

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022568

OTHER REVIEW(S)

Aricept PMR/PMC Development Template
PMR 1662-1

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: A single-dose oral neurotoxicity study in female rats with donepezil and memantine, alone and in combination, at doses ranging from those resulting in plasma exposures similar to those in humans given 23 mg/day donepezil and/or 28 mg/day NAMENDA XR, up to maximum tolerated doses.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>12/31/2010</u>
	Study Completion Date:	<u>12/31/2011</u>
	Final Report Submission Date:	<u>06/30/2012</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Donepezil is an approved drug (NDA 20-690). However, since the approval, a published study (Creeley et al., 2008) has reported that coadministration of donepezil exacerbated the neurodegeneration induced by memantine in rat brain; both drugs were administered by intraperitoneal injection. A study is needed to further investigate this finding, using the clinical route of administration.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A published study by Creeley et al. (2008) reported that coadministration of donepezil exacerbated the neurodegeneration induced by memantine in rat brain when both drugs were given by intraperitoneal injection. This information was not available at the time of NDA approval. Clinically, memantine and donepezil are commonly used in combination. Therefore, there is a need for greater understanding of the potential for donepezil to exacerbate memantine-induced neurotoxicity when administered by the clinical route (oral), especially since plasma exposures for donepezil will be increased approximately 2-fold with the new 23 mg dosage strength.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Aricept PMR/PMC Development Template
PMR 1662-2

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: An *in vitro* study to evaluate the potential of donepezil as an inhibitor of CYP2B6, CYP2C8 and CYP2C19.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>12/31/2010</u>
	Study Completion Date:	<u>06/30/2011</u>
	Final Report Submission Date:	<u>12/31/2011</u>
	Other:	<u>MM/DD/YYYY</u>

5. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern due to lack of information about potential for donepezil to inhibit CYP2B6, CYP2C8 and CYP2C19. The study requested in this PMR is based on the FDA guidance "Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>.

6. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The sponsor did not conduct an *in vitro* study to determine the inhibition potential of donepezil on CYP2B6, CP2C8 and CYP2C19. The new safety information is that CYP2B6, CYP2C8, and CYP2C19 were not well characterized in the NDA when donepezil was approved in 1996. There is a theoretical concern regarding the potential for an unexpected serious risk of adverse events due to increased exposure to CYP2B6, 2C8 and 2C19 substrates if donepezil is an inhibitor of these CYP enzymes and co-administered with their substrates. The goal of this study is to evaluate the potential effect of donepezil on CYP2B6, CYP2C8 and CYP2C19. Based on the results of this *in vitro* study, a further *in vivo* study may be needed.

7. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An <i>in vitro</i> study to evaluate the potential of donepezil as an inhibitor of CYP2B6, CYP2C8, and CYP2C19.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

6. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

**Aricept PMR/PMC Development Template
PMR 1662-3**

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: *In vitro* study to evaluate whether donepezil is a P-glycoprotein (P-gp) substrate.

PMR/PMC Schedule Milestones:	Final protocol Submission Date:	<u>12/31/2010</u>
	Study Completion Date:	<u>06/30/2011</u>
	Final Report Submission Date:	<u>12/31/2011</u>
	Other:	<u>MM/DD/YYYY</u>

8. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern for lack of the information about whether donepezil is a P-gp substrate. The study request as a PMR is based on the FDA guidance “Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling”
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>.

9. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor did not perform an *in vitro* study to determine whether donepezil is P-gp substrate. The new safety information is that P-gp is a transporter that was not well characterized when donepezil was approved in 1996 and for which several recent publications by Summerfield et al. (*J Pharmacol Exp Ther.* 2007 Jul;322(1):205-13), Wager et al. (*ACS Chem Neurosci.* 2010, 1, 420-434), Yoshihiro (*Drug Metab Rev.* 2005 Nov; 37 (suppl 2): 177-178), and Ishiwata et al. (*J Nucl Med.* 2007 Jan;48(1):81-7) show conflicting results and were not performed according to recommendations provided in the FDA guidance “Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072101.pdf>. There is a theoretical concern of unexpected serious risk of increased exposure to donepezil, which may result in safety issues, if donepezil is a P-gp substrate and co-administered with P-gp inhibitors. The goal of this study is to evaluate whether donepezil is P-gp substrate. Based on the results of the *in vitro* study, an *in vivo* study may be necessary.

10. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
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Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

7. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

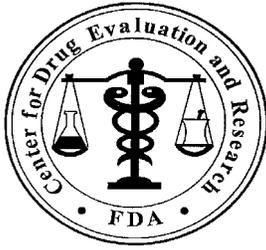
(signature line for BLAs)

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

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

/s/

SALLY U YASUDA
07/19/2010
PMR/PMC development template



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: July 14, 2010

To: Russell Katz, M.D., Director
Division of Neurology Products

Through: Melina Griffis, RPh, Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Irene Z. Chan, Pharm.D., BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Aricept (Donepezil Hydrochloride) Tablets 23 mg

Application Type/Number: NDA 022568

Applicant: Eisai, Inc.

OSE RCM #: 2009-1917

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1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis' (DMEPA) evaluation of the proposed container labels, insert labeling, and patient package insert for Aricept Tablets 23 mg. We provide recommendations in Section 4 that aim at reducing the risk of medication errors with regard to the proposed product labels and labeling.

2 METHODS AND MATERIALS

For this review, DMEPA searched the FDA Adverse Event Reporting System (AERS) database and reviewed proposed container labels and carton labeling.

2.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Aricept tablets are currently marketed; therefore, DMEPA conducted a search of the FDA Adverse Event Reporting System (AERS) database on January 29, 2010, to identify medication errors involving Aricept or Donepezil Hydrochloride.

The MedRA High Level Group Terms (HLGT) "Medication Errors" and "Product Quality Issues" were used as search criteria for Reactions. The search criteria used for Products were active ingredients "donepezil" and "donepezil hydrochloride," trade name "Aricept" and verbatim substance search "donep%" and "Aricep%." No date limitations were set.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were combined into cases. The cases that described a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors. If a root cause was associated with the labels or labeling of the product, the case was considered pertinent to this review. Those reports that did not describe a medication error or did not describe an error applicable to this review were excluded from further analysis.

2.2 LABEL AND LABELING

Using failure mode and effects analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the labels and labeling of products. This review focuses on the labels and labeling submitted as part of the June 3, 2010, submissions (see Appendices A and B). In addition, DMEPA reviewed approved labels and labeling for currently marketed Aricept products (see Appendix C, D, E, F, and G). These were reviewed so that comparisons could be made across the product line.

3 RESULTS AND DISCUSSION

3.1 FDA ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

The AERS search conducted on January 29, 2010, yielded 164 cases. Of these cases, 140 were excluded from further evaluation for the reasons presented in Appendix H. The remaining 24 cases were considered relevant to this review (see Appendix I for a list of relevant cases).

Of the 24 relevant cases, 23 reported a wrong drug error involving Aricept and Aciphex. Causes of error included the following: Similarity in packaging, similar bottle size and appearance, storage close to each other, orthographic and phonetic similarity, illegible handwriting, labels appear similar, and busy pharmacy.

Name confusion between Aricept and Aciphex was previously reviewed in September of 2001 (OSE Review # 01-0190), and the following contributing factors were identified at that time: orthographic and phonetic similarity between Aciphex and Aricept, similar container labels, and similar NDC numbers. Based on these root causes, DMEPA provided container label recommendations to help decrease the

potential for confusion between Aciphex and Aricept. New labels for Aricept were approved May 29, 2002. Since then the number of medication errors involving confusion between Aricept and Aciphex has decreased with no errors reported in 2008, 2009, or as of the date of our AERS search. These results suggest that labeling was a contributing factor to the name confusion errors between Aricept and Aciphex.

