

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022568**

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

## EXCLUSIVITY SUMMARY

NDA # 22-568

SUPPL #

HFD # 120

Trade Name Aricept 23 mg Tablet

Generic Name donepezil hydrochloride

Applicant Name Eisai Medical Research

Approval Date, If Known July 23, 2010

### **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?

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# 20690 Aricept Tablets 5mg, 10mg

NDA# 21719 Aricept Liquid

NDA# 21720 Aricept ODT

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

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

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

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

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

summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☐

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

E2020-G000-326 , "A Double Blind, Parallel Group Comparison of 23mg Donepezil Sustained Release to 10 mg Donepezil Immediate Release in Patients with Moderate to Severe Alzheimer's Type Disease

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☐

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

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

E2020-G000-326 , "A Double Blind, Parallel Group Comparison of 23mg Donepezil Sustained Release to 10 mg Donepezil Immediate Release in Patients with Moderate to Severe Alzheimer's Type Disease

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 # 35,974	YES <input checked="" type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

Investigation #2		!
		!
IND #	YES <input type="checkbox"/>	! NO <input type="checkbox"/>
		! Explain:

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

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! Explain:

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

YES ☐

NO ☒

If yes, explain:

=====

Name of person completing form: Teresa Wheelous, R. Ph.

Title: Sr. Regulatory Management Officer

Date: August 9, 2010

Name of Office/Division Director signing form: Russell Katz, M.D.

Title: Director, Division of Neurology Products

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



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
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NDA-22568	ORIG-1	EISAI INC	DONEPEZIL HYDROCHLORIDE

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/s/

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TERESA A WHEELOUS  
08/10/2010

RUSSELL G KATZ  
08/11/2010

**From:** [Martina\\_Struck@Eisai.com](mailto:Martina_Struck@Eisai.com)  
**To:** [Wheelous, Teresa A.](#)  
**Subject:** Re: NDA 22568 Aricept 23 mg - PMRs  
**Date:** Thursday, July 08, 2010 11:42:26 AM

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Teresa,

Eisai agrees with the three postmarketing requirements as outlined below, and proposes the following timelines for PRM 1662-1:

Final Protocol Submission: 12/31/2010  
Study/Trial Completion: 12/31/2011  
Final Report Submission: 06/30/2012

Please do not hesitate to contact me with any questions.  
regards  
Martina

Martina Struck, Ph.D.  
Senior Director, Global Regulatory Affairs CFU  
Neuroscience Product Creation Unit  
Eisai, Inc.  
Tel: 201 949 4966  
Mobile: (b) (4)  
Fax: 201 949 4595  
Email: [martina\\_struck@eisai.com](mailto:martina_struck@eisai.com)

From: "Wheelous, Teresa A" <[Teresa.Wheelous@fda.hhs.gov](mailto:Teresa.Wheelous@fda.hhs.gov)>  
To: [Martina\\_Struck@Eisai.com](mailto:Martina_Struck@Eisai.com)  
Date: 07/07/2010 10:26 AM  
Subject: NDA 22568 Aricept 23 mg - PMRs

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Martina,

Please review and comment on the following postmarketing requirement dates.  
Please provide dates for PMR 1662-1 for our consideration.

## **PMR 1662 – 1    A Single-Dose Oral Neurotoxicity Study in Female Rats**

A single dose oral neurotoxicity study in female rats (at least 10 per group) with donepezil and memantine, each administered alone and in combination. Doses of donepezil and memantine should range from those estimated to result in plasma exposures similar to those observed at the maximum recommended clinical doses (i.e., 23 mg/day donepezil and 28 mg/day memantine), up to maximum tolerated doses. Two positive control groups should be included, one treated with 30 mg/kg i.p. memantine + 10 mg/kg i.p. donepezil (for comparison to the results of Creeley et al., 2008) and one treated with 3 mg/kg i.p. MK-801. Neurohistopathology should be assessed at 48 hrs after dosing using standard cupric silver staining methods, and should include examination of all brain regions shown to be affected by Creeley et al. (2008). Toxicokinetic analyses of donepezil and memantine should be performed for the oral and i.p. treated groups. The timetable you submitted on July ??, 2010, states that you will conduct this study according to the following schedule:

Final Protocol Submission:    MM/YY  
Study/Trial Completion:       MM/YY  
Final Report Submission:       MM/YY

## **PMR 1662-2    An *in vitro* study to evaluate the potential of donepezil as an inhibitor of CYP2B6, CYP2C8, and CYP2C19.**

Final Protocol Submission:    12/31/2010  
Study/Trial Completion:       6/30/2011  
Final Report Submission:       12/31/2011

## **PMR 1662-3    An    *in vitro* study to evaluate whether donepezil is a P-glycoprotein substrate.**

Final Protocol Submission:    12/31/2010  
Study/Trial Completion:       6/30/2011  
Final Report Submission:       12/31/2011

