BLA 761269/S-001

GENERAL ADVICE
CORRECTION OF POSTMARKETING REQUIREMENT (PMR)
AND POSTMARKETING COMMITMENT (PMC) SET/NUMBERS

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

Dear Ms. O'Sullivan:

Please refer to your supplemental biologics license application (sBLA), dated and received on January 6, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Leqembi (lecanemab-irmb) injection.

We also refer to your BLA Supplement Approval letter issued July 6, 2023.

The purpose of this letter is to provide you with new PMR/PMC set and numbers for the 505(o)(3) PMRs and non-reportable PMC listed in the July 6, 2023, Approval letter. Please reference the PMR/PMC set and numbers listed below when reporting on or referencing these PMRs and PMC instead of those listed in the July 6, 2023, Approval letter.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Leqembi was approved on January 6, 2023, we have become aware of clinical trial data showing an increased risk of symptomatic, serious, and severe radiographic amyloid related imaging abnormalities (ARIA) in ApoE ε4 homozygotes who are treated with Leqembi compared to heterozygotes and noncarriers. We have also become aware of clinical trial data showing intracerebral hemorrhage greater than 1 cm in patients taking Leqembi who have risk factors for intracerebral hemorrhage that include findings on neuroimaging suggestive of cerebral amyloid angiopathy (CAA) and use of anticoagulants. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of ARIA and of intracerebral hemorrhage greater than 1 cm in patients taking Leqembi.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

4497-1 Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with lecanemab-irmb, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	03/2024
Final Protocol Submission:	01/2025
Interim Study Report Submissions:	10/2025
	04/2026
	10/2026
	04/2027
	10/2027
	04/2028
	10/2028
	04/2029

Interim Study Report Submissions (cont'd):	10/2029
	04/2030
	10/2030
	04/2031
	10/2031
	04/2032
	10/2032
	04/2033
	10/2033
	04/2034
	10/2034
Study Completion:	01/2035
Final Report Submission:	01/2036

4497-2 Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage greater than 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4497-1 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer's disease untreated with lecanemab-irmb. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with lecanemab-irmb.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Algorithm Development):	07/2024
Interim Report Submission (Algorithm Development Final Protocol):	11/2025
Interim Report Submission (Outcome Algorithm):	05/2027
Interim Report Submission (Draft Retrospective Cohort Study Protocol):	02/2028
Final Study Protocol Submission (Retrospective Cohort):	12/2028

Study Completion (Retrospective Cohort):	12/2029
Final Report Submission:	12/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[1]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of amyloid related imaging abnormalities in patients who are homozygous for ApoE ε4.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4497-3 Further characterize the safety of treatment with lecanemab-irmb in patients who are homozygous for ApoE ε4. We would accept information on this risk from a randomized, clinical trial in participants with early preclinical Alzheimer's disease and intermediate amyloid (i.e., AHEAD 3-45 Study). Ensure that approximately 15% of the population, distributed equally among lecanemab-irmb and control, is homozygous for ApoE ε4.

The timetable you submitted on July 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2023
Final Protocol Submission:	05/2024
Trial Completion:	08/2029
Final Report Submission:	02/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 105081, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)"**, **"Required**

[1] See the guidance for Industry Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019). https://www.fda.gov/RegulatoryInformation/Guidances/default htm.

Postmarketing Final Report Under 505(o)”, **“Required Postmarketing Correspondence Under 505(o)”**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4497-4 Conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with Leqembi. The results of the validation studies are intended to inform product labeling.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sally Yasuda, MS, PharmD
Deputy Director for Safety
Division of Neurology 1
Office of Neuroscience
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SALLY U YASUDA
08/22/2023 03:16:01 PM

BLA 761269/S-001

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING REQUIREMENT
NEW POSTMARKETING REQUIREMENT
NEW POSTMARKETING COMMITMENT

Eisai Inc.
Attention: Stacie P. O'Sullivan
Director, Global Regulatory Strategy
200 Metro Boulevard
Nutley, NJ 07110

Dear Ms. O'Sullivan:

Please refer to your supplemental biologics license application (sBLA), dated and received on January 6, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Leqembi (lecanemab-irmb) injection.