We identified one case where the reporter noted that the net quantity and the marketers' names were more prominent than the drug name, Aricept, and the strength.

3.2 LABEL AND LABELING

The label and labeling risk assessment indicates the presentation of information on the proposed labels and labeling introduces vulnerability to confusion that can lead to medication errors. During our review of the proposed labels and labeling, we considered the relevant AERS case in which the reporter noted that the net quantity and the marketers' names were more prominent than the drug name, Aricept, and the strength. The Applicant has proposed a new trade dress for Aricept Tablets 23 mg. As part of the new trade dress, both the proprietary name and strength presentations are larger than the net quantity presentation. However, the graphics denoting the marketers' names, Eisai and Pfizer, are still large and distracting from the most important information on the label.

It was determined that the labels and labeling need improvement in the following areas: Increased prominence of the strength presentation, decreased prominence of the graphics denoting the marketers' names, inclusion of the dosage form, moving the net quantity statement away from the strength presentation, minimizing the graphic above the proprietary name, removal of the gradient color strip on container labels, improved contrast between the strength presentation box coloring and font within the box, and removal of ambiguous abbreviations and trailing zeros in the insert labeling. Our recommendations are further explained in Section 4 below.

4 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container labels and insert labeling noted areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 4.1 Comments to the Division to be discussed. We request the recommendations for the carton labeling and container labels in Section 4.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley, at 301-796-5068.

4.1 COMMENTS TO THE DIVISION

A. GENERAL COMMENTS

1. The Applicant has utilized the abbreviations "IV" and "µg" within the insert labeling to represent intravenous and micrograms. The abbreviation I.V can be misinterpreted to mean I.U or I.N. The abbreviation "µg" can be misinterpreted to mean "mg." As part of a national campaign to decrease the use of dangerous abbreviations, FDA agreed to not use such abbreviations in the approved labeling of products because these abbreviations can be carried over to prescribing. Therefore we recommend that "IV" be replaced with the text *intravenous* and "µg" be replaced with the text *micrograms* or *mcg*.
2. The Applicant has utilized trailing zeros within the insert labeling. Trailing zeros can lead to 10-fold errors in dosing. DMEPA recommends removing all trailing zeros with the exception of when it is required to demonstrate the level of precision of the value being reported, such as for laboratory results, imaging studies that report size of lesions, or catheter/tube sizes

4.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS FOR LABELS AND LABELING

1. As currently presented, the dosage form is not present. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form on all labels and labeling for Aricept Tablets 23 mg immediately following the active ingredient presentation. Ensure the dosage form presentation is commensurate with the prominence of the active ingredient presentation.
2. As currently presented, the graphic located above the proprietary name is oversized and distracting from the proprietary name, established name, and strength presentation. Minimize the size of the graphic located above the proprietary name on all labels and labeling.
3. The 30 count and 90 count bottles may be considered unit-of-use containers. Please ensure these bottles utilize child-resistant closures to comply with the Poison Prevention Packaging Act of 1970.

B. RETAIL CONTAINER LABELS FOR 30 AND 90 COUNT BOTTLES, PROFESSIONAL SAMPLE BLISTER FOIL LABEL, AND PROFESSIONAL SAMPLE CARTON LABELING

As currently presented, the net quantity statement is located directly beneath the strength presentation, which is distracting from the strength presentation and may be difficult to find on the label. Move the net quantity statement to the upper right hand corner of the principle display panel so it is more easily identified and will not be confused with the strength presentation.

C. RETAIL CONTAINER LABELS FOR 30 AND 90 COUNT BOTTLES

The principle display panel appears crowded due to the manufacturer statement, distributor statement, and the logos containing the names “Eisai” and “Pfizer.” We recommend revising to a condensed statement such as *Manufactured by Eisai for Pfizer* and removing or minimizing the logos.

D. PROFESSIONAL SAMPLE BLISTER FOIL

In the event that tablets are removed individually by separating at the perforation lines, the tablets are not identifiable. Ensure the proprietary name, established name, and strength, are printed on each unit-of-use blister. If this is not feasible, then consider repetitive listing of the proprietary name, established name, and strength, as is seen on lidding foils for other drug products, such that the information is visible after a tablet is removed.