Regards,

*CDR Teresa Wheelous, R. Ph.*  
*Sr. Program Management Officer Consultant*  
*FDA*  
*Division of Neurology*  
*10903 New Hampshire Avenue, Bldg. #22, Room 4344*  
*Silver Spring, MD 20993-0002*  
*(telephone) 301-796-1161*  
*(fax) 301-796-9842*

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

TERESA A WHEELIOUS  
07/20/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022568

**PROPRIETARY NAME REQUEST  
UNACCEPTABLE**

Eisai Inc.  
300 Tice Boulevard  
Woodcliff Lake, New Jersey 07677

ATTENTION: Martina Struck, Ph.D.  
Senior Director, Global Regulatory Affairs

Dear Dr. Struck:

Please refer to your New Drug Application (NDA) dated September 24, 2009, received September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Donepezil Hydrochloride Tablets, 23 mg.

We also refer to your January 7, 2010, correspondence, received January 8, 2010, requesting review of your proposed proprietary name, Aricept<sup>(b) (4)</sup> and to the April 6, 2010 correspondence from the Agency that the proposed proprietary name Aricept<sup>(b) (4)</sup> was acceptable for this product.

Further reference is made to the May 14, 2010 teleconference between representatives of Eisai Inc, the Division of Neurology Products, and the Division of Medication Error Prevention and Analysis<sup>(b) (4)</sup>

We recommend that your Donepezil Hydrochloride Tablets 23 mg product be managed under the existing name, Aricept. We request submission of revised container labels, carton and insert labeling to reflect this recommendation.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Teresa Wheelous at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

LAURIE A KELLEY  
05/24/2010

CAROL A HOLQUIST  
05/24/2010





NDA 22-568

**INFORMATION REQUEST**

Eisai Medical Research Inc.  
Attention: Kevin M. McDonald  
Associate Director, Global Regulatory Affairs  
300 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Mr. McDonald:

Please refer to your new drug application (NDA) dated September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Aricept (donepezil hydrochloride) (b) (4) tablets 23 mg.

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

1. The effect of particle size on dissolution profile was evaluated using the drug substance lot # 17090304 that has a D90 value of (b) (4) and the study was concluded as “no effect of particle size on dissolution”. Provide comparative dissolution data of the established drug product formulation using different lots of API with various particle size limits in order to justify such conclusion and the limit of (b) (4) drug substance specification.
2. Clarify how you control the drug substance polymorphic form in the API as well as in the drug product.
3. Provide batch analysis data for the drug substances lot(s) that were used to manufacture clinical and stability batches.
4. From the pharmaceutical development, 3.2.P.2.2, it appears that the optimization of the functional (rate controlling) excipients were done by doing formulation trials mainly on the lower strength (b) (4) of the product. Clarify how this information was transcribed to the final formulation of non dose proportional 23 mg product.
5. Clarify if the ratio between EC and MAC throughout the entire study (Figures 3, 4 and 5 of 3.2.P.2.2) was kept constant.

6. Clarify what viscosity grade of the ethyl cellulose was used. If there any effect of viscosity grade of EC on dissolution, we suggest you establish appropriate specification.
7. Clarify if the film integrity study was done with the debossed tablets. If not then provide film integrity study with the actual debossed tablets.
8. From the given photograph of the finished product provided in section 3.2.P.1.1 (Fig. 1), it appears that the product has a logo filling problem. The letters “I” , “E” and “P” can be barely recognized. Clarify if there was any logo filling problem with the given amount of film coat on top of the finished product. Provide tablet samples in support of your justification.

9.

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(b) (4)

16. Include an in-process core tablet friability test.
17. In your control strategy for process parameter, you have mentioned that if a different equipment or different batch size is used, the PARs would change. Describe what strategy will be applied to make such changes?
18. As per the ICH guideline Q6A, Identification should be done by either using specific test or a combination of tests into a single procedure, such as HPLC/UV diode array. Provide either a combination test procedure or a specific test such as IR test.
19. Provide updated DMF authorization letter as follows:
  - (a) DMF (b) (4) : [REDACTED] (b) (4)
  - (b) DMF (b) (4) : [REDACTED] (b) (4)

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

RAMESH K SOOD  
05/05/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022568

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Eisai Inc.  
300 Tice Boulevard  
Woodcliff Lake, New Jersey 07677

ATTENTION: Martina Struck, Ph.D.  
Senior Director, Global Regulatory Affairs

Dear Dr. Struck:

Please refer to your New Drug Application (NDA) dated September 24, 2009, received September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Donepezil Hydrochloride (b) (4) Tablets, 23 mg.

We also refer to your January 7, 2010, correspondence, received January 8, 2010, requesting review of your proposed proprietary name, Aricept (b) (4). We have completed our review of the proposed proprietary name, Aricept (b) (4) and have concluded that it is acceptable.

