categorical Exclusion	Tab Q
• Review & FONSI	not applicable
• Review & Environmental Impact Statement	not applicable
❖ Microbiology (validation of sterilization & product sterility) review(s)	Tab Q
❖ Facilities inspection (provide EER report)	Tab Q **(X)** Acceptable ( ) Withhold recommendation
❖ Methods validation	Tab Q
❖ Pharm/tox review(s), including referenced IND reviews	Tab P
❖ Nonclinical inspection review summary	not applicable
❖ Statistical review(s) of carcinogenicity studies	not applicable
❖ CAC/ECAC report	not applicable

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/s/

Doris Bates
9/19/2006 03:01:06 PM
Action due date is September 30, 2006. See signature page of approval letter for action date.

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Bates, Doris J

From: Susan.Behling@bms.com on behalf of Susan H Behling [Susan.Behling@bms.com]
Sent: Monday, September 18, 2006 3:34 PM
To: Bates, Doris J
Cc: Mallikaarjun, Kusuma
Subject: 21-866 commitment

Hi Doris- Due to some technical difficulties with the e-mail system, I am sending a separate e-mail with your note embedded below. We commit to providing the requested technology report prior to December 30, 2006.

Best regards,

Sue

From: Bates, Doris J <doris.bates@fda.hhs.gov>
To: Susan.Behling@bms.com <Susan.Behling@bms.com>
CC: Mallikaarjun, Kusuma; Bates, Doris J <doris.bates@fda.hhs.gov>
Sent: Mon Sep 18 15:02:58 2006
Subject: RE: 21-866: Microbiology Phase 4 Commitment Request

Good afternoon Ms. Behling and Dr. Mallikaarjun:

We are requesting the following Phase 4 Commitment with respect to this NDA, for microbiology:

Please provide the following as a Phase 4 Commitment:
Global Pharmaceutical Technology Report PT-337039-R-232, issued July 15, 2004.
Specifically, this report should provide the data which resulted from the subject drug product container closure integrity testing.

Submission of report with requested data: On or before December 30, 2006.

We have proposed the same date for this report submission as has been agreed to for the prior Phase 4 Commitment, i.e. the labeling request for the vial.

If you can agree to this commitment request, please confirm agreement via reply e-mail for our records.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

"EMF <fda.hhs.gov>" made the following annotations.

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/s/

Doris Bates
9/18/2006 03:56:52 PM
CSO

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Bates, Doris J

From: Bates, Doris J
Sent: Monday, September 18, 2006 3:03 PM
To: 'Susan.Behling@bms.com'
Cc: 'Mallikaarjun, Kusuma'; Bates, Doris J
Subject: RE: 21-866: Microbiology Phase 4 Commitment Request
Importance: High

Good afternoon Ms. Behling and Dr. Mallikaarjun:

We are requesting the following Phase 4 Commitment with respect to this NDA, for microbiology:

Please provide the following as a Phase 4 Commitment:
Global Pharmaceutical Technology Report PT-337039-R-232, issued July 15, 2004.
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If you can agree to this commitment request, please confirm agreement via reply e-mail for our records.

Sincerely,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
9/18/2006 03:12:43 PM
CSO

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Bates, Doris J

From: Susan.Behling@bms.com on behalf of Susan H Behling [Susan.Behling@bms.com]
Sent: Wednesday, September 13, 2006 2:21 PM
To: Bates, Doris J
Cc: Mallikaarjun, Kusuma
Subject: Re: 21-866 Labeling Agreement: Carton Label and CMC Phase 4 Commitment Confirmations Request

Hi Doris- We agree to change the label and submit the vial label proposal or an explanation as to why it is not feasible by December 30, 2006 as per the language below.

Regards,

Sue

Bates, Doris J wrote:

>Good afternoon Susan and Kusuma
>
>Thank you for the labeling agreement and attached files, which are very helpful. Dr. Laughren has the information; given your acceptance of the changes explained by me on September 11, 2006, we appear to have reached final agreement on labeling at this time.
>
>We need you to confirm agreement to the carton label revision and to the Phase 4 commitment for CMC [vial label] in writing:
>
>"We have one change to request to your carton label: per 21 CFR 201.100 (5)iii, please change the statement on the carton label to read: 'It also contains tartaric acid, sodium hydroxide, and 150 mg/mL of sulfobutylether-ß-cyclodextrin.' "
>
>"We also request the following Phase 4 Commitment: In order to facilitate the proper I.M. dosing of aripiprazole injection, we request that you modify the immediate container label (vial label) to incorporate dosing information as presented in Table 6 of the proposed package insert. We ask that you submit a proposal for modified vial labeling to include this information, or an explanation as to why the requested modification is not feasible. We request that this be submitted no later than December 30, 2006. Since this is a Phase 4 commitment and prior approval of the labeling revisions [if feasible] will be required, we do not object to your using the currently proposed vial labeling for product launch and up until such time as revised labeling is approved."
>
>A reply e-mail including this message in the thread, and accepting the above language, will suffice.
>
>Thank you again,
>
>Doris J. Bates, Ph.D.
>Regulatory Project Manager
>Division of Psychiatry Products
>Office of Drug Evaluation I
>Center for Drug Evaluation and Research
>Food and Drug Administration
>White Oak Federal Research Center
>
>
>
>

"EMF <fda.hhs.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/

Doris Bates
9/13/2006 03:36:11 PM
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: **July 21, 2006**

To: **Doris Bates**
Division of Psychiatry Products, HFD-130

From: **Bob Dean, Regulatory Review Officer**
Iris Masucci, Pharm.D., Label Reviewer

Subject: **NDA 21-866**
DDMAC Labeling comments for Abilify

DDMAC has reviewed the proposed PI for Abilify and offer the following comments:

Clinical Pharmacology - Proposed Intramuscular Administration (page 3)

- [redacted]

Clinical Studies - Agitation Associated with Schizophrenia or Bipolar Mania (page 8)

- (2) "At 2 hours post-injection, aripiprazole for injection was statistically superior to placebo in the PANSS Excited Component and on the CGI-I scal[redacted]

- (3) "At 2 hours post-injection, both doses were statistically superior to placebo in the PANSS Excited Component [redacted]

[redacted]

- "The 10-mg aripiprazole dose was superior to placebo on all five of the individual items of the PANSS Excited Component; the 5-mg and 15-mg doses were statistically superior to placebo on three of the five individual items."

Did the study design and data analysis plan allow for analyses of the individual questionnaire subscales? If not, we recommend their deletion. Note that similar statements are made for each of the three studies presented here.

Indications and Usage - Agitation Associated with Schizophrenia or Bipolar Mania (page 9)

- "Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care (eg, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior), leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation."

DDMAC's concern is with the use of the word "immediate." The implication here is that all products used in this setting, including Abilify, have an "immediate" onset of action. Is this accurate, given that the evaluations in the Abilify studies were at 2 hours post-dose, and given what is know about other drugs used this way (e.g., benzodiazepines, haloperidol)?

Adverse Reactions – Oral Administration (page 22 & 24)

Dosage and Administration – Intramuscular Injection (page 32)

- "The efficacy of aripiprazole injection in controlling agitation in these disorders was demonstrated in a dose range of [redacted]mg to 15 mg. The recommended dose in these patients is [redacted]mg. A lower dose of [redacted]mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given."

This discussion of recommended dosing is somewhat confusing. Are we recommending 15 mg as an initial dose? If not, the first sentence (giving the dosage range of 5-15 mg) should be deleted. It would be adequate to recommend 10 mg for most patients, with the option of 5 mg for some. This is further confused by the sentence that 2 doses can be given, up to a total of 30 mg/day. Please clarify what is intended here.

- "To administer [redacted] Abilify Injection, draw up [redacted] solution into the syringe [redacted]."

These instructions are confusing and incomplete. Are we trying to say that the entire vial contents should first be drawn up into a syringe, and then expelled until the needed dose remains? [redacted] Please clarify these preparation and administration instructions.

How Supplied (page 33)

- "Abilify (aripiprazole) Injection for intramuscular use is available as a ready-to-use, [redacted] mg/mL solution in clear, Type I glass vials as follows: [redacted] mg/mL single-dose vial"

As noted under Dosage and Administration, the total volume contained in the vial is necessary here for completeness. To give only the concentration of the solution is inadequate.

Thank you for this opportunity to provide comments. If you have any questions, please contact Bob Dean at (301) 796-2215 or robert.dean@fda.hhs.gov

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/s/

Robert Dean
8/24/2006 11:32:53 AM

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MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology WO 22, Mailstop 4447, HFD-420 Center for Drug Evaluation and Research

To: Thomas Laughren, MD
Director, Division of Psychiatry Products
HFD-130

Through: Linda Kim-Jung, PharmD, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: August 10, 2006

Subject: OSE Review# 06-0002-1, Abilify (Aripiprazole Injection), 9.75 mg/1.3 mL; NDA 21-866

This memorandum is in response to a July 26, 2006 request from your Division for a review of the revised container labels, carton and insert labeling for Abilify injection. DMETS initially reviewed the labels and labeling of Abilify injection in ODS consult 06-0002 dated March 23, 2006. In that review, several areas of improvement were identified and those areas of concern were communicated to the sponsor in a letter dated June 6, 2006. The revised labels and labeling submitted in response to DMETS' recommendations are the subject of this review.

The sponsor has addressed most of our recommendations. However, we note the following additional area that can be improved.

Package Insert Labeling

Dosage and Administration Section, Administration of Abilify Injection Subsection: Remove the trailing zero presented in table 6. The use of trailing zeroes is specifically listed as a dangerous abbreviation, acronym, or symbol. The FDA in conjunction with the ISMP launched a campaign on June 14, 2006 to reduce medication mistakes caused by unclear medical abbreviations. Thus in order to comply with these recommendations, we request all trailing zeroes be removed from the insert.

In summary, DMETS recommends implementation of the container label revision outlined above in order to minimize potential user error. If you have further questions or need clarification, please contact Diane Smith at 301-796-0538.