11 Pages have been Withheld in Full immediately following this page as B4 (Draft Labeling).

Appendix H: Excluded AERS search results

The AERS search conducted on January 29, 2010, yielded 164 cases. Of these cases, 140 were excluded from further evaluation for the reasons below.

- Report of an adverse drug reaction (n=41)
- Report of an accidental exposure in a child (n=1)
- Product quality complaint that is beyond the scope of this review (n=2)
- Drug monitoring error not relevant to this review (n=3)
- Wrong patient error where one patient received another patient's medicine (n=4)
- Improper dose errors, including intentional overdoses where labels and labeling were not cited as cause (n=64)
- Wrong frequency errors not related to labels and labeling (n=4)
- Incorrect drug administration error where labels and labeling were not cited as a cause (n=1)
- Dose omission error (n=1)
- Aricept was reported as a concomitant medication only and no error occurred (n=6)
- Wrong drug errors where labels and labeling were not a contributing factor (n=13)

Appendix I: Relevant AERS search results

1. ISR 3644688-1
2. ISR 3698305-5
3. ISR 3702751-0
4. ISR 3705915-5
5. ISR 3705919-2
6. ISR 3718070-2
7. ISR 3717655-7
8. ISR 3717666-1
9. ISR 3734664-2
10. ISR 3734717-9
11. ISR 3762592-5
12. ISR 3779859-7
13. ISR 3779885-8
14. ISR 3786945-4
15. ISR 3794767-3
16. ISR 3932292-7
17. ISR 4383122-3
18. ISR 4075996-0
19. ISR 3654128-4
20. ISR 4421704-0
21. ISR 4840618-5
22. ISR 5086261-7
23. ISR 5427288-2
24. ISR 3644659-5

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/

IRENE Z CHAN
07/14/2010

MELINA N GRIFFIS
07/14/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER
07/14/2010
Signing on behalf of Denise Toyer

CAROL A HOLQUIST
07/14/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: May 17, 2010

TO: Teresa Wheelous, Regulatory Health Project Manager
Ranjit Mani, M. D., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-568

APPLICANT: Eisai Medical Research Inc.

DRUG: Aricept^{(b) (4)} (donepezil hydrochloride) ^{(b) (4)} 23 mg Tablets

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of moderate to severe dementia of the Alzheimer's Type Disease

CONSULTATION REQUEST DATE: November 18, 2009

DIVISION ACTION GOAL DATE: June 10, 2010

PDUFA DATE: July 24, 2010

I. BACKGROUND:

The Sponsor, Eisai Medical Research Inc. submitted a New Drug Application for the marketing approval of Aricept^{(b) (4)} (donepezil hydrochloride) for the use in patients with advanced Alzheimer's Disease (AD), whom the proposed increased dose of donepezil will benefit. The tablet was developed as a sustained release (SR) formulation of donepezil at a dose of 23 mg for once a day use. The pivotal study submitted in support of the application, Protocol E2020-G000-326: "A Double-Blind, Parallel-Group Comparison of 23 mg Donepezil Sustained Release to 10 mg Donepezil Immediate Release in Patients with Moderate-To-Severe Alzheimer's Type Disease (AD)."

The study was a randomized double-blind, multicenter, parallel-group study comparing 23 mg of donepezil SR to 10 mg donepezil IR (2:1 randomization) in patients with moderate to severe AD. The study consisted of 24 weeks of daily administration of study medication, with clinic visits at Screening, Baseline, 3 weeks (safety only), 6 weeks, 12 weeks 18 weeks and 24 weeks or early termination. Eligible patients who completed the study were then eligible to participate in an open-label extension phase referred to as Study E2010-G000-328. The Applicant chose to develop the SR formulation at 23 mg/day, which they contend will provide a formulation that could be given at a higher dosage without the associated risk of increase adverse events (AEs). In addition, the Applicant contends that the once-daily dosing regimen in an Alzheimer's disease population will provide additional convenience and simplify administration for the caregiver. The study included male and female patients 49 to 90 years of age inclusive.