The proposed proprietary name, Aricept (b) (4), will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 7, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Teresa Wheelous at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

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

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NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

DENISE P TOYER on behalf of CAROL A HOLQUIST  
04/06/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Silver Spring, MD 20993

NDA 022568

**PROPRIETARY NAME REQUEST  
WITHDRAWN**

Eisai Inc.  
300 Tice Boulevard  
Woodcliff Lake, New Jersey 07677

ATTENTION: Kevin McDonald  
Associate Director, Global Regulatory Affairs

Dear Mr. McDonald:

Please refer to your New Drug Application (NDA), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Donepezil Hydrochloride (b) (4) Tablets, 23 mg.

We acknowledge receipt of your December 10, 2009 correspondence, on December 11, 2009, notifying us that you are withdrawing your October 6, 2009 request for a review of the proposed proprietary name (b) (4). This proposed proprietary name request is considered withdrawn as of December 11, 2009.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Laurie Kelley, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application, contact the Office of New Drugs (OND) Regulatory Project Manager, Teresa Wheelous at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

CAROL A HOLQUIST  
12/23/2009





NDA 22568

**FILING COMMUNICATION**

Eisai Medical Research Inc.  
Attention: Kevin M. McDonald  
Associate Director, Global Regulatory Affairs  
300 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Mr. McDonald:

Please refer to your new drug application (NDA) dated September 24, 2009, received September 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Aricept (donepezil hydrochloride) extended release tablets 23 mg.

We also refer to your October 6, 2009 submission.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is July 24, 2010.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by June 24, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. 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 review.

We have the following information requests:

**CLINICAL PHARMACOLOGY**

Please provide all datasets (NONMEM format) for population PK analyses along with programs and outputs.

### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Teresa Wheelous, Sr. Regulatory Management Officer, at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

RUSSELL G KATZ  
11/30/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="text-align: center;">REQUEST FOR CONSULTATION</h2>	
TO (Office/Division): <b>Patrick Marroum, Biopharmaceutics, ONDQA</b>		FROM (Name, Office/Division, and Phone Number of Requestor): <b>Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of Martha Heimann</b>	
DATE <b>10/5/2009</b>	IND NO.	NDA NO. <b>22-568</b>	TYPE OF DOCUMENT <b>original submission</b>
NAME OF DRUG <b>donepezil hydrochloride</b>		PRIORITY CONSIDERATION <b>standard</b>	DESIRED COMPLETION DATE <b>2/24/2010</b>
NAME OF FIRM: <b>Eisai Medical Research</b>			
<b>REASON FOR REQUEST</b>			
<b>I. GENERAL</b>			
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<b>IV. DRUG SAFETY</b>			
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<b>V. SCIENTIFIC INVESTIGATIONS</b>			
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> NONCLINICAL	
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> The dissolution method and acceptance criteria requires an evaluation. Additionally, the applicant is proposing a change in debossing for commercial manufacturing from the drug product manufactured for the pivotal clinical trials. An evaluation of the dissolution data to support this change is requested.			
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PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC.	DONEPEZIL HYDROCHLORIDE

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/s/

DON L HENRY  
10/05/2009

MARTHA R HEIMANN  
10/05/2009



NDA 22-568

**NDA ACKNOWLEDGMENT**

Eisai Medical Research Inc.  
Attention: Kevin M. McDonald  
Associate Director, Global Regulatory Affairs  
300 Tice Boulevard  
Woodcliff Lake, NJ 07677

Dear Mr. McDonald:

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

Name of Drug Product: Aricept (b) (4) (donepezil hydrochloride) extended release Tablet 23 mg

Date of Application: September 24, 2009

Date of Receipt: September 24, 2009

Our Reference Number: NDA 22-568

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 November 23, 2009 in accordance with 21 CFR 314.101(a).

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

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

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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at (301) 796-1161.

Sincerely,

*{See appended electronic signature page}*

Teresa Wheelous, R. Ph.  
Sr. Regulatory Management Officer  
Division of Neurology Products  
Office of Drug Evaluation 1  
Center for Drug Evaluation and Research

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC.	DONEPEZIL HYDROCHLORIDE

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/s/

TERESA A WHEELIOUS  
09/29/2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<h2 style="margin: 0;">REQUEST FOR CONSULTATION</h2>			
TO (Office/Division): <b>Patrick Marroum, Biopharmaceutics, ONDQA</b>			FROM (Name, Office/Division, and Phone Number of Requestor): <b>Don Henry Project Manager, ONDQA, 301-796-4227 on behalf of A. Khairuzzaman/R. Sood</b>		
DATE 2/25/2010	IND NO.	NDA NO. 22-568	TYPE OF DOCUMENT original submission	DATE OF DOCUMENT September 24, 2009	
NAME OF DRUG <b>donepezil hydrochloride</b>		PRIORITY CONSIDERATION standard	CLASSIFICATION OF DRUG Neurology	DESIRED COMPLETION DATE 3/24/2010	
NAME OF FIRM: <b>Eisai Medical Research</b>					
<b>REASON FOR REQUEST</b>  <b>I. GENERAL</b>					
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22568	ORIG-1	EISAI MEDICAL RESEARCH INC	DONEPEZIL HYDROCHLORIDE