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/s/

Kristina Arnwine
8/11/2006 04:35:51 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/11/2006 04:42:23 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: OSE/DMETS

FROM: HFD-130

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
July 26, 2006	42,776 & 60,158	21-866	new NDA labeling amendment	July 13, 2006 Received July 14, 2006 In EDR July 20, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE:
Aripiprazole intramuscular injection		tx agitation associated with manic episodes or with Schizophrenia	August 14, 2006 Dr. Temple's briefing is Aug 30 06 10 month due date Sep. 30 '06

NAME OF FIRM: Otsuka America and Bristol-Myers Squibb.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Link to EDR: May not be live in DFS rendering. This is for entire EDR submission. \\Cdsesub1\n21866\N_000\2006-07-13

This is the response to our IR letter of June 6, 2006 regarding the proposed labeling for the IM dosage form. A hard copy of the cover letter, container and carton artwork, and the side by side presentation for the package insert only is attached to the hard copy of this consult for reference. The EDR submission also includes additional files [WORD file of proposed labeling, labeling history, etc.].

SIGNATURE OF REQUESTER see DFS signature	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
7/26/2006 06:17:37 PM
Please link consult review to N 000 (BL) submission dated 13-JUL-2006.

Thomas Laughren
7/27/2006 08:15:21 AM

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660 (203) 677-6000

AMENDMENT to
NDA 21-866 ABILIFY® (aripiprazole) Injection

July 13, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Laughren:

Reference is made to Submission No. 223 (dated November 16, 1999) and to Submission No. 233 (dated January 4, 2000) to IND 42, 776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co. Ltd. (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA 21-866 for ABILIFY Injection, submitted November 29, 2005 and to the FDA Information Request Letter of June 6, 2006. In that letter, the Division requested changes to the proposed dosing instructions and product description for this formulation.

This amendment is submitted to address the FDA's Information Request Letter of June 6, 2006. To address the concerns about an accurate description and precision of the dosing instructions in labeling, we propose to change the recommended dose of ABILIFY Injection to 9.75 mg, administered as a 1.3 mL injection of the 7.5 mg/mL solution and that the effective dose range would be stated as 5.25 mg (0.7 mL)- 15 mg (2 mL). In addition, we propose to change the vial and carton label to describe the product as a 9.75 mg/1.3 mL vial and propose that the 7.5 mg/mL concentration be given less prominence. The proposed revisions to the USPI, cartons and labels are provided herewith for your review and input.

One recommendation in the June 6, 2006 letter was to remove reference to the 'ready to use' statement on the proposed labels. We believe this is important information to include on the labels in order to differentiate this product from concentrates and other products, which according to USPI, could also be named as 'Injection' formulations, but require further dilution or reconstitution, unlike our product. We believe this description is useful and will help to avoid unnecessary questions from health care providers, especially given that other products used in this same clinical setting often require further dilution or reconstitution.

We would be happy to discuss these changes with you at your convenience. If you have any questions or concerns, please contact the undersigned at 203-677-3810 or via e-mail at Susan.Behling@bms.com.

Sincerely,

Susan H. Behling, Director
Global Regulatory Science

CC: Dr. Kusuma Mallikaarjun, Sr. Director, OMRI

/lh

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Electronic Media Information

July 13, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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 2 MB and is being provided on 1 CD-ROM disk to the Central Document Room. There are 11 files and 1 folder. The files have been checked for viruses using McAfee Virus Scan Software (Version 8.0*i*) and no viruses were detected.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-866

Otsuka Maryland Research Institute
Attention: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs / Abilify
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your November 29, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Injection.

We also refer to your submissions dated January 10, 2006; January 30, 2006, May 9, 2006, May 11, 2006, and May 25, 2006.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our review of your NDA.

1. The CMC information for Captisol was referenced to the DMF # [redacted] DMF # [redacted] was reviewed and found to be deficient and the deficiencies have been conveyed to the DMF holder.

2. In the product specifications, the HPLC identification test based on the retention time match is not a specific test. You can either make the IR (IR-ATR) identification test a routine control test or include the UV spectrum together with the HPLC identification test to make the identification test a specific test.

3. In the product specifications, please include a test and an acceptance criterion for subvisible (microscopic) particles to control any potential subvisible insoluble particles, as per USP <788>.

4. In the product specifications, please include a test and an acceptance criterion for osmolarity or provide justification for the absence of such test.

5. The impurity levels (130 weeks) of [redacted] for all [redacted] batches ranged from [redacted] to [redacted]. The accelerated stability data (26 weeks) indicated that the highest impurity level of [redacted] was [redacted]. Therefore, based on the results of stability studies, please tighten the limit for the impurity level of [redacted] It is noted that [redacted] is an active metabolite but it is necessary to control the impurity level of [redacted] for quality control of the product.

6. The highest total impurity level observed (from the long term stability studies and accelerated stability studies) was [redacted]. Therefore, based on the results of stability studies, please tighten the limit for the total impurity level.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-1040, or contact her via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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Thomas Laughren
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DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

INFORMATION REQUEST LETTER

NDA 21-866

Otsuka Maryland Research Institute
Attention: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs / Abilify
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your November 29, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Injection.

We also refer to your submissions dated January 10, 2006; January 30, 2006, May 9, 2006, May 11, 2006, and May 25, 2006.

We are reviewing the Clinical, Chemistry, Manufacturing and Controls, and Labeling sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our review of your NDA.

General Comment - Labels and Labeling, Injection Concentration, Total Drug Content, Recommended Dose and Dosing Instructions

1. We are concerned about the way in which the concentration of aripiprazole, and /or the total aripiprazole content, are presented on the immediate container label, on the carton label, and in the package insert.

- The total drug content of each vial of Abilify Injection is approximately 10 mg [actual amount is 9.975 mg] in 1.33 mL [excluding overfill], with a milligram per milliliter concentration of 7.5 mg/mL.
- The immediate container and carton labeling and the package insert [DESCRIPTION, HOW SUPPLIED] list the injection concentration as [redacted] mg/mL, with this quantity prominently displayed.
- The immediate container label and carton labeling do not list the total drug content per vial at all, and the total volume of fill is listed as 1.3 mL; this is presented with much less prominence in the labels than the milligram per milliliter concentration is given.

These discrepancies are very likely to give practitioners an incorrect impression that each vial contains 7.5 mg of Abilify, rather than the larger amount noted above. This increases the potential for medication errors. Post marketing evidence has shown that when the total drug content is not included on the labels and labeling, practitioners assume that the amount listed on

the labels and labeling (i.e. [redacted] ng/mL) is the total amount included in the vial/syringe. The assumption that the vial only contains 7.5 mg of Abilify may lead to overdoses.

2. We are also concerned about the degree of approximation a practitioner must perform in order to administer Abilify Injection at the recommended doses. The recommended dose in the proposed indications [DOSING AND ADMINISTRATION: Agitation Associated with Schizophrenia or Bipolar Mania] is [redacted] mg. Single doses of [redacted] nd 15 mg are also discussed, as well as cumulative doses, two hours apart, up to a total daily dose of 30 mg.

- The 7.5 mg/mL injection concentration makes administration of accurate [redacted] mg an[redacted] ng doses challenging for the practitioner. Calculating the accurate dosing volume will be difficult. To administer an accurate [redacted] mg dose, the practitioner would need to withdraw and inject [redacted] L from the vial. To administer a [redacted] mg dose, the practitioner would need to approximate an injection volume of [redacted] mL. These volumes will be difficult to obtain using a commercially available medical syringe.
- The instructions in the package insert direct practitioners to administer the recommended [redacted] mg dose as an injection of [redacted] L; however, as noted, this volume will result in an actual dose of less than [redacted] mg. The package insert indicates that this volume of injection actually contains less than the recommended dose.
- There are no dosing instructions on the vial or carton label. This, combined with the size of the [redacted] mL concentration displayed on these labels, again presents a risk of medication errors.

We realize that differences of the magnitude described here, in estimated single doses of aripiprazole, are unlikely to be of any clinical significance. However, the product labeling is legally required to express an accurate statement of the quantity of contents in the package, and the dosing instructions should correlate with the stated quantity of contents. It should be possible for a practitioner to administer the recommended doses routinely, with precision and accuracy, by referring to this information.

Based on the above issues, we are requesting that you submit revised labeling for this product to eliminate the discrepancies among the labels, to assure that the net quantity of contents is prominently displayed on the container and carton labels, and to provide instructions for dosing that utilize easily measured volumes for injection and accurately cite the dosages delivered in these volumes.

We have the following recommendations for you to consider. We recognize, however, that certain of these recommendations may be difficult to implement. We would be happy to further discuss with you how best to resolve these issues.

GENERAL RECOMMENDATIONS

1. As discussed above, the total drug content in each vial is not 7.5 mg; to avoid the risk of medication errors, revise the total drug content statement to include the total amount of drug per total volume, followed by the milligram per milliliter concentration.

For example:

X mg/Y mL
(7.5 mg/mL)

where X is the actual total drug content per vial, and Y is the prespecified fill volume per vial [without overage], respectively.
2. Revise the statement, [redacted] to read, "For Intramuscular Use Only." We do not recommend the use of abbreviations on labels and labeling, in order to prevent medication errors due to misinterpretation.
3. Revise the statement [redacted] to read "Single use container. Discard any unused portion."
4. Remove the statement, [redacted] from labels and labeling.

VIAL LABEL
1. See General Recommendations above.
2. The color scheme currently used for "7.5 mg/mL" (i.e. blue font on light blue background) does not provide adequate contrast and makes the information difficult to read. When you change the declared net quantity of contents, as requested above, change the color scheme to provide more contrast and make the information easier to read.
3. Include a total volume statement (i.e. 1.33 mL vial) at the top of the label.
4. Relocate the "Rx only" to the bottom portion of the vial in order to increase the prominence of the "Rx only" statement as well as the product strength and concentration.

CARTON LABELING
1. See General Recommendations above.
2. Revise the [redacted] statement to read, "Usual Dosage: See package insert," per 21 CFR 201.55.

PACKAGE INSERT
1 See General Recommendations above.
2. Revise the statement of strength throughout the insert labeling to read X mg/ Y mL (with the numerical quantities for X and Y defined as described above) instead of [redacted] ng/mL.
3. In the DESCRIPTION Section, Third Paragraph:
Revise the statement, "Abilify Injection is available in single-dose vials…" to read, [redacted]

4. In the DOSAGE AND ADMINISTRATION Section, Administration of Abilify Injection Sub-Section:
a. Revise the statement, [redacted] to read, [redacted] As noted above, however, at the current concentration, it will be difficult to measure accurate volumes to administer the recommended doses of [redacted]
b. Delete the statement [redacted] as it will no longer be necessary after revision of labels and labeling to present accurate dosing information.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-1040, or contact her via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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Thomas Laughren
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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE:

TO: Doris J. Bates, Ph.D,Reg ulatory Project Manager
Earl D. Hearst, M.D., Clinical Revie wer
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Sherbet Samuels, R.N., M.P.H.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-866

APPLICANT: Otsuka Pharmaceutical Company, Ltd.