The primary objective of study Protocol E2010-G000-326 was to compare 23 mg donepezil SR with 10 mg donepezil IR in the treatment of patients with moderate to severe Alzheimer's disease and to determine the efficacy (as measured by the change from Baseline to Week 24 clinician's Interview- Based Impression of Change-Plus version (CIBIC-Plus) rating score and the change from Baseline to Week 24 in Severe Impairment Battery (SIB). Donepezil SR was administered once daily and compared with 10 mg donepezil IR and matching placebo tablets.

The review division requested inspections of two clinical investigators, one foreign and one domestic, that enrolled subjects in Protocol E2010-G000-326 as data from this study is considered essential to the approval decision. The data from this pivotal study would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, and it is desirable to include one foreign site to verify the quality of conduct of the study. These two sites were targeted for inspection due to enrollment of relatively large number of subjects and site specific protocol violations.

II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Manuel L. Montes, M.D Especialidades Medicas Ly S (Consulta privada) Av. Kenedy 5757 Of.608 Torre Oriente, Edificio Marriott, Las Condes Santiago 7560356, Chile Site #7069	Protocol 2010- G000-326 38 subjects	4/5-9/10	NAI(pending)
Reinaldo D. Verson, M.D. Columbus Research and Wellness 3645 Gentian Blvd, # 3B Columbus, GA 31907 Site # 6108	Protocol 2010- G000-326 29 subjects	1/25-2/3/10	VAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol E2010-G000-326

**1. Manuel I. Montes, M.D.
Chile**

a. What Was Inspected: At this site, a total of 42 subjects were screened, and 4 subjects were reported as screen failures. Thirty eight (38) subjects were randomized and 26 subjects completed the study. Six subjects discontinued the study: four due to adverse events, one moved to another city and one lost to –follow-up. Informed consent documents, for records reviewed, verified that subjects signed consent forms prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 9 subjects were reviewed in depth, including drug accountability records, vital signs,

safety assessment, inclusion/exclusion criteria, use of concomitant medications, laboratory test results, SIB, CIBIC plus, MMSE and ADC-ADL scores, IRB records, and source documents were compared to data listings, including primary efficacy endpoints and adverse events. One subject experienced UTI and was reported as not drug related.

b. General observations/commentary: Our investigation found no evidence of under reporting of adverse events and the primary endpoint data were verified. No significant violations were noted and a Form FDA 483 was not issued.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be in order and verifiable. There were no known limitations to this inspection.

c. Assessment of Data Integrity

The data from Dr. Montes's site are considered reliable and appear acceptable in support of the pending application.

Note: Observations noted above are based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

2. **Reinaldo D. Verson, M.D.**
Columbus, Gerogia

a. What Was Inspected: At this site, a total of 42 subjects were screened, and 12 subjects were reported as screen failures. Thirty (30) subjects were randomized into the study and twenty three (23) subjects completed the study and rolled over to the open-label extension phase of the study. Informed consent documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for 20 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, inclusion/exclusion criteria, and source documents were compared to case report forms and to data listings for primary efficacy endpoints and adverse events.

b. General Observations/Commentary: Our investigation revealed that Dr. Verson did not adhere to the protocol in that he did not report to the IRB all unanticipated events within the 10 day reporting frame as specified in the protocol. Dr. Verson adequately responded to the inspectional findings in a letter dated February 21, 2010.

Despite regulatory deficiencies, which were minor, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication. In general, the records reviewed were found to be in order and the data verifiable. There were no limitations to this inspection.

c. Assessment of Data Integrity

The data from Dr. Verson's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two clinical investigators were inspected in support of this application. The inspections of Drs. Montes, and Verson revealed no significant problems that would adversely impact data acceptability. The data submitted from these two sites are acceptable in support of the pending application.