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/s/

DON L HENRY  
02/26/2010

RAMESH K SOOD  
02/26/2010

**Pre-NDA PRELIMINARY MEETING COMMENTS**

**MEETING DATE:** February 11, 2009

**TIME:** 3 PM – 4 PM

**LOCATION:** White Oak, Building #22,

**APPLICATION:** IND 35,974 Donepezil SR

**TYPE OF MEETING:** Pre-NDA

**MEETING CHAIR:** Dr. Russell Katz

**DISCLAIMER**

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 11, 2009 between Eisai Medical Research Inc and the Division of Neurology Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting /to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

**Draft Response To Sponsor's Questions****Question 1**

Given that the planned NDA submission will include data from a single randomized double-blind clinical trial, Eisai believes that Module 2.7.3 – Summary of Clinical Efficacy as described in the ICH Guidance “M4E: The CTD-Efficacy” is sufficient to characterize the efficacy of Aricept SR. Eisai, therefore, proposes not to prepare an Integrated Summary of Efficacy (ISE). Is this proposal acceptable to the Division?

**Assuming that the planned NDA submission will include the full clinical study report for Study E2020-A001-326, your proposal is acceptable.**

**Question 2**

The NDA submission will include safety data from a single randomized double-blind clinical trial, E2020-G000-326 and limited supporting safety data from the ongoing open-label extension study, E2020-G000-328.

**Question 2a**

Eisai proposes not to prepare an Integrated Summary of Safety (ISS). However, in addition to Module 2.7.4 – Summary of Clinical Safety as described in the ICH Guidance “M4E: The CTD-Efficacy”, additional safety analyses that would

typically be included in an ISS will be provided in the clinical study report (CSR) for Study 326 as appropriate and clinically necessary. Eisai believes this proposal is sufficient to characterize the safety of Aricept SR. Does the Division agree?

**Assuming that the planned NDA submission will include the full clinical study report for Study E2020-A001-326, your proposal is acceptable.**

**Question 2b**

Does the Division agree that the overall content and presentation of clinical safety information described in Section 9.1.1 of this briefing document is adequate for the planned NDA submission?

**Yes. Please also see our response to Question 2a**

**Question 3**

All information pertaining the CMC (Modules 2.3 and 3) drug substance portion of this New Drug Application will cross reference the original Aricept Tablet 5 and 10 mg NDA, (NDA # 20-690), in addition to all amendments/supplements thereto. Is this proposal acceptable to the Division?

**The proposal to cross-reference the approved NDA 20-690 is acceptable; however, the following drug substance information should be provided in the planned NDA submission.**

- **A list of all facilities involved in manufacturing, testing, or packaging of the bulk drug substance should be provided. This list should include complete addresses, registration numbers and contact information for each facility. All functions (e.g., drug substance testing, tablet manufacture, stability testing, etc.) that will be performed by each facility should be identified.**
- **Please provide a summary table for the drug substance specification. It is not necessary to submit detailed descriptions or methods validation data for analytical methods that were previously reviewed to support the approved application.**

**Question 4**

As agreed at the End-of-Phase II/Pre-Phase III meeting on 19 March 2007, no additional non-clinical studies are needed to support an NDA for Aricept SR. Therefore, Eisai intends to cross-reference Module 4 (Non-Clinical Study Reports), Module 2.4 (Non-Clinical Overview) and Module 2.6 (Non-Clinical Written and Tabulated Summaries) to NDA 20-690. Is this proposal acceptable to the Division?

**Yes.**

**Question 5**

Eisai intends to provide Case Report Forms (CRFs) for all deaths, SAEs and discontinuations due to AEs from the double-blind pivotal efficacy study, E2020-

G000-326, and from the ongoing open-label extension study, E2020-G000-328. In the initial NDA submission, completed CRFs for the ongoing study -328 will be provided up to a cut-off point of 6 months prior to the NDA submission date. For the 4-month safety update, Eisai also proposes to use a cut-off date of 6 months prior to that submission date for the inclusion of the additional open-label CRFs. Is this proposal acceptable to the Division?

**Yes.**

**Question 6**

Eisai proposes to submit electronic datasets in accordance with the current "Study Data Specifications" document posted on CDER's Electronic Regulatory Submissions and Review (ERSR) website provided in **Appendix 1**. Eisai intends to submit datasets for only the Phase III pivotal efficacy study, E2020-G000-326, and not for the Phase I clinical pharmacology studies. Is this proposal acceptable to the Division?