DRUG: Abilify® (Aripiprazole)

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed.

CONSULTATION REQUEST DATE: February 3, 2006

DIVISION ACTION GOAL DATE: September 30, 2006

PDUFA DATE: September 30, 2006

I. BACKGROUND:

Abilify® (Aripiprazole) is approved as tablets and solution for oral administration for the treatment of schizophrenia and treatment of acute manic and mixed episodes associated with bipolar disorder. The intramuscular formula of the drug was studied in protocols CN138012, CN138013, and CN138050 for the treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare. Dr. Tam K. Tran-Johnson's site was selected for inspection due to large enrollment, and without this site the 5 mg arm of study # CN138050 is not statistically significant. Dr. Bum Soo Lee's and Dr. Michael Lesem's sites were selected for inspection due to large enrollments in both study numbers CN138012 and CN 1388013. The following protocols were audited:

#CN138012 entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Haloperidol, or Placebo in the Treatment of Acutely Agitated Patients with a Diagnosis of Schizophrenia or Schizoaffective Disorder."
#CN138013 entitled "A Randomized, Double-Blind Comparison of the Efficacy and Safety of Aripiprazole Intramuscular Formula, Lorazepam, or Placebo in the Treatment of Acutely Agitated Patients Diagnosed with Bipolar I Disorder, Manic or Mixed."
#CN138050 entitled "A Randomized, Double-Blind, Dose-Ranging Study of Intramuscular Aripiprazole in the Treatment of Acute Agitation in Patients with a Diagnosis of Schizophrenia, Schizoaffective, or Schizophreniform Disorder."

Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #. if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
PharmD PsyD/40		CN138050	Mar.21-29, 2006	Apr. 12, 2006	NAI
/37		CN138012	Mar. 21-29, 2006	Apr. 20, 2006	NAI
/31		CN138013	Mar. 21-29, 2006	Apr. 20, 2006	NAI
/36		CN138012	Mar. 20-29, 2006	May 12, 2006	NAI
/30		CN138013	Mar. 20-29, 2006	May 12, 2006	NAI

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 from regulations. Data unreliable.

A. Protocol # CN138050

1.

a. What was inspected: Dr. enrolled 25 subjects. The inspection encompassed an audit of all subjects' records. Primary endpoint efficacy data were verified for all subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued.

d. Data from this site are acceptable.

B. Protocol # CN138012

1.

a. What was inspected: enrolled 30 subjects. The inspection encompassed an audit of 16 subjects' records. Primary endpoint efficacy data were verified for 16 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued.

d. Data from this site are acceptable.

2. [redacted]

a. What was inspected: Dr. [redacted] enrolled 29 subjects. The inspection encompassed an audit of 15 subjects' records. Primary endpoint efficacy data were verified for 15 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued.

d. Data from this site are acceptable.

C. Protocol # CN138013

1. [redacted]

a. What was inspected: [redacted] enrolled 21 subjects. The inspection encompassed an audit of 11 subjects' records. Primary endpoint efficacy data were verified for 11 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued.

d. Data from this site are acceptable.

2. [redacted]

a. What was inspected: Dr. [redacted] enrolled 23 subjects. The inspection encompassed an audit of 12 subjects' records. Primary endpoint efficacy data were verified for 12 subjects.

b. Limitations of inspection: none

c. General observations/commentary: No deviations from FDA regulations were observed. Form FDA 483, Inspectional Observations, was not issued.

d. Data from this site are acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As noted above, inspection of Drs. [redacted], and [redacted] revealed that these investigators appear to have conducted the studies noted in accordance with FDA regulations. Data from these three clinical investigators are acceptable in support of NDA 21-866.

{See appended electronic signature page}

Sherbet Samuels, R.N., M.P.H.

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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

/s/

Sherbert Samuels
6/5/2006 12:44:25 PM
CSO

Constance Lewin
6/5/2006 01:45:36 PM
MEDICAL OFFICER

Appears This Way
On Original

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660

May 25 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: AMENDMENT to NDA #21-866 for ABILIFY® (aripiprazole) Injection

Dear Dr. Laughren,

Reference is made to the approved NDA #21-436 for ABILIFY Tablets, and to Submission No. 223 (dated November 16, 1999) for IND #42,776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co., Ltd., (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA #21-866 for ABILIFY (aripiprazole) Injection, 7.5 mg/mL, which was submitted to the Agency by BMS on behalf of OPC on November 30, 2005.

In follow-up to the May 18, 2006 teleconference with Drs. Andre Jackson and Ray Baweja, Office of Clinical Pharmacology, we are providing in this submission matched plasma concentration/QT datasets used in the linear regression analyses presented in the PK/QT report of Study CN138050 (DCN 930008544). Also provided are the program codes and variable definitions, as well as a summary of our responses to questions from Dr. Jackson regarding the data analyses. This information was also sent informally to Dr. Jackson via e-mail on May 23, 2006.

If you have any questions or concerns, please contact me at 203-677-3810 or via email at Susan.Behling@bms.com.

Sincerely,

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

cc: Kusuma Mallikaarjun, Ph.D., Sr. Director, Regulatory, OMRI

Electronic Media Information

May 25, 2006

AMENDMENT to NDA No. 21-866 ABILIFY (aripiprazole) Injection

The archival copy of the Content of Labeling for this submission is being provided electronically in lieu of paper as per the Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format, dated December 11, 2003, 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 1.44 MB and is being provided on 1 CD-ROM disk to the Central Document room. There are approximately 40 files and 15 folders. The files have been checked for viruses using virus definitions available on May 19, 2006 with McAfee VirusScan Software (Version 8.0i) and no viruses were detected.

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660

May 11, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: AMENDMENT to NDA #21-866 for ABILIFY® (aripiprazole) Injection

Dear Dr. Laughren,

Reference is made to the approved NDA #21-436 for ABILIFY Tablets, and to Submission No. 223 (dated November 16, 1999) for IND #42,776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co., Ltd., (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA #21-866 for ABILIFY® (aripiprazole) Injection, 7.5 mg/mL, which was submitted to the Agency, by Bristol-Myers Squibb Company on behalf of Otsuka Pharmaceutical Company, Ltd., on November 30, 2005.

In follow-up to the telephone conversation of May 1, 2006 between the undersigned and Dr. Andre Jackson, Office of Clinical Pharmacology, provided herewith are responses to questions regarding the analyses presented in the study report entitled "'Assessment of the Relationship Between Aripiprazole and Dehydo-aripiprazole Plasma Concentrations and QTc Changes from Baseline in Study CN138050 (DCN 930008544)". This study report was included in the Human Pharmacology and Bioavailability/Bioequivalence (Item 6) section of this NDA. Please note that these responses were previously sent to Dr. Jackson via e-mail on May 10, 2006.

If you have any additional questions or concerns, please do not hesitate to contact me at 203-677-3810 or via e-mail at Susan.Behling@bms.com.

Sincerely,

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

cc: Kusuma Mallikaarjun, Ph.D., Sr. Director, Regulatory Affairs, Otsuka Maryland Research Institute

Doris Bates, Ph.D., FDA/CDER Regulatory Management Officer

Dr. Andre Jackson, Office of Clinical Pharmacology

Electronic Media Information

May 11, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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 1.0 MB and is being provided on 1 CD-ROM disk to the Central Document Room. There are 28 files and 12 folders. The files have been checked for viruses using McAfee Virus Scan Software (Version 8.0*i*) and no viruses were detected.

Bristol-Myers Squibb Company

5 Research Parkway Wallingford, CT 06492-7660

May 9, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: AMENDMENT to NDA #21-866 for ABILIFY® (aripiprazole) Injection

Dear Dr. Laughren,

Reference is made to the approved NDA #21-436 for ABILIFY Tablets, and to Submission No. 223 (dated November 16, 1999) for IND #42,776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co., Ltd., (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA #21-866 for ABILIFY® (aripiprazole) Injection, 7.5 mg/mL, which was submitted to the Agency, by Bristol-Myers Squibb Company on behalf of Otsuka Pharmaceutical Company, Ltd., on November 30, 2005.

In follow-up to the e-mail request of May 5, 2006 from Dr. Andre Jackson, Office of Clinical Pharmacology, provided herewith are validation reports of the analytical methods for measurement of aripiprazole plasma concentrations in support of the 4 human pharmacology studies included in this NDA (Studies CN138017, CN138132, CN138016 and CN138050).

For study CN138016, the validation method is included in the report with DCN 920010507; all study standard and QCs are summarized in the PK CSR in Tables S11.1.1A through S11.1.2B. The dates of the runs do not appear to be reported in the CSR but they span the range 17 Jan 2001 through 2 March 2001 (Source: Study CN138-016 in Watson LIMS).

For study CN138017 the validation method is described in the report with DCN 920010810; all study standard and QCs are summarized in the PK CSR in Tables S11.1.1.1A through S11.1.1.2B. The dates of each run are also in these tables and span the range 27 June 2000 through 15 Jan 2001.

CN138032 references two validation reports (analytical method for aripiprazole/dehydro-aripiprazole, DCN 930004340 and a validation report for lorazepam, DCN 930005600). All study standard and QCs are summarized in the PK CSR in Tables S11.1.1A through S11.1.3B. The dates of each run are also in these tables and span the range 25 Mar 2004 through 26 Aug 2004 (aripiprazole/dehydro-aripiprazole) and 2 Apr 2004 through 2 Aug 2004 (lorazepam).

The report for CN138050 (DCN 930008544) gives an overview of the analytical methods in Section 7.1.2 and references two validation reports (DCN 920010507 and 930004340). Individual run Std and summary QC data are provided for each analyte in Supp. Tables S10.1.1.1A through

S10.1.2.1B. This report does not provide individual run standard and QC concentrations. These can be provided to the reviewer in a separate submission if needed.