This Prior Approval sBLA provides the final clinical study report for Study BAN2401-G000-301 (Study 301) to address PMR 4384-1. Study 301 was conducted to verify the clinical benefit of Leqembi (lecanemab-irmb) as required under 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

SUBPART E FULFILLED

We approved this BLA under the regulations at 21 CFR 601 Subpart E for Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses. Approval of this supplement fulfills your commitments made under 21 CFR 601.41.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study(ies) requirement for this application because necessary studies are impossible or highly impracticable, as Alzheimer's disease only occurs in the adult population.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have received your submission dated January 6, 2023, containing the final report for the following postmarketing requirement listed in the January 6, 2023, accelerated approval letter for BLA 761269.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4384-1: In order to verify the clinical benefit of lecanemab-irmb, conduct a randomized, controlled trial to evaluate the efficacy of lecanemab-irmb compared to an appropriate control for the treatment of Alzheimer's disease. The trial should be of sufficient duration to observe changes on an acceptable endpoint in the patient population enrolled in the trial.

We have reviewed your submission and conclude that the above requirement was fulfilled.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Leqembi was approved on January 6, 2023, we have become aware of clinical trial data showing an increased risk of symptomatic, serious, and severe radiographic amyloid related imaging abnormalities (ARIA) in ApoE ε4 homozygotes who are treated with Leqembi compared to heterozygotes and noncarriers. We have also become aware of clinical trial data showing intracerebral hemorrhage greater than 1 cm in patients taking Leqembi who have risk factors for intracerebral hemorrhage that include findings on neuroimaging suggestive of cerebral amyloid angiopathy (CAA) and use of anticoagulants. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risks of ARIA and of intracerebral hemorrhage greater than 1 cm in patients taking Leqembi.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

4384-5 Conduct a registry-based, prospective, observational study to evaluate clinical safety outcomes among Alzheimer's disease patients treated with lecanemab-irmb, using, for example, the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) registry, including patients who are ApoE ε4 homozygotes, and/or exposed to antithrombotics, and/or have a diagnosis of, or imaging findings consistent with a high risk for, cerebral amyloid angiopathy. The primary clinical safety outcomes should include amyloid related imaging abnormalities (ARIA)-edema (ARIA-E), and ARIA-hemosiderin deposition (ARIA-H) and any associated clinical symptoms, and intracerebral hemorrhage >1 cm in size. Additional outcomes of interest should also include seizures, anaphylaxis, and death. Baseline

characterization of the registry population should include demographic data, diagnosis and stage of disease, ApoE genotype, baseline MRI findings (e.g., microhemorrhages, evidence of cerebral amyloid angiography or other imaging findings consistent with high risk of cerebral amyloid angiography, etc.), other biomarkers that are potential predictors of disease course or adverse outcomes, and prior medications including prior Alzheimer's disease (AD) therapy and antithrombotic therapy. The registry should also collect information on concomitant medications (e.g., antiplatelet and antithrombotic drugs, other AD treatments). When available, the study should provide a comparison of safety outcomes to estimated background rates in an appropriate comparator population.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 03/2024
Final Protocol Submission: 01/2025
Interim Study Report Submission: 10/2025
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10/2031
04/2032
10/2032
04/2033
10/2033
04/2034
10/2034
Study Completion: 01/2035
Final Report Submission: 01/2036

4384-6 Use emerging safety data from ongoing studies and published literature, validate administrative claim codes for intracerebral hemorrhage in patients with Alzheimer's disease. The outcome of intracerebral hemorrhage should distinguish between amyloid related imaging abnormalities-hemosiderin deposition (ARIA-H) and cerebral hemorrhage greater than 1 cm. Secondary outcomes of interest include ARIA-edema (ARIA-E) and ARIA-H, seizures, anaphylaxis, and death. For secondary