**No. In addition to submitting electronic datasets for Study E2020-G000-326, you should submit electronic datasets for all four of the Phase I clinical pharmacology studies whose full reports you intend to include in the application.**

**Question 7**

As agreed at the End-of-Phase II/Pre-Phase III meeting on 19 March 2007, Eisai has conducted an in vitro study, W-20080032, where dose-dumping was evaluated in various concentrations of alcohol. The results of this study show that no dose dumping occurred in the presence of ethanol (Detailed in Section 9.2.1 and **Appendix 4**). Based on these findings, Eisai believes that no additional in vivo studies should be necessary to further evaluate the potential for dose dumping with alcohol. Does the Division agree?

**We agree with your proposal, but that agreement is conditional upon the outcome of our full review of the results of the *in vitro* study when the planned NDA is submitted.**

**Question 8**

Eisai has conducted a literature review on CYP2D6 inhibitors and cholinesterase inhibitors, and the existing literature on this topic is sparse. Therefore, Eisai proposes to conduct population PK analyses with the large number of subjects in Study E2020-G000-326 who participated in the population PK assessments (Detailed in Section 9.2.2). These analyses would (1) evaluate CYP2D6 status and plasma levels of donepezil; and (2) the impact, if any, on donepezil plasma concentrations from concomitant use of commonly used CYP2D6 inhibitors in the AD patient population. In lieu of an additional in vivo study, the results of these analyses would be used to support the labeling of Aricept SR with regard to the potential for CYP2D6 inhibitors to affect the metabolism of donepezil. Does the Division agree with this approach?

**Your proposed approach is acceptable to us. Please include the relevant medical literature and the report of the population pharmacokinetic analysis for Study E2020-G000-326 in your planned NDA for Aricept SR.**

**Question 9**

Eisai plans to submit the Aricept SR draft labeling in Physician's Labeling Rule (PLR) format in accordance with 21 CFR 201.56(d), 201.57 and the draft Guidance for Industry entitled "Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements". Eisai will use the same format as in the pending PLR labeling supplement for Aricept 5 and 10 mg tablets submitted as of 25 November 2008. Is this proposal acceptable to the Division?

**Yes.**

**Question 10**

(b) (4)

**Question 11**

As per the ICH guidance "Q1C – Stability Testing for New Dosage Forms", Eisai will be filing the NDA with 6 months stability data on the drug product. Eisai will amend the application with an additional 6 months stability data within the first 4 months after the original submission, so as to have a total of 12 months stability data on file with the Division well before the action date. Eisai plans to request a 24-month expiry (as per the ICH guidance "Q1E – Evaluation of Stability Data"). Is this proposal acceptable to the Division?

**The proposed stability package is acceptable for filing. The expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data.**

**You propose to submit additional stability data within 4 months after the original submission. Additional data received prior to mid cycle (i.e., 5 months for a standard submission or 3 months for a priority submission) will be reviewed as part of the original application; however, data received later may not be reviewed during the same review cycle.**

**Question 12**

Eisai proposes to provide one executed batch record with Japanese to English translation included for the proposed 23 mg (b) (4) dosage strength in the NDA. Is this proposal acceptable to the Division?

**Yes.**

**Question 13**

Does the Division consider the proposed drug product's dissolution method and specifications provided in **Appendix 2** acceptable for the NDA filing?

**The adequacy of the proposed dissolution method and acceptance criteria will be determined during review of the application based on the supporting data to be provided in the planned NDA. Provide the full dissolution development report in the NDA.**

**Question 14**

As discussed in the End-of Phase II /Pre-Phase III Meeting with the Division, Eisai proposed the trade name [REDACTED] (b) (4)

[REDACTED] However, Eisai is considering using a completely different trade name for this product [REDACTED] (b) (4) Would the Division provide comment on the acceptability of this proposal? Following further input from the Division on this question, Eisai will prepare a formal submission for the review of the trade name in accordance with the November 2008 draft Guidance for Industry, "Contents of a Complete Submission for the Evaluation of Proprietary Names".

**We do not concur with your proposal to use a completely new trade name for your product. In our view, the trade name for your proposed [REDACTED] (b) (4) formulation of donepezil should include the name "Aricept."**

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** March 19, 2007  
**Application:** IND 35,974; Sustained Release Aricept  
**Indication:** Alzheimer's Disease  
**Type of Meeting:** EOP2  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

Russell Katz, M.D., Division Director  
Kun Jin, Ph.D., Statistics Supervisor  
Veneeta Tandon, Ph.D., PK

Ranjit Mani, M.D., Team Leader  
Julia Luan, Ph.D., Statistics  
Melina Griffis, R.Ph.

### Eiasai Attendees:

Jiro Hasegawa, Ph.D.  
Margaret Moline, Ph.D.  
Zhengning Lin, Ph.D.  
Libbie Mansell, Ph.D., M.B.A.  
Kevin McDonald

Timothy Hsu, M.D.  
Chukwuemeka Okereke, R. Ph, MBA, PH.D.  
Qin Wang, Ph.D.  
Martina Struck, Ph.D.