If you have any additional questions or concerns, please do not hesitate to contact me at 203-677-3810 or via e-mail at Susan. Behling@bms.com.

Sincerely,

Susan H Behling

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

cc: Kusuma Mallikaarjun, Ph.D., Sr. Directory, Regulatory Affairs, Otsuka Maryland Research Institute
Keith Kiedrow, R.Ph., FDA/CDER Regulatory Management Officer
Dr. Andre Jackson, Office of Clinical Pharmacology

Electronic Media Information

May 9, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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 6.4 MB and is being provided on 2 CD-ROM disks to the Central Document Room. There are 34 files and 12 folders. The files have been checked for viruses using McAfee Virus Scan Software (Version 8.0*i*) and no viruses were detected.

MINUTES: FILING MEETING
NDA 21-866
Otsuka Pharmaceutical Co., Ltd: ABILIFY (aripiprazole) Injection, 7.5 mg/mL
Indications: (1) treatment of agitation in schizophrenia patients
(2) treatment of agitation in bipolar mania patients

Meeting Date/Time/Place: Wednesday, January 25, 2006; 3:00 P.M.: White Oak CR 4270

Reviewer Roster:

Discipline	**TL/Reviewer**
Regulatory Project Management:	Bates
Clinical:	Andreason/Hearst
Clinical Safety:	N/A
Controlled Substances:	N/A
DDRE:	Birdsong/Saini
Statistical:	Yang/Chen (Y.F.)
Pharmacology:	Rosloff/Tabacova
Statistical Pharmacology:	--
Chemistry:	Sood/Oliver/Lu (Donghao)
Environmental Assessment (if needed):	Lu
Biopharmaceutical:	Baweja/Kumi/Jackson [post-filing]
Microbiology, sterility:	Consult sent by CMC Reviewer
Microbiology, clinical (for antimicrobial products only):	--
DSI:	Samuels (Sherbet)
DDMAC:	Gray (Catherine)

Other Consults:	Micro, sterility (i.m. injection dosage form) sent By CMC
505(b)(2)?	NO
LETTER DATE:	29NOV2005
STAMP DATE:	30NOV2005
FILING DATE:	29JAN2006
74-DAY LETTER ISSUE DATE:	12FEB2006 [10FEB2006, Friday]
DATE OF MIDCYCLE MEETING:	26APR2006 3:00 P.M.
BRIEFING FOR OFFICE DIRECTOR:	15AUG2006 1:00 P.M.

ACTION LETTER SIGNATORY AUTHORITY: ***Division Director*** or Office Director

DATE REVIEWS ARE DUE:

To Team Leaders:	12AUG2006
To Clinical Team Leader:	29AUG2006
To Division Director:	09SEP2006
To Office Director:	not applicable

~~~PDUFA GOAL DATE IS 30SEP2006~~~

Meeting Details:

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

CLINICAL FILE X REFUSE TO FILE
- Clinical site inspection needed? YES X NO
- Domestic or foreign? Domestic X Foreign
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- Is application affected by AIP N/A X YES NO
- Has Division made a recommendation regarding exception to the AIP to permit review based on medical necessity or public health significance? N/A X YES NO
- Summarize Clinical Issues. See attached summary
- Clinical Questions for 74-Day Letter? N/A YES **NO**
- When Are Questions Due to RPM?
- Were Questions Provided on time?

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE
- Questions for 74-Day Letter?
- When Are Questions Due to RPM?
- Were Questions Provided on time?

STATISTICS N/A FILE X REFUSE TO FILE
- Questions for 74-Day Letter? See attached summary
- When Are Questions Due to RPM?
- Were Questions Provided on time?

BIOPHARMACEUTICS N/A FILE X REFUSE TO FILE
- Biopharm. inspection needed? YES NO X
- Domestic or foreign? Domestic Foreign
- Questions for 74-Day Letter?
- When Are Questions Due to RPM?
- Were Questions Provided on time?

PHARMACOLOGY N/A FILE X REFUSE TO FILE
- GLP inspection needed? YES NO X
- Carc Studies? [Separate statistical consult?] YES NO X
- Date of CAC
- Questions for 74-Day Letter? NO
- When Are Questions Due to RPM?
- Were Questions Provided on time?

CHEMISTRY N/A FILE X REFUSE TO FILE
- Establishment(s) ready for inspection? YES X NO
- Microbiology consult needed? YES X NO
- Other expert consult needed? YES NO X
- Methods validation needed? YES X NO
- Questions for 74-Day Letter? YES NO X
- When Are Questions Due to RPM?
- Were Questions Provided on time?

ELECTRONIC SUBMISSION:	Available to Team December 7, 2005
Format:	TOC is NDA format, contents are CTD format
ELIPS labeling included?	SPL provided
Any comments:	SPL interface not functional as of 29-DEC-05. WORD files also provided by firm.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

	The application is unsuitable for filing. See attached summary of deficiencies.

XX	The application, on its face, appears to be sufficiently well-organized and indexed to permit filing. This decision does not guarantee that no deficiencies will be identified during review. It also does not guarantee a first cycle approval action.

	No filing issues identified. ~~ See comments below
	Filing issues to be communicated by Day 74 (see above for date due to RPM).

ACTION ITEMS:

1. Statistics request for datafiles to be conveyed to company immediately following meeting.
2. DSI consult to be completed based on sites to be identified post meeting.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

Additional Comments

CMC: **EA was missing from submission, this was identified and requested by Dr. Bates. EA was provided as an amendment to the file prior to the filing meeting.**

Clinical: **Patient population included patients with schizoaffective and schizophreniform disorders as well as schizophrenia and bipolar disorder. Post meeting it was confirmed that the applicant was advised to conduct efficacy analyses on the identified schizophrenic population specifically in order to support the agitation claim for schizophrenia. [During the meeting it was clarified that no claims were being made for agitation in schizoaffective or schizophreniform disorders.]**

Stats: **One potentially problematic site was identified [San Diego, Dr. Tran-Johnson.] This site will be included in the DSI inspection for this NDA. Applicant will be requested to provide all of the SAS programs used to produce all efficacy results for all pivotal studies. If these programs have been submitted as part of the original NDA, the applicant will be requested to provide details of their location in the electronic submission. This request will be made immediately following the meeting.**

Biopharm: **Dr. Kumi will complete the initial filing assessment, and post-filing the NDA will be reassigned to Dr. Andre Jackson.**

Pediatrics: **The initial submission did not address PREA. Dr. Bates followed up with the applicant and a request for waiver was submitted on 29DEC2005. The waiver was granted in the acknowledgement letter sent on 04JAN2006.**

Labeling: **SPL was included.**

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

/s/

Doris Bates
2/3/2006 02:14:23 PM

Appears This Way
On Original

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-866

Otsuka Maryland Research Institute
Attention: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs / Abilify
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your November 29, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify® (aripiprazole) Injection.

We also refer to your submission dated January 10, 2006; to our secure electronic mail communication of January 26, 2006; and to your secure reply of January 27, 2006.

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 29, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we did not identify any potential review issues beyond the question already conveyed in our January 26, 2006 communication. There are therefore no filing review issues to be communicated at this time.

Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our substantive review of your submission.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-1040, or contact her via secure electronic mail at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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
2/7/2006 02:05:56 PM

Appears This Way
On Original

DSI CONSULT: Request for Clinical Inspections

Date: February 3, 2006

To: Constance Lewin, M.D., Acting Branch Chief, GCP1, HFD-45
Joanne L. Rhoads, M.D., Director, HFD-45

From: Doris J. Bates, Ph.D., Regulatory Project Manager, HFD-130
Division of Psychiatry Products
(with concurrence)

Subject: **Request for Clinical Site Inspections**
NDA 21-866
Otsuka Pharmaceutical Company, Ltd.
Abilify (aripiprazole) injection, 7.5 mg/mL

Protocol/Site Identification:

As agreed, the following protocols/sites essential for approval have been identified for inspection. There are two indications in this NDA, and therefore all sites are of equal priority.

Site # (Name and Address)	Protocol #	No. of Subjects	Indication
Tam K. Tran-Johnson, Pharm.D, Psy.D. California Neuropsychopharmacology Clinical Research Institute, LLC 9466 Black Mountain Rd, Suite 100 San Diego, CA Note: Large enrollment: without this site, the 5 mg arm is not significant, per statistician.	CN138050 [Center 040]	25	agitation associated with schizophrenia
Bum Soo Lee, MD. Anaheim Research Center, LLC 1801 West Romney Drive Anaheim, CA 92801 Note: Large enrollment for both studies	CN138012 [Center 036]	30	agitation associated with schizophrenia
	CN138013 [Center 030]	24	agitation associated with bipolar disorder
Michael Lesem, MD Calghorn –Lesem Research Clinic, LLC 6750 West Loop South, Suite 1050 Bellaire, TX 77401 Note: Large enrollment for both studies	CN138012 [Center 037]	31	agitation associated with schizophrenia
	CN138013 [Center 031]	23	agitation associated with bipolar disorder

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by July 28 2006. We intend to issue an action letter on this application by September 30, 2006. The PDUFA due date for this application is September 30, 2006.

Should you require any additional information, please contact Doris J. Bates, Ph.D., at 301-796-1040 or via email at doris.bates@fda.hhs.gov.

Concurrence: (see attached electronic signature page)

Paul J. Andreason, M.D., Medical Team Leader

Thomas P. Laughren, M.D., Division Director (for foreign inspection requests only)

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

/s/

Doris Bates
2/3/2006 03:23:05 PM

Paul Andreason
2/5/2006 04:17:28 AM

MINUTES: FILING MEETING
NDA 21-866
Otsuka Pharmaceutical Co., Ltd: ABILIFY (aripiprazole) Injection, 7.5 mg/mL
Indications: (1) treatment of agitation in schizophrenia patients
(2) treatment of agitation in bipolar mania patients

Meeting Date/Time/Place: Wednesday, January 25, 2006; 3:00 P.M.: White Oak CR 4270

Reviewer Roster:

Discipline	**TL/Reviewer**
Regulatory Project Management:	Bates
Clinical:	Andreason/Hearst
Clinical Safety:	N/A
Controlled Substances:	N/A
DDRE:	Birdsong/Saini
Statistical:	Yang/Chen (Y.F.)
Pharmacology:	Rosloff/Tabacova
Statistical Pharmacology:	--
Chemistry:	Sood/Oliver/Lu (Donghao)
Environmental Assessment (if needed):	Lu
Biopharmaceutical:	Baweja/Kumi/Jackson [post-filing]
Microbiology, sterility:	Consult sent by CMC Reviewer
Microbiology, clinical (for antimicrobial products only):	--
DSI:	Samuels (Sherbet)
DDMAC:	Gray (Catherine)
Other Consults:	Micro, sterility (i.m. injection dosage form) sent By CMC
505(b)(2)?	NO
LETTER DATE:	29NOV2005
STAMP DATE:	30NOV2005
FILING DATE:	29JAN2006
74-DAY LETTER ISSUE DATE:	12FEB2006 [10FEB2006, Friday]
DATE OF MIDCYCLE MEETING:	26APR2006 3:00 P.M.
BRIEFING FOR OFFICE DIRECTOR:	15AUG2006 1:00 P.M.

ACTION LETTER SIGNATORY AUTHORITY: ***Division Director*** or Office Director

DATE REVIEWS ARE DUE:

To Team Leaders:	12AUG2006
To Clinical Team Leader:	29AUG2006
To Division Director:	09SEP2006
To Office Director:	not applicable