{ See appended electronic signature page }

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTOINE N EL HAGE
05/17/2010

TEJASHRI S PUROHIT-SHETH
05/17/2010

DSI CONSULT: Request for Clinical Inspections

Date: November 18, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ranjit Mani, MD – Clinical Reviewer & Team Leader
Russell Katz, M.D. – Director
Division of Neurology Products

From: Teresa Wheelous, Sr. Regulatory Management Officer

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-22568

Applicant: Eisai Medical Research Inc.

Contact: Kevin M. McDonald, Associate Director, Global Regulatory Affairs

Phone (201) 627-2292

Kevin.McDonald@eisai.com

300 Tice Blvd.

Woodcliff Lake, NJ 07677

Drug Proprietary Name: Aricept^{(b) (4)} (donepezil) Tablets

NME or Original BLA: No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): treatment of moderate to severe dementia of the Alzheimer's type

PDUFA: July 24, 2010

Action Goal Date: July 24, 2010

Inspection Summary Goal Date: June 10, 2010

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #7069 Manuel Lavados Montes, MD Especialidades Médicas L y S (Consulta Privada) Av. Kennedy 5757 Of. 608 Torre Oriente, Edificio Marriott, Las Condes Santiago 7560356, Chile (Phone number not available)	E2020-G000-326	37	Moderate to severe Alzheimer’s Disease
Site #6108 Reinaldo D Verson, MD Columbus Research and Wellness 3645 Gentian Blvd, #3B Columbus, GA 31907 USA Phone: 706-653-0419	E2020-G000-326	29	Moderate to severe Alzheimer’s Disease

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *A specific safety concern at a particular site based on review of AEs, SAEs, deaths, or discontinuations*
- *A specific efficacy concern based on review of site specific efficacy data*

- *Specific concern for scientific misconduct at one or more particular sites based on review of financial disclosures, protocol violations, study discontinuations, safety and efficacy results*

*See*** at end of consult template for DSI's thoughts on things to consider in your decision making process*

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study). [Largest study site with impact on primary efficacy analysis](#)

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites.*

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Teresa Wheelous at 301-796-1161 or Ranjit Mani, M.D. at 301-796-1116.

Concurrence: (as needed)

Ranjit Mani, M.D. x Medical Team Leader / Medical Reviewer

Russell Katz, M.D. Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
 - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
 - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

TERESA A WHEELIOUS
11/18/2009

RUSSELL G KATZ
11/18/2009

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information				
NDA # 22-568				
Proprietary Name: Aricept Established/Proper Name: donepezil hydrochloride Dosage Form: Tablets Strengths: 23 mg				
Applicant: Eisai Medical Research Inc. Agent for Applicant (if applicable): Kevin McDonald, 201-627-2292				
Date of Application: 09/24/09 Date of Receipt: 09/24/09 Date clock started after UN:				
PDUFA Goal Date: July 24, 2010		Action Goal Date (if different):		
Filing Date: November 23, 2009		Date of Filing Meeting: November 4, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 3				
Proposed indication(s)/Proposed change(s): the treatment of moderate to severe dementia of the Alzheimer's type.				
Type of Original NDA:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		
Review Classification:		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority		
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>				
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device		
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)		
List referenced IND Number(s): 35,974				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?	X			
<i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>				
Are the proprietary, established/proper, and applicant names	X			

correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>				
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
<i>If yes, explain in comment column.</i>				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.</i>	Payment for this application: X Paid – 3009675 9/14/09 <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).</i>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission, does it follow the eCTD guidance¹? If not, explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)	X			
If no, explain.				

Forms and Certifications				
<p><i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature? <i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?				
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455	X			

included with authorized signature? <i>Forms must be signed by the APPLICANT, not an Agent.</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>) <i>If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.</i> <i>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...”</i>	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>				

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>				
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>				
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>				

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?			X	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)			X	
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	X			

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): 3/19/2007 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 2/11/2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>