**Discussion Points and Decisions (agreements) reached: Below are the sponsors proposed questions and the Divisions preliminary responses followed by any further discussion that occurred during the meeting.**

### CLINICAL/STATISTICAL

1. We believe that studies E2020-A001-021 (single dose study), -022 (multiple dose study), and -023 (food effect study) are adequate to characterize the pharmacokinetic (PK) profile of Aricept® SR tablets in the Aricept SR prescribing information and that no further clinical pharmacology studies are necessary. Does the Agency agree?

#### Pre-Meeting Comments

Yes. However, the following information will also be required for the NDA filing:

- The sponsor should provide relative bioavailability (steady state exposure comparisons) of the Aricept SR compared to IR formulations. This can probably be done with the data from the Phase III Study 326, provided the data is collected appropriately with adequate sparse sampling.
- Dose dumping with alcohol should be evaluated. First in vitro dissolution studies in various concentrations of alcohol (e.g. 5, 20 and 40%) should be conducted. Once results are available, the sponsor should discuss this with the Office of Clinical Pharmacology for assessing the need for in vivo study.



- In the current label no information has been given for an in vivo interaction study with a CYP 2D6 inhibitor. The sponsor should conduct a literature search to gather information on the ability of donepezil metabolism to be inhibited by CYP 2D6 inhibitors. In the absence of any literature information, an in vivo study may be necessary unless adequately justified.

#### Additional Discussion At Meeting

The sponsor's plans to address the above comments were outlined at the meeting, and found acceptable by the Agency. The sponsor was advised to collect blood samples at different times in different individuals to characterize the pharmacokinetic profile with the two formulations.

2. We believe that, taken together with the extensive safety database that exists for Aricept 5 mg and 10 mg tablets, the studies summarized in the briefing document (E2020-A001-021, -022, and -023) should provide sufficient safety and tolerability information on Aricept SR tablets to initiate the Phase III program. Does the Agency agree?

#### Pre-Meeting Comments

We agree that Study E2020-G000-326 may be initiated, assuming that the inclusion criteria, study drug dosing regimen, and safety monitoring are as specified in the version of that protocol included in this submission.

#### Additional Discussion At Meeting

None

3. Aricept (donepezil HCl) 5 and 10 mg IR tablets have been approved for marketing in the US since November 1996. The effectiveness of Aricept has been well-established in patients with mild to moderate and with severe Alzheimer's disease. Given that Aricept SR 23 mg represents a new dose/dosage form of the approved product, does the Agency agree that data from a single pivotal efficacy study would be sufficient to obtain product approval?

#### Pre-Meeting Comments

A single adequate and well-controlled study that demonstrates substantial evidence of effectiveness is likely to be sufficient to obtain product approval. Please also see our response to Question 4.

#### Additional Discussion At Meeting

None

4. As described in the protocol for Study E2020-G000-326, the primary efficacy analysis has been designed so that in order for the study to be declared positive, the cognitive co-primary endpoint, the Severe Impairment Battery (SIB), must reach statistical significance with Aricept SR 23 mg demonstrating superiority over the current 10 mg Aricept IR formulation, and the global co-primary endpoint, the Clinician's Interview-Based Impression of Change (Plus version) (CIBIC+), must reach significance with Aricept SR 23 mg demonstrating non-inferiority to the 10 mg IR formulation. Could a positive study under these circumstances support registration and be the basis for a statement in the Clinical Trials section of the prescribing information regarding the superiority of Aricept SR 23 mg in cognitive performance as assessed by the SIB?

#### Pre-Meeting Comments

The current regulatory standard requires that the effectiveness of a treatment for Alzheimer's Disease be demonstrated on both a cognitive and a global (or functional) primary efficacy measure; underlying this standard is the need to confirm that an effect on the cognitive primary efficacy measure that is statistically significant is also clinically meaningful. Thus, Study E2020-G000-326 can be considered to provide substantial evidence of effectiveness for the 23 mg/day dose (b) (4) formulation of Aricept® only if that dose is demonstrated to have a statistically significant superiority over the 10 mg/day dose of the immediate-release formulation on both primary efficacy measures, the SIB and the CIBIC-Plus. Under those circumstances, the results of that trial can be described in the CLINICAL TRIALS section of the product labeling.

Evidence that the 23 mg/day dose of Aricept® is non-inferior to the 10 mg/day dose of the immediate-release formulation on the CIBIC-Plus cannot be considered to support the efficacy of the former since the efficacy of the latter formulation on that measure in this population cannot be assumed. In that context, we note that in your earlier clinical trial E2020-A001-315 which was conducted in patients with severe Alzheimer's Disease and in which about 85% of those receiving the immediate-release formulation donepezil reached a dose of 10 mg/day, there was no evidence for the efficacy of donepezil on the CIBIC-Plus, the global primary efficacy measure.