~~~PDUFA GOAL DATE IS 30SEP2006~~~

Meeting Details:

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

CLINICAL FILE X REFUSE TO FILE
- Clinical site inspection needed? YES X NO
- Domestic or foreign? Domestic X Foreign
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- Is application affected by AIP N/A X YES NO
- Has Division made a recommendation regarding exception to the AIP to permit review based on medical necessity or public health significance? N/A X YES NO
- Summarize Clinical Issues. See attached summary
- Clinical Questions for 74-Day Letter? N/A YES **NO**
- When Are Questions Due to RPM?
- Were Questions Provided on time?

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE
- Questions for 74-Day Letter?
- When Are Questions Due to RPM?
- Were Questions Provided on time?

STATISTICS N/A FILE X REFUSE TO FILE
- Questions for 74-Day Letter? See attached summary
- When Are Questions Due to RPM?
- Were Questions Provided on time?

BIOPHARMACEUTICS N/A FILE X REFUSE TO FILE
- Biopharm. inspection needed? YES NO X
- Domestic or foreign? Domestic Foreign
- Questions for 74-Day Letter?
- When Are Questions Due to RPM?
- Were Questions Provided on time?

PHARMACOLOGY N/A FILE X REFUSE TO FILE
- GLP inspection needed? YES NO X
- Carc Studies? [Separate statistical consult?] YES NO X
- Date of CAC
- Questions for 74-Day Letter? NO
- When Are Questions Due to RPM?
- Were Questions Provided on time?

CHEMISTRY N/A FILE X REFUSE TO FILE
- Establishment(s) ready for inspection? YES X NO
- Microbiology consult needed? YES X NO
- Other expert consult needed? YES NO X
- Methods validation needed? YES X NO
- Questions for 74-Day Letter? YES NO X
- When Are Questions Due to RPM?
- Were Questions Provided on time?

ELECTRONIC SUBMISSION:	Available to Team December 7, 2005
Format:	TOC is NDA format, contents are CTD format
ELIPS labeling included?	SPL provided
Any comments:	SPL interface not functional as of 29-DEC-05. WORD files also provided by firm.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

	The application is unsuitable for filing. See attached summary of deficiencies.

XX	The application, on its face, appears to be sufficiently well-organized and indexed to permit filing. This decision does not guarantee that no deficiencies will be identified during review. It also does not guarantee a first cycle approval action.

	No filing issues identified. ~~ See comments below
	Filing issues to be communicated by Day 74 (see above for date due to RPM).

ACTION ITEMS:

1. Statistics request for datafiles to be conveyed to company immediately following meeting.
2. DSI consult to be completed based on sites to be identified post meeting.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Doris J. Bates, Ph.D.
Regulatory Project Manager, HFD-130

Additional Comments

CMC: **EA was missing from submission, this was identified and requested by Dr. Bates. EA was provided as an amendment to the file prior to the filing meeting.**

Clinical: **Patient population included patients with schizoaffective and schizophreniform disorders as well as schizophrenia and bipolar disorder. Post meeting it was confirmed that the applicant was advised to conduct efficacy analyses on the identified schizophrenic population specifically in order to support the agitation claim for schizophrenia. [During the meeting it was clarified that no claims were being made for agitation in schizoaffective or schizophreniform disorders.]**

Stats: **One potentially problematic site was identified [San Diego, Dr. Tran-Johnson.] This site will be included in the DSI inspection for this NDA. Applicant will be requested to provide all of the SAS programs used to produce all efficacy results for all pivotal studies. If these programs have been submitted as part of the original NDA, the applicant will be requested to provide details of their location in the electronic submission. This request will be made immediately following the meeting.**

Biopharm: **Dr. Kumi will complete the initial filing assessment, and post-filing the NDA will be reassigned to Dr. Andre Jackson.**

Pediatrics: **The initial submission did not address PREA. Dr. Bates followed up with the applicant and a request for waiver was submitted on 29DEC2005. The waiver was granted in the acknowledgement letter sent on 04JAN2006.**

Labeling: **SPL was included.**

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

/s/

Doris Bates
2/3/2006 02:14:23 PM

Appears This Way
On Original

NDA REGULATORY FILING CHECKLIST
(Including Memo of Filing Meeting)

NDA # 21-866 Supplement # --------- Efficacy Supplement Type SE- ------

Trade Name:	Abilify
Established Name:	aripiprazole
Dosage Form:	Injection
Strengths:	7.5 mg/mL
Route of Administration:	Intramuscular
Indication(s):	**(1) treatment of agitation in schizophrenia patients** **(2) treatment of agitation in bipolar mania patients**
Applicant:	Otsuka Pharmaceutical Co. Ltd.
Agent for Applicant:	Kusuma Mallikaarjun, Ph.D. [Otsuka MD Research Institute] c/o Susan Behling [Bristol-Myers Squibb] or Angelina Verna [BMS, for CMC only]
Date of Application:	29NOV2005
Date of Receipt:	30NOV2005
Date clock started after UN:	N/A, UF paid on time
Date of Filing Meeting:	23 or 25JAN2006
Filing Date:	29JAN2006
Action Goal Date (optional):	User Fee Goal Date: 30SEP2006

Type of Original NDA: **(b)(1) XX** (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (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 is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

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

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

User Fee Status: ***Paid*** **X** ☐
PD3006289 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. 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 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 an approved (b)(1) or (b)(2) application? **YES** ☒ NO ☐
  If yes, explain: N21713 Oral solution: NCE exclusivity expires 15-NOV-2007
  N21436 Tablets: NCE exclusivity expires 15-NOV-2007

- 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 ☒
  Index is extremely limited in scope and depth, esp. w. regard to CMC section for drug product:

- 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:

- If an electronic NDA, does it follow the Guidance? N/A ☐ YES ☒ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format? **CMC, PharmTox, Biopharm, Clinical, Stats, Labeling, Cover Letter, Miscellaneous Administrative [copies for reference].**

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☐ YES ☒ NO ☐

- Is it an electronic CTD (eCTD)? N/A YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? **YES, three** Years NO ☐
  NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? **YES** ☒ 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 . . . ."

- Financial Disclosure forms included with authorized signature? **YES** ☒ NO ☐
  (Forms 3454 and 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)? **Y** ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? **YES** ☒ 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. 356H SHOULD also list 60,158.**

- End-of-Phase 2 Meeting(s)? Date(s) _____ **NO** ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) **June 9, 2004** NO ☐
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? **YES** ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES** ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? **N/A** ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? N/A **YES** ☒ NO ☐
  Tradename consult not applicable

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A** ☒ YES ☐ NO ☐
  DSRCS consult typically originates from DMETS.

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?

N/A ☒ YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  N/A ☒ YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ **NO** ☒
  EA was missing from submission, identified and requested by RPM and provided as an amendment to the file prior to the filing meeting.

  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to [Florian Zielinski](HFD-357)? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? **YES** ☒ NO ☐
  This is the responsibility of the CMC review team.

- If a parenteral product, consulted to Microbiology Team (HFD-805)? **YES** ☒ NO ☐
  This is also the responsibility of the CMC review team.

Additional comments:

PEDIATRIC STATUS: PREA not addressed in initial submission; identified and requested by Project Manager. Firm requested waiver, which was granted. See acknowledgement letter for details.

DSI: Inspection of three sites will be requested. A consult will be prepared by the RPM based on information provided by DSI and the clinical reviewer.

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/s/

Doris Bates
2/2/2006 05:22:09 PM
CSO

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Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

January 30, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: AMENDMENT to NDA #21-866 for ABILIFY® (aripiprazole) Injection

Dear Dr. Laughren,

Reference is made to the approved NDA #21-436 for ABILIFY Tablets, and to Submission No. 223 (dated November 16, 1999) for IND #42,776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co., Ltd., (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division. Further reference is made to NDA #21-866 for ABILIFY (aripiprazole) Injection, 7.5 mg/mL, which was submitted to the Agency, by Bristol-Myers Squibb Company on behalf of Otsuka Pharmaceutical Company, Ltd., on November 30, 2005.

This correspondence is submitted in response to the e-mail correspondence of January 26, 2006, in which the Division requested provision of the SAS programs used for the analyses of the pivotal clinical trials in this application. We are providing these SAS programs electronically in this submission. These were also transmitted to the Division via e-mail on January 27, 2006.

If you have any additional requests or concerns regarding this NDA, please do not hesitate to call me at 203-677-3810, or contact me via e-mail at Susan.Behling@bms.com.

Sincerely,

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

Cc: Kusuma Mallikaarjun, Ph.D., Sr. Directory, Abilify Regulatory, Otsuka Maryland Research Institute
Dr. Yeh-Fong Chen, Statistical Reviewer
Dr. Doris Bates, Sr. Regulatory Project Manager

Electronic Media Information

January 30, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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 3 MB and is being provided on 2 CD-ROM disks to the Central Document Room. There are 17 files and 2 folders. The files have been checked for viruses using virus definitions available on January 27, 2006 with McAfee Virus Scan Software (Version 8.0i) and no viruses were detected.

Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

January 30, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

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Sincerely,

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

Cc: Kusuma Mallikaarjun, Ph.D., Sr. Directory, Abilify Regulatory, Otsuka Maryland Research Institute
Dr. Yeh-Fong Chen, Statistical Reviewer
Dr. Doris Bates, Sr. Regulatory Project Manager

Electronic Media Information

January 30, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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Bates, Doris J

From: Bates, Doris J
Sent: Thursday, January 26, 2006 1:50 PM
To: 'Susan H Behling'
Cc: 'Mallikaarjun, Kusuma'; Chen, Yeh-Fong; Bates, Doris J
Subject: RE: NDA 21-866

Hello Dr. Mallikaarjun and Ms. Behling,

This is the email I had mentioned in my voicemail to Ms. Behling, during which I also indicated that your NDA will be filed; the filing date is January 29.

Our statistics team asks that you please provide all of the SAS programs used to produce all efficacy results for all pivotal studies. If these programs have been submitted as part of the original NDA, please provide details of their location in the electronic submission.

Depending on the volume of information in the reply, feel free to use reply e-mail or a CD-ROM review aid, to provide a courtesy copy. We do also need the information submitted to the EDR, however, if it is not already part of the application.

I am including the statistical reviewer as a CC recipient on this message in case you are able to reply by e-mail, so that she does not have to wait for me to forward the message.

Thanks and best regards,

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research
Food and Drug Administration
White Oak Federal Research Center

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/s/

Doris Bates
1/26/2006 02:11:37 PM
CSO

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: David Hussong, NEW DRUG MICROBIOLOGY STAFF OC/OO/CDER/OPS/NDMS - HFD-805

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Scott N. Goldie, PhD for Tom Oliver, PhD Division of Pre-Marketing Assessment I, Off. of New Drug Quality Assessment

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 26, 2005		21866	New NDA Application	10 January 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Abilify (Aripiprozole) Inj 7.5mg/mL	Standard	Type 1 S (Standard)	10 April 2006

NAME OF FIRM: Otsuka Pharm

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☒ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of New NDA application. Please direct questions to Tom Oliver, PhD at 61728. All documents are available electronically (EDR).

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
{See appended electronic signature page}	☒ DFS ☐ EMAIL ☐ MAIL ☒ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Scott Goldie
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-866

NDA ACKNOWLEDGMENT

Otsuka Maryland Research Institute
Attention: Kusuma Mallikaarjun, Ph.D.
Senior Director, Regulatory Affairs / Abilify
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

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

Name of Drug Product:	Abilify® (aripiprazole) Injection
Review Priority Classification:	Standard (S)
Date of Application:	November 29, 2005
Date of Receipt:	November 30, 2005
Our Reference Number:	NDA 21-866

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 January 29, 2006 in accordance with 21 CFR 314.101(a). If the application is filed, the [ten month] user fee goal date will be September 30, 2006.

Under the provisions of the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients, unless this requirement is waived or deferred. We note your request of December 29, 2005 for a waiver of this requirement; we are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application.

Please send all submissions to this NDA, whether 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 / HFD-130
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call the undersigned at (301) 796-2260.

Sincerely,

{See appended electronic signature page}

Doris J. Bates, Ph.D.
Regulatory Project Manager
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doris Bates
1/4/2006 10:42:37 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: ODS/DDRE (S. Birdsong)

FROM: HFD-130 (Dr. Bates)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Dec. 9, 2005	42,776 & 60,158	21-866	new NDA submission	Nov.29, 2005 Received Nov. 30, 2005. In EDR Dec. 7, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aripiprazole intramuscular injection		tx agitation associated with manic episodes or with Schizophrenia	Filing Meeting Jan. 23 or 25, '06; filing date Jan 30, '06. 10 month due date Sep. 30 '06

NAME OF FIRM: Otsuka America and Bristol-Myers Squibb.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Link to EDR: May not be live in DFS rendering. \\CDSESUB1\N21866\N_000\2005-11-29 This is for entire EDR submission. The following link is for the labeling only: \\Cdsesub1\n21866\N_000\2005-11-29\labeling

Applicant did not provide full size mockups as hard copy. Please let Dr. Bates know if these are needed or if provision of EDR link via email is sufficient in future. No Risk Management Plan was seen in the submission. [An IO consult will be submitted if an RMP is received from the firm.]

The trademark will remain Abilify for this dosage form, no trademark consult will be needed. A separate consult has been sent to DDMAC, but not to DSRCS. Thanks!

SIGNATURE OF REQUESTER see DFS signature	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
12/29/2005 06:55:33 PM
Please let me know if you need a live link emailed, I can send a WORD copy of the consult via email.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: DDMAC (C. Gray)

FROM: HFD-130 (Dr. Bates)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Dec. 29, 2005	42,776 & 60,158	21-866	new NDA submission	Nov.29, 2005 Received Nov. 30, 2005. In EDR Dec. 7, 2005 (link sent)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aripiprazole intramuscular injection		tx agitation associated with manic episodes & schizophrenia	Filing Meeting Jan. 23 or 25, '06; filing date Jan 29, '06. 10 month due date Sep. 30 '06

NAME OF FIRM: Otsuka America and Bristol-Myers Squibb.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
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- ☐ ADVERSE REACTION REPORT
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Consult form provided as courtesy before filing meeting. Please let Dr. Bates know if consults are preferred or if provision of EDR link via email and meeting notice is sufficient in future. Thanks!

SIGNATURE OF REQUESTER see DFS signature	METHOD OF DELIVERY (Check one) ☒ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Doris Bates
12/29/2005 06:46:45 PM

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Bristol-Myers Squibb
Pharmaceutical Research Institute

Richard L. Gelb Center for Pharmaceutical Research and Development

5 Research Parkway P.O. Box 5100 Wallingford, CT 06492-7660

January 10, 2006

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: AMENDMENT to NDA #21-866 for ABILIFY® (aripiprazole) Injection

Dear Dr. Laughren,

Reference is made to the approved NDA #21-436 for ABILIFY Tablets, and to Submission No. 223 (dated November 16, 1999) for IND #42,776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co., Ltd., (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division.

Further reference is made to NDA #21-866 for ABILIFY® (aripiprazole) Injection, 7.5 mg/mL, which was submitted to the Agency, by Bristol-Myers Squibb Company on behalf of Otsuka Pharmaceutical Company, Ltd., on November 30, 2005. This submission was in electronic format. The statement of a categorical exclusion from submission of an "Environmental Assessment" was inadvertently omitted from the NDA. This amendment provides the required statement, shown on the next page, and as provided in the enclosed CD. In addition, we are providing the establishment information, consistent with section 3.2.P.3.1 of the application, as an attachment to the 356h form. Please note that the inspection readiness date is included in this submission.

Please direct any CMC-related questions or concerns regarding this submission to Ms. Angelina Verna, Associate Director, Global Regulatory Sciences-CMC, BMS, by telephone at 609-818-4063 or via e-mail at angelina.verna@bms.com.

Sincerely,

Susan H. Behling, Director, Global Regulatory Science
Bristol-Myers Squibb Company

cc: Kusuma Mallikaarjun, Ph.D., Sr. Directory, Abilify Regulatory, Otsuka Maryland Research Institute
Keith Kiedrow, R.Ph., FDA/CDER Regulatory Management Officer

Electronic Media Information

January 10, 2006

NDA 21-866 ABILIFY® (aripiprazole) Injection

AMENDMENT

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 816 KB and is being provided on 2 CD-ROM disks to the Central Document Room. There are 4 files and 1 folder. The files have been checked for viruses using virus definitions available on January 6, 2006 with McAfee Virus Scan Software (Version 8.0i) and no viruses were detected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-710 (Dr. Yang, Dr. Y.F. Chen)

FROM: HFD-120 (Dr. Bates)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Dec. 9, 2005	42,776 & 60,158	21-866	new NDA submission	Nov.29, 2005 Received Nov. 30, 2005. In EDR Dec. 7, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Aripiprazole intramuscular injection		tx agitation associated with manic episodes	Filing Meeting Jan. 23 or 25, '06; filing date Jan 30, '06. 10 month due date Sep. 30 '06

NAME OF FIRM: Otsuka America and Bristol-Myers Squibb.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☒ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
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/s/

Doris Bates
12/9/2005 04:22:21 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
iFD-860 (Dr. Baweja, Dr. Kumi?)

FROM:
HFD-120 (Dr. Bates)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Dec. 9, 2005	42,776 & 60,158	21-866	new NDA submission	Nov.29, 2005 Received Nov. 30, 2005. In EDR Dec. 7, 2005

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE:
Aripiprazole intramuscular injection		tx agitation associated with manic episodes	Filing Meeting Jan. 23 or 25, '06; filing date Jan 30, '06. 10 month due date Sep. 30 '06

NAME OF FIRM: Otsuka America and Bristol-Myers Squibb.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
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- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☒ DISSOLUTION
- ☒ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
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Please let Doris know if reviewer assignment changes. Thanks!

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/s/

Doris Bates
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Otsuka Maryland Research Institute, Inc.

2440 Research Boulevard
Rockville, Maryland 20850
Telephone 301.417.0900
Facsimile 301.990.0036
www.otsuka.com

November 29, 2005

Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: **NDA 21-866 ABILIFY ® (aripiprazole) Injection**
NEW DRUG APPLICATION

Reference is made to approved NDA 21-436 for ABILIFY Tablets and to Submission No. 223 (dated November 16, 1999) to IND 42, 776 in which the Division was informed of the collaborative agreement between Otsuka Pharmaceutical Co. Ltd. (OPC) and Bristol-Myers Squibb Company (BMS) such that BMS is delegated to act on behalf of OPC in correspondence with this Division.

Further reference is made to the following key interactions with the Division concerning the development program for this formulation:

-April 17, 2002 correspondence from the Division provided in lieu of an EOP2 meeting
-November 17, 2003 teleconference regarding the required nonclinical toxicology program for registration of this drug product
-June 9, 2004 pre-NDA meeting and
-July 27, 2004 discussion with Dr. Tom Oliver in which agreement was reached to cross-refer to NDA 21-436 for aripiprazole API in this NDA

Provided herein is the New Drug Application for ABILIFY Injection in electronic format. This dossier includes data to support the approval of this formulation for use as an intramuscular injection for the treatment of patients with agitation associated with schizophrenia and bipolar mania. We believe that the results of the three pivotal clinical studies demonstrate the safety and efficacy of this formulation for use in the proposed indications. In addition, the dossier includes the results of all required nonclinical toxicology and reproductive toxicity studies which further support the safety of this formulation in patients. All summaries in this NDA are in CTD format. The proposed product labeling is provided in our usual side-by-side format showing the changes to the current labeling (submitted as FPL on November 18, 2005) on the right-hand side. In addition, we are providing the label in SPL format.