outcomes not well validated, develop algorithms and/or computable phenotypes using data leveraged from PMR 4384-5 and other sources for the outcomes of interest. Describe an approach to identifying an appropriate comparator group with Alzheimer's disease untreated with lecanemab-irmb. Obtain FDA agreement with the outcome algorithm specifications and comparator population prior to proceeding to conducting the retrospective cohort study. Based upon validated algorithms agreed to by the Sponsor and FDA, conduct a comparative retrospective cohort study using claims data with available medical chart review as needed or electronic health record data to assess clinical safety outcomes in a broad population of Alzheimer's disease patients treated with lecanemab-irmb.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol for Algorithm Development Submission:	07/2024
Final Protocol for Algorithm Development Submission:	11/2025
Outcome Algorithm Submission:	05/2027
Draft Retrospective Cohort Study Protocol Submission:	02/2028
Final Retrospective Cohort Study Protocol Submission:	12/2028
Retrospective Cohort Study Completion:	12/2029
Final Report Submission:	12/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of amyloid related imaging abnormalities in patients who are homozygous for ApoE ε4.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4384-7 Further characterize the safety of treatment with lecanemab-irmb in patients who are homozygous for ApoE ε4. We would accept information on this risk from a randomized, clinical trial in participants with early preclinical Alzheimer's disease and intermediate amyloid (i.e., AHEAD 3-

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

45 Study). Ensure that approximately 15% of the population, distributed equally among lecanemab-irmb and control, is homozygous for ApoE ε4.

The timetable you submitted on July 6, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 07/2023
Final Protocol Submission: 05/2024
Trial Completion: 08/2029
Final Report Submission: 02/2030

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o)

Submit the protocol(s) to your IND 105081, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4384-8	Conduct adequate analytical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect ApoE e4 alleles that is safe and effective for identifying patients at increased risk of ARIA if treated with Leqembi. The results of the validation studies are intended to inform product labeling.

The timetable you submitted on July 5, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/2025

REQUESTED PHARMACOVIGILANCE

We request expedited reporting of any deaths in ongoing studies and expedited reporting of events of cerebral hemorrhage greater than 1 centimeter in size in ongoing studies or in the postmarketing setting.

We request that you perform postmarketing pharmacovigilance to characterize the risk of ARIA and the monitoring for ARIA associated with the use of Leqembi. Please provide biannual reports of ARIA-E and ARIA-H (specifying microhemorrhage or superficial siderosis), along with any incident cerebral hemorrhage greater than 1 centimeter in size. Provide a synthesized summary and analysis, including incidence of clinical trial cases, postmarketing cases, and total cases. Include an evaluation of central nervous system hemorrhage in patients with pre-existing risk factors for bleeding, including concomitant medications that could increase the risk for bleeding. Include an analysis that addresses the monitoring recommendations provided for in the prescribing information. The summary should provide an analysis for all subjects and a separate analysis for those in the United States and for those in the rest of the world. For each case, provide line listings that include:

- Case ID
- Whether the case was a clinical trial case, postmarketing spontaneous report, or postmarketing from a registry
- Age
- Alzheimer's disease stage
- Patient characteristics, including ApoE ε4 genotype if available

- Country where patient is treated
- Concomitant medications
- Time from first Leqembi dose to ARIA
- Listing of dates of Leqembi dosing
- Dates of MRI, including baseline MRI
- Description of MRI findings, including baseline MRI
- Whether patient was symptomatic and if so, list symptoms
- Whether initial finding was symptom or MRI
- Patient outcome (e.g., death, permanent disability, resolved)
- Date of resolution of MRI and of symptoms
- Whether the patient was hospitalized
- Whether and what treatment was received for ARIA
- Whether Leqembi was held, and date that Leqembi dosing resumed
- Whether Leqembi was discontinued
- Specialty of the prescribing physician (e.g., neurologist, psychiatrist, internist)

We request that you perform postmarketing pharmacovigilance and provide biannual reports to identify and analyze cases of central nervous system vasculitis that occur after use of Leqembi.

We request that you perform postmarketing pharmacovigilance to characterize the risk of infusion reactions associated with the use of Leqembi. Please provide biannual reports of serious infusion reactions, including line listings of the cases, FAERS reports, and a synthesized summary and analysis including incidence of clinical trial cases, postmarketing cases, and total cases.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

[5] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Teresa Buracchio, MD
Director (Acting)
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
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