We have the following additional comments about your proposed study:

- While the Severe Impairment Battery has been considered an appropriate measure to use in evaluating the effect of a treatment on cognition in patients with moderate to severe Alzheimer's Disease, it has generally been used in clinical trials that have enrolled patients with a Mini-Mental Status Examination score at entry  $\leq 14$ , whereas your trial proposes the enrollment of patients with an entry Mini-Mental Status Examination score  $\leq 20$ . We, therefore, ask that you justify the applicability of that measure to the entire range of Mini-Mental Status Examination scores that you are proposing to enroll

- You have proposed that an analysis of covariance be the primary method of analyzing the CIBIC-Plus which you refer to as a continuous variable. In our view, the CIBIC-Plus is more appropriately considered a categorical variable that should be analyzed using a non-parametric method

#### Additional Discussion At Meeting

The sponsor proposed the use of the modified ADCS-ADL as the co-primary outcome measure in lieu of the CIBIC-Plus, with Study E2020-G000-326 then being required to demonstrate evidence for the superiority of the 23 mg/day dose of the sustained-release formulation of donepezil (over the 10 mg/day dose of the immediate-release formulation) on the SIB and non-inferiority of that dose (in relation to the 10 mg/day dose of the immediate-release formulation) on the modified ADCS-ADL, for the study to be considered to provide substantial evidence for efficacy. In the Division's view, the experience with immediate-release donepezil in patients with severe Alzheimer's Disease on either measure is insufficiently robust, for it to be assumed that the 10 mg/day dose of that formulation can be assumed to have efficacy in Study E2020-G000-326. Thus for that study to be considered to show substantial evidence of efficacy for the 23 mg/day dose of the sustained-release formulation of donepezil, the superiority of the 23 mg/day dose of the sustained-release formulation (over the 10 mg/day dose of the immediate-release formulation) on both the SIB (cognitive primary efficacy measure), and CIBIC-Plus or ADCS-ADL (global or functional primary efficacy measure) would need to have been demonstrated.

The sponsor is to submit an amended version of E2020-G000-326 to the Division with a request for a Special Protocol Assessment.

The sponsor is also to submit, with the request for a Special Protocol Assessment, a detailed argument supporting the use of the SIB as an efficacy outcome measure in those with a Mini-Mental Status Examination score in the 15 to 20 range. The Division recommended that a prospectively-described sample size calculation take into consideration the possibility that the sponsor's argument might not be acceptable, in which event enrollment might have to be restricted to those with a Mini-Mental Status Examination score < 15.

A discussion was held about the appropriateness of using an analysis of covariance model to analyze the CIBIC-Plus; the sponsor is to provide an argument in favor of that model with the above request for a Special Protocol Assessment.

5. If Aricept SR 23 mg demonstrates non-inferiority to the 10 mg IR formulation on the CIBIC+, then a further analysis for testing the superiority of Aricept SR 23 mg to the 10 mg IR formulation will be performed as described in the protocol for Study E2020-G000-326. Does the Agency agree that a statistically significant superiority result from this proposed analysis could result in a statement in the Clinical Trials section of the prescribing information regarding the superiority of Aricept SR 23 mg in global function as assessed by the CIBIC+?

#### Pre-Meeting Comments

Please see our response to Question 4.

#### Additional Discussion At Meeting

Please see discussion under Question 4

6. An interim analysis is planned for E2020-G000-326, and will be conducted when approximately one third of the total subjects complete the study. Does the Agency agree with the plan for this interim analysis as detailed in the Independent Data Monitoring Committee (IDMC) draft charter, and in particular, the objectives of stopping enrollment early?

#### Pre-Meeting Comments

Please see our response to Question 4. As we have indicated in that response, your proposed study will need to demonstrate the superiority of the 23 mg/day dose of the sustained-release formulation of Aricept® over the 10 mg/day dose of the immediate-release formulation on both the SIB and the CIBIC-Plus to support the approval of the new formulation and your interim efficacy analysis should therefore be modified accordingly.

Please provide full details of the statistical methods that you will use at both your interim and final analyses. Please also clarify how the studywise Type I error will be controlled for the final efficacy analysis.

Please also explain in detail your calculation of conditional probabilities for the interim analysis and justify your choice of stopping boundaries.

We recommend that the interim analysis be confined to the 400 patients who have completed the study at that timepoint.

#### Additional Discussion At Meeting

The planned interim analysis was outlined briefly by the sponsor; the analysis is to be performed on the 400 patients who have completed the study at that timepoint and the methods that are to be used at the interim analysis to determine if there is likely to be evidence for efficacy once 800 patients have completed the study specified. The planned interim analysis

was then discussed further; the sponsor is to provide evidence for why the conduct of that analysis will not introduce bias or inflation of the Type I error in the conduct of the final analysis, should the study proceed to completion.