In accordance with 21 CFR314.108, OPC believes that upon approval of this application, it will be entitled to three years marketing exclusivity, during which no person shall submit a 505 (b)(2) application or abbreviated new drug application under section 505 (j) of the Act for a drug containing the same active moiety. In accordance with 21 CFR314.50 (j), OPC is claiming such exclusivity as described in 21 CFR314.108 (b)(4).

ABILIFY Injection is formulated as a 7.5 mg/mL solution in Captisol® (cyclodextrin), and we cross-refer to the Cydex DMF and amendments in support of the use of this noncompendial excipient. We seek approval of one presentation, a single-use vial containing an adequate amount of solution to deliver the recommended dose of —ng (actual amount 9.75 mg). In the clinical program, given the availability of the product strengths, and to preserve the blind, doses were rounded to the nearest — mL; hence the recommended dose of — mg was actually administered as 1.3 mL (or 9.75 mg). Given the wide therapeutic window for aripiprazole, we believe this small difference is clinically insignificant and we are thus seeking approval of a recommended dose of — ng.

In accordance with PDUFA III, payment in the amount of $767, 400 has been sent to the Food and Drug Administration, Philadelphia, Pennsylvania. This NDA has been assigned the User Fee Identification Number 3006289.

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 are looking forward to the Division's review and approval of this important new formulation for ABILIFY. Please direct any CMC-related questions or concerns regarding this application to Ms. Angelina Verna, Associate Director, Global Regulatory Sciences-CMC, BMS by telephone at 609-818-4063 or via e-mail at Angelina.Verna@bms.com. All other questions or concerns regarding this application should be directed to Ms. Susan Behling, Director, Global Regulatory Strategy, BMS, at 203-677-3810, or via e-mail at Susan.Behling@bms.com.

Sincerely,

Kusuma Malllikaarjun

Kusuma Malllikaarjun, Ph.D.
Senior Director, Regulatory Affairs/Abilify™
Otsuka Maryland Research Institute

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Electronic Media Information

November 29, 2005

NDA 21-866 ABILIFY® (aripiprazole) Injection

NEW DRUG 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 652 MB and is being provided on 2 CD-ROM disks to the Central Document Room. There are 493 files and164 folders. The files have been checked for viruses using virus definitions available on November 23, 2005 with McAfee Virus Scan Software (Version 8.0i) and no viruses were detected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2005
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Otsuka Pharmaceutical Co., Ltd.	11/29/05
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(301) 990-0030	(301)990-0036
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2-9 Kanda Tsukasa-cho Chiyoda-ku Tokyo, 101-8535, Japan	Otsuka Maryland Research Institute, Inc. 2440 Research Boulevard Rockville, MD 20850 Phone (301)990-0030 Fax (301)990-0036

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-866

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Aripiprazole	Abilify

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*
7-[4-[4-(2,3-dichlorophenyl)-1piperazinyl]butoxy]-3,4-dihydro-2(1H)-quinolinone

CODE NAME *(If any)*
OPC-14597, BMS-337039

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	7.5mg/ml	Intramuscular

(PROPOSED) INDICATION(S) FOR USE:
Treatment of agitation in schizophrenia and bipolar mania patients.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug N/A Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Original Application

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 2 CDs THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA No. 21-436; NDA No. 21-713; IND No. 42,776; DMF ____

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☒	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☒	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☒	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☒	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☒	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☒	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify) Confidentiality Statement*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Kusuma Mallikaarjun	Kusuma Mallikaarjun, Ph.D., Senior Director, Regulatory Affairs/Abilify™	11/29/05

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2440 Research Boulevard, Rockville, MD 20850	(301) 990-0030

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

NDA 21-866

ARIPIPRAZOLE INJECTION

FIELD COPY CERTIFICATION

Chemistry, Manufacturing, and Control Submission:

Otsuka America Pharmaceutical, Inc and Bristol-Myers Squibb Company certifies that a field copy of the Chemistry, Manufacturing and Control (CMC) section of this application has been provided to the Food and Drug Administration, 6000 Metro Drive, Suite 101, Baltimore, MD 21215. An additional copy of the CMC section of this application has also been provided to the Mayaguez, Puerto Rico office of the Food and Drug Administration, Martinez Nadal Street #59 North, Park Plaza Building, Mayaguez, PR 00680. We further certify that these copies are true copies of the CMC section of this application.

Susan H Behling

28 Nov 05

Susan H. Behling

Date

Director, Global Regulatory Science

Bristol Myers Squibb Company

5 Research Parkway, Dept 718

Signature91 Building

Wallingford, CT 06492

(203) 677-3810

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,158

Otsuka Maryland Research Institute, Inc.
Attention: Susan H. Behling, Director
2440 Research Boulevard
Rockville, MD 20850

Dear Ms. Behling:

Please refer to the meeting between representatives of your firm and FDA on June 9, 2004. The purpose of the meeting was to discuss the clinical development program for Intramuscular Aripiprazole.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Renmeet Gujral, Pharm.D., Regulatory Health Project Manager, at (301) 594-5535.

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

Enclosure

MEMORANDUM OF MEETING

IND 60,158

Date: June 9, 2004
Drug: Intramuscular Aripiprazole
Sponsor: Otsuka Maryland Research Institute, Inc.

Attendees:

Agency

Russell Katz, M.D.	Division Director
Thomas Laughren, M.D.	Clinical Team Leader
Gregory Dubitsky, M.D	Medical Officer
Lois Freed, M.D.	Pharmacology/Toxicology Team Leader
Raman Baweja, Ph.D.	Biopharmaceutics Team Leader
Kumi, Kofi	Biopharmaceutics Reviewer
Kun Jin, Ph.D.	Biometrics Team Leader
Chen, Yeh-Fong	Biometrics Reviewer
Racoosin, Judith, M.D.	Safety Team Leader
Steven Hardeman,	Regulatory Project Manager
Renmeet Gujral, Pharm.D.	Regulatory Project Manager

Firm

BMS

Donald Archibald, M. Phil, Director, Biostatistics and Programming
Susan Behling, Director, Global Regulatory Science
Jack Grebb, M.D., Vice President, Neuroscience Clinical Research
David Kornhauser, M.D., Executive Director, Clinical Pharmacology
Thomas Mably, D.V.M, Drug Safety Evaluation
Ronald Marcus, M.D., Group Director, Neuroscience Clinical Research
Claude Nicaise, M.D., Vice President, Global Regulatory Science
Dan Oren, M.D., Director, Neuroscience Clinical Research
Elyse Stock, M.D., Vice President, Abilify Development Champion
Nimish Vachharajani, Ph.D., Director, Clinical Pharmacology
Charles Wolleben, Ph.D., Group Director, Global Regulatory Science

Otsuka Pharmaceuticals, Inc.

Taro Iwamoto, Ph.D., Abilify Global Leader
Kusuma Mallikaarjun, Ph.D., Director, Regulatory Affairs

RE: The purpose of this meeting was to discuss the clinical development program for IM Aripiprazole.

Background:
The firm requested this meeting to discuss the clinical development program for IM Aripiprazole.

Discussion:

1. Does the Division agree that the program will support an indication for the treatment of agitation associated with schizophrenia and bipolar I disorder?

   FDA Response: *The proposed program should be adequate, however, it was noted that, for the schizophrenia program, the results would need to be positive for the schizophrenia subgroup alone, since this is the population for which the oral formulation is approved.*

2. We have prospectively defined (in the Statistical Analysis Plan for CN 1378050 and the Protocols for CN 138013) key secondary endpoints and a hierarchiacal testing procedure to protect the overall alpha-level. These endpoints and the testing order are ACES, CABS, CGI-I, and CGI-S.

   Does the Division agree that these secondary measures are appropriate for labeling?

   FDA Response: *We noted that most of the proposed secondary outcomes would be redundant with the primary. However, we did indicate that one of the two proposed globals would be acceptable as a key secondary outcome, i.e., either CGI-I or CGI-S.*

3. ***Is the Division in agreement that there will be adequate safety data to support the proposed claims and to include in the label statements on dosing the product as single and multiple injections?***

   FDA Response: *We indicated that there would likely be sufficient safety data to support single doses, however, we discussed that it might not be appropriate to recommend doses beyond the first dose if the studies were not designed to demonstrate the effectiveness of these subsequent doses. In addition, we asked that they submit lab results for glucose and bicarbonate levels.*

4. **In Study CN138013, if the 15mg dose is effective, will this study support a recommendation for a 15mg dose for treating agitation associated with bipolar I disorder?**

   FDA Response: *We agreed that one positive study for each indication would be sufficient to support both claims. However, we noted that, for the bipolar study, if there was no added efficacy for the 15 mg dose compared to the 10 mg dose, the 10 mg dose would be the recommended dose.*

5. **If an indication for the use of aripiprazole tablets for the treatment of psychosis in the elderly is not obtained, is an indication for the IM formulation for the treatment of agitation in elderly dementia patients still feasible?**

FDA Response: *Yes, but we indicated that there would need to be a warning statement on stroke, based on recently available data.*

6. **a) Does the Division agree that there will be sufficient ECG data available for appropriate assessment of potential QT changes?**

   b) Are the proposed ECG analyses as exemplified in Appendix 8D (Section 4.2.2) appropriate and adequate?

   FDA Response: *We indicated that, overall, the planned program appears to be adequate. We noted that the time period following the first dose should be well-covered, i.e., readings at 0.5, 1.5, and 3 hours, based on standard ECG recordings. We asked that detailed information be provided on the approach to reading the ECGs.*

7. **Does the Division agree that the proposed reports of the nonclinical toxicology studies for the NDA will support the registration of IM aripiprazole?**

   FDA Response: *Yes, however, we reminded them that we needed the segment 3 report within 120 days of submitting the application.*

8. **Is the Division in agreement that the clinical pharmacology program is sufficient to support the application as proposed?**

   FDA Response: *Yes, however, we reminded them that we needed complete data and analysis for study 050.*

9. **Does the Division agree that the proposed electronic dossier, including the proposed content and formats of the SAS datasets, will allow for an appropriate review?**

   FDA Response: *Yes*

10. **a) Is the proposed presentation of data in the clinical summaries of safety and efficacy acceptable?**

    b) Does the Division agree with the appendices that are proposed for inclusion with the clinical study reports in the NDA (as described in Appendix 9B)?

    c) For the analysis of pooled safety data in the clinical safety summary (see Section 8.2), we believe excluding the data for the ineffective 1-mg aripiprazole dose is a better reflection of the safety of the drug. Does the Division agree?

    d) Since we are submitting 1 NDA for the indication of agitation associated with schizophrenia and bipolar I disorder, manic or mixed type, does the Division agree that only 1 User Fee would apply?

e) Does the Division have any additional issues or concerns with the proposed dossier?

FDA Response: *In general, we were in agreement on the proposals for the ISE and ISS. However, we did note that there needs to be safety and efficacy subgroup analysis done for, age, gender, and race. During the meeting the sponsor was directed to the correct office to address any questions they had about user fees.*

Renmeet Gujral, Pharm.D.
Regulatory Project Manager

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
8/13/04 02:46:21 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA **21-866**	Efficacy Supplement Type ***Original NDA***	Supplement Number --Not applicable--	
Drug: ABILIFY (aripiprazole) Injection		Applicant: Otsuka Pharmaceutical Company Ltd.	
RPM: Bates		HFD-130	Phone # 6-2260
Application Type: **(X)** 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.)		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	**(X)** Standard **( )** Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	not applicable
❖ User Fee Goal Dates	30SEP2006
❖ Special programs (indicate all that apply)	**(X)** 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	**(X)** Paid UF ID number 3006289
• 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 **(X)** No
• This application is on the AIP	**( )** Yes **(X)** No
• Exception for review (Center Director's memo)	not applicable
• OC clearance for approval	not applicable
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X)** Verified
❖ Patent	

• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• 505(b)(2) status?	**Not a 505(b)(2) application.**
❖ Exclusivity (approvals only)	
• 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.)	Summary: Tab F not applicable
• 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 #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA)	not applicable
General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	none, first cycle
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter **(X) Press Office Decision**
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	See Tab D and AP letter
• Most recent applicant-proposed labeling	See Tab D
• Original applicant-proposed labeling	See Tab D
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings	See Tab M and clinical, pharmtox, biopharm, CMC reviews
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	not applicable
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	not applicable
• Applicant proposed	See Tab D
• Reviews	See CMC review
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	See Tab R
• Documentation of discussions and/or agreements relating to post-marketing commitments	See Tab R
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	See Tab R
❖ Memoranda and Telecons	See Tab S
❖ Minutes of Meetings --- See Tab S	

• EOP2 meeting	unspecified meeting type, held on 8 July 2004: no apparent pre-NDA meeting minutes on file
• Pre-NDA meeting	
• Pre-Approval Safety Conference	not applicable
• Other	filing meeting 03FEB2006
❖ Advisory Committee Meeting	
• Date of Meeting	Not applicable
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	Not applicable
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader)	Tab J, Tab K
Clinical Information	
❖ Clinical review(s)	Tab L
❖ Microbiology (efficacy) review(s)	Not applicable
❖ Safety Update review(s)	Tab L
❖ Risk Management Plan review(s)	Not applicable
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	Tab G
❖ Demographic Worksheet	Not applicable
❖ Statistical review(s)	Tab N
❖ Biopharmaceutical review(s)	Tab O
❖ Controlled Substance Staff review(s) and recommendation for scheduling	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Tab I
• Bioequivalence studies	Not applicable
CMC Information	
❖ CMC review(s)	Tab Q
❖ Environmental Assessment	
• Categorical Exclusion	Tab Q
• Review & FONSI	not applicable
• Review & Environmental Impact Statement	not applicable
❖ Microbiology (validation of sterilization & product sterility) review(s)	Tab Q
❖ Facilities inspection (provide EER report)	Tab Q (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	Tab Q
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews	Tab P
❖ Nonclinical inspection review summary	not applicable
❖ Statistical review(s) of carcinogenicity studies	not applicable
❖ CAC/ECAC report	not applicable

Hardeman, Steven D

From: Hardeman, Steven D
Sent: Tuesday, February 17, 2004 9:34 AM
To: 'Susan H Behling'
Subject: IND 60,158 (N-065)

Sue,

We have completed the review of your submission and have the following comments:

1) The statistical analysis plans for these studies are acceptable except for the non-inferiority testing in study CN138012. You should be advised that non-inferiority analyses are not currently accepted as the basis for a labeling claim at this time. Thus, our examination of efficacy in study CN138012 will focus only on the comparison of mean change from baseline in the PEC between IM aripiprazole and IM placebo.

2) Based on preliminary pharmacokinetic data, you indicate that > 80% Cmax was achieved within one hour of IM injection. Although continuous Holter monitoring will be performed up to 22 hours post-first IM dose, Holter tracings are not very useful for accurately measuring ECG parameters such as the QT interval. No 12- lead ECG tracings are planned until 24 hours after dosing in either study. Thus, in order to adequately capture ECG findings that may be associated with near maximal plasma levels of drug, we suggest that a 12-lead ECG be performed at one hour post-dose following all IM administrations of study drug in both trials.

3) These studies will, by design, discourage the administration of second and third doses of IM aripiprazole if the initial dose is effective. You were advised in our 4-17-02 letter that if there are few patients who receive multiple IM aripiprazole doses, then exposure to such a regimen may be considered inadequate and multiple dosing may not be approved. Although the results from study CN138- 017, which utilized three 15mg IM doses 2 hours apart, are somewhat reassuring, only 4 patients received this regimen and this number would likely be considered insufficient in itself to recommend such a regimen in labeling. It may be useful to further advise the sponsor that if, in the end, few patients receive multiple IM doses of aripiprazole, a study specifically designed to examine the safety of three IM doses of aripiprazole, at the maximum recommended dose, given two hours apart may be required to support labeling of such use.

Regards,
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@cder.fda.gov

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

/s/

Steve Hardeman
2/17/04 09:32:58 AM
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 60,158

Bristol-Myers Squibb Pharmaceutical Research
Attention: Susan H. Behling
Director, Global Regulatory Science
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Ms. Behling:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (aripiprazole) intramuscular injection.

We also refer to your amendment dated February 21, 2002 (serial # 034), containing a request for review and comments on the design of study CN138-050.

We have completed the clinical review of your submission and have the following comments and recommendations (your questions are presented in italics):

1) *We believe that the design of pivotal study CN138-050, as amended, is appropriate for determining the safety and efficacy of IM aripiprazole in schizophrenic patients with agitation. Does the Division have any comments or concerns with the design (i.e. endpoints, patient population, statistics, controls) of trial CN138-050 in the context of the planned development program?*

   a) There are two comments with respect to study CN138-050 which apply to the other Phase 3 studies as well:

      i) An optimal assessment of the effect of IM aripiprazole on vital signs and ECG parameters includes measurement at the plasma Cmax for the parent drug. Page 10 of the submission summarizes pharmacokinetic findings from schizophrenic patients in study CN138-017. This summary states that, after single IM doses in the range of 1 to 30mg, aripiprazole concentrations greater than 80% of Cmax were achieved within 2 hours of dosing. Furthermore, after multiple dosing with IM aripiprazole 7.5mg and 15mg (three doses given 2 hours apart), aripiprazole Cmax occurred within 15 to 45 minutes after administration of the last dose. Thus, we recommend that vital sign measurements and ECG tracings be added at 30 minutes, 1.5 hours, and 3 hours after the first IM dose and at 30 minutes after the second and third doses to better characterize vital sign and ECG changes at Cmax. This is of particular concern since the summary of safety data from study CN138-017 (page 13 of the submission) indicates that two of the four subjects who received three IM aripiprazole 15mg doses

two hours apart experienced QTc elevations on one or more occasions on the dosing day.

ii) Page 33 of the study protocol indicates that lorazepam may be administered for "anxiety or insomnia." As written, it appears that this administration is in addition to the use of lorazepam as a rescue medication for agitation. This should be clarified in the protocol. If such use is to be permitted, it is recommended that no lorazepam be administered until the 2 hour post-first IM dose assessments are complete.

2) *Positive data from two Phase III randomized trials in agitated patients with schizophrenia, schizoaffective disorder and schizophreniform disorder (CN138-050 and CN138-012) is proposed for the registration of IM aripiprazole. Data from a single trial in bipolar mania patients with agitation and one in dementia patients with agitation would be submitted as subsequent sNDA's. Assuming statistically significant data on the primary outcome measure for these trials, does the Division agree that the proposed studies would produce sufficient information to support registration of this formulation for these uses?*

Positive efficacy findings from these studies would support approval for the treatment of acute agitation in these patient populations.

3) *The expected numbers of subjects/patients exposed to IM aripiprazole in the initial NDA for agitation in schizophrenia is approximately four hundred. Some blinded data from the bipolar and dementia trials will also be available at filing. We believe that together with the observed safety of the IM product thus far, and our extensive safety experience for aripiprazole tablets, this should be an adequate safety database. Does the Division agree?*

Exposure of four hundred patients, with at least 50 patients exposed to IM aripiprazole 15mg from study CN138-050, should be sufficient for the assessment of safety. However, these studies will, by design, discourage the administration of second and third doses of IM aripiprazole if the initial dose is effective. Thus, if there are few patients who receive multiple IM aripiprazole doses, particularly at higher doses, then exposure to such a regimen may be considered inadequate and multiple dosing may not be approved. Although the results from study CN138-017, which utilized three 15mg IM doses 2 hours apart, are somewhat reassuring, only 4 patients received this regimen and this number would likely be considered insufficient in itself to recommend such a regimen in labeling.

4) *Does the Division have any additional concerns with the program?*

We suggest that you consider conducting a study to assess the pharmacodynamic and pharmacokinetic interaction between IM aripiprazole and a commonly used adjunctive treatment for acute agitation, such as IM lorazepam, since such combined treatment may be frequently instituted in clinical practice. We would be happy to assist you in the design of such a study.

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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