7. Approximately 1200 patients are expected to be enrolled in Study E2020-G000-326. However, as described above, enrollment may be stopped early based on the results of the interim analysis. In this case, we expect to have a minimum of 300 patients treated with Aricept SR 23 mg who have completed the 26-week double-blind study at the time of NDA submission. In addition, we anticipate that at least 100 of these patients will have been treated with Aricept SR for at least one year. Does the Agency agree that the proposed overall safety data on Aricept SR obtained from Study E2020-G000-326 and the open label extension, Study -328, will be sufficient for submission of a New Drug Application (NDA) for Aricept SR?

#### Pre-Meeting Comments

The size of the proposed safety database for the (b) (4) formulation of Aricept® may be sufficient to support the proposed NDA, unless any currently-unanticipated safety concerns are not revealed by that database.

(b) (4)

#### Additional Discussion At Meeting

None

#### **NON-CLINICAL TOXICOLOGY**

8. We believe that the existing non-clinical/toxicological data on Aricept 5 and 10 mg IR tablets are sufficient to support approval of Aricept SR. Does the agency agree that no additional non-clinical/toxicology studies are necessary?

#### Pre-Meeting Comments

Based on the available information, we agree that no additional non-clinical studies will be needed to support an NDA for Aricept SR.

#### Additional Discussion At Meeting

None

**CHEMISTRY, MANUFACTURING, AND CONTROL (CMC)**

9. At the time of NDA submission, it is anticipated that 6 months stability data will be available. In accordance with the ICH Q1C Guidance, *Stability Testing for New Dosage Forms*, we intend to file the NDA with the 6 months data with a commitment to amend the application with an additional 6 months stability data during the first 5 months of the review period. Is this proposal acceptable to the Agency?

Pre-Meeting Comments

Yes

Additional Discussion At Meeting

None

**TRADE NAME**

10.

(b) (4)

Pre-Meeting Comments

We do not have any concerns about the acceptability of the proposed name at this time, however, it will have to be reviewed by the Division of Medication Errors and Technical Support at the time of the NDA submission. Additionally, the established name should read "donepezil hydrochloride" (b) (4)

Additional Discussion At Meeting

The above pre-meeting comments were confirmed

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

-----  
Russell Katz  
3/28/2007 10:23:43 AM

## ACTION PACKAGE CHECKLIST

### APPLICATION INFORMATION<sup>1</sup>

NDA # 22568		
Proprietary Name: Aricept Established/Proper Name: donepezil hydrochloride Dosage Form: 23 mg Tablet		Applicant: Eisai Medical Research Agent for Applicant (if applicable): Martina Struck
RPM: Teresa Wheelous		Division: Division of Neurology Products
NDAs: NDA Application Type: X 505(b)(1)		
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>July 24, 2010</u></li> </ul>		X AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received
❖ Application Characteristics <sup>2</sup>		
<p>Review priority:    X Standard</p> <p>Chemical classification (new NDAs only):        3</p> <p>Comments:</p>		

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

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



Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul>	

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

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

☐ Yes ☐ No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of

☐ Yes ☐ No

certification?

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

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

*If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*

### CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist<sup>3</sup>

yes

#### Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (*approvals only*)

☐ Included

Documentation of consent/non-consent by officers/employees

☐ Included

#### Action Letters

❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) 7/23/10

#### Labeling

❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

- Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

❖ Medication Guide/Patient Package Insert/Instructions for Use (*write submission/communication date at upper right of first page of each piece*)

☐ Medication Guide  
☐ Patient Package Insert  
☐ Instructions for Use  
☒ None

- Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.
- Original applicant-proposed labeling
- Example of class labeling, if applicable

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

6 Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
• Most-recent draft labeling	
6 ❖ Proprietary Name • Acceptability/non-acceptability letter(s) (indicate date(s)) • Review(s) (indicate date(s))	4/1/10
4 ❖ Labeling reviews (indicate dates of reviews and meetings) 7/14/10	<input type="checkbox"/> RPM <input checked="" type="checkbox"/> DMEPA <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
1 ❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (indicate date)	<input checked="" type="checkbox"/> Not a (b)(2)
3 ❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo (indicate date) ○ If yes, OC clearance for approval (indicate date of clearance communication)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
4 ❖ Pediatrics (approvals only) • Date reviewed by PeRC 4/21/10 If PeRC review not necessary, explain: _____ • Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input type="checkbox"/> Included <i>Waived</i>
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
L ❖ Outgoing communications (letters (except action letters), emails, faxes, telecons)	
M ❖ Internal memoranda, telecons, etc.	
N ❖ Minutes of Meetings	
• Regulatory Briefing (indicate date of mtg)	<input type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (indicate date of mtg)	<input type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (indicate date of mtg)	<input type="checkbox"/> No mtg
• EOP2 meeting (indicate date of mtg)	<input type="checkbox"/> No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) (indicate dates of mtgs)	

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	
• Clinical review(s) ( <i>indicate date for each review</i> )	
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 7/9/10

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (include copies of DSI letters)	<input type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Microbiology Reviews	<input type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (indicate date of each review)	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	

Facilities Review/Inspection	
<input type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>6</sup>)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>6</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

## Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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