DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761029

BLA APPROVAL

Biogen Inc.
Attention: Trevor Mill,
Senior Vice President, Regulatory Affairs
14 Cambridge Center
Cambridge, MA 02142

Dear Mr. Mill:

Please refer to your Biologics License Application (BLA) dated and received February 27, 2015, and your amendments, submitted under section 351(a) of the Public Health Service Act for Zinbryta (daclizumab) injection 150 mg/ml.

We acknowledge receipt of your major amendment dated April 2, 2015, which extended the goal date by three months.

LICENSING

We have approved your BLA for Zinbryta (daclizumab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Zinbryta under your existing Department of Health and Human Services U.S. License No. 1697. Zinbryta (daclizumab) is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture daclizumab drug substance at Biogen, Inc., in Research Triangle, North Carolina. The final formulated drug product prefilled syringe will be manufactured, filled, labeled, and packaged at (b) (4) . You may label your product with the proprietary name, Zinbryta, and will market it in a 150 mg/mL prefilled syringe for subcutaneous injection.

DATING PERIOD

The dating period for Zinbryta shall be 36 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored at (b) (4).

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Zinbryta to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Zinbryta, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

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 text.

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 [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the Instructions for Use, and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

In addition, within 14 days of the date of this letter, amend any pending supplement that includes labeling changes for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted May 19, 2016, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

(June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761029**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for daclizumab was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of relapsing forms of multiple sclerosis and because the clinical trial design is similar to that of trials of previously approved drugs for the treatment of relapsing forms of multiple sclerosis.

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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric studies requirement for this application because there is evidence strongly suggesting that the drug product would be unsafe in all pediatric age groups. Significant safety concerns include hepatotoxicity, autoimmune diseases, and serious skin reactions.

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.

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 known serious risks of drug-induced liver injury, serious infections, and immune-mediated disorders including hepatitis, non-infectious colitis, serious skin reactions, Type I diabetes, thyroid disease, sarcoidosis, and other immune disorders resulting from the use of Zinbryta (daclizumab);
- assess a signal of a risk of breast cancer related to the use of Zinbryta (daclizumab);
- identify an unexpected serious risk of adverse maternal, fetal, and infant outcomes resulting from the use of Zinbryta (daclizumab) during pregnancy;
- identify an unexpected serious risk of therapeutic failure due to the presence of neutralizing anti-drug antibodies resulting from the use of Zinbryta (daclizumab).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

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

3084-1 Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) Risk Evaluation and Mitigation Strategies (REMS) registry, with the primary objective of determining the incidence rates of drug-induced liver injury, serious infections, and immune-mediated disorders, including hepatitis, non-infectious colitis, serious skin reactions, Type I diabetes, thyroid disease, sarcoidosis, and other immune disorders. All patients enrolled in the registry should be followed for the duration of treatment and at least 6 months following discontinuation of treatment. The protocol should specify at least two appropriate comparator populations to which the observed incidence rates will be compared.

The timetable you submitted on May 26, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2016
Final Protocol Submission:	12/2016
Study Completion:	12/2029
Final Report Submission:	12/2030

3084-2 Conduct a prospective observational study of patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining the incidence and mortality rates of breast cancer. All patients enrolled in the registry should be followed for a minimum of 10 years or until death following their first exposure to Zinbryta (daclizumab). The protocol should specify at least two appropriate comparator populations to which the observed incidence and mortality rates will be compared.

The timetable you submitted on May 26, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2016
Final Protocol Submission:	01/2017
Interim Report Submission:	06/2019
	06/2021
	06/2023
	06/2025
	06/2027
	06/2029
Study Completion:	06/2030
Final Report Submission:	06/2031

3084-3 Conduct a nested case-control study among patients enrolled in the Zinbryta (daclizumab) REMS registry, with the primary objective of determining which clinical attributes are risk factors or protective factors for developing liver disorders and serious skin reactions. Determine whether there are biomarkers that are earlier indicators of liver injury than standard liver function tests. Patient blood samples will need to be analyzed at baseline, 3 months, and 6 months after initiating therapy and possibly when ending therapy. At a minimum, the following potential risk factors must be evaluated:

a) Demographic characteristics (age, gender, race).
b) Cumulative dose exposure to daclizumab.
c) Prior history of immune disorders, including autoimmune hepatitis.
d) Genomic risk factors.
e) T-cell markers, such as FOX-3, CD-25 and others.
f) Other concomitant drug use.
g) Comorbidities.
h) Prior drug use to treat MS.
i) Prior adverse events as a result of MS drug treatment, including drug-induced liver injury.
j) Exposure to high-dose intravenous methylprednisolone, steroids, and other immunosuppressants.
k) Time between exposures (daclizumab, other MS drugs, and immunosuppressants) and development of serious adverse events.

The timetable you submitted on May 26, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2016
Final Protocol Submission:	12/2016
Study Completion:	12/2027
Final Report Submission:	12/2028

3084-4 Conduct prospective pregnancy exposure registry cohort analyses in the United States that compare the maternal, fetal, and infant outcomes of women with multiple sclerosis exposed to Zinbryta (daclizumab) during pregnancy with two unexposed control populations: one consisting of women with multiple sclerosis who have not been exposed to Zinbryta (daclizumab) before or during pregnancy and the other consisting of women without multiple sclerosis. The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational-age births, and any other adverse outcomes, including postnatal growth and development. Outcomes will be assessed through at least the first year of life.

The timetable you submitted on May 26, 2016, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2016
Final Protocol Submission:	08/2016
Interim Report Submission:	08/2018
	08/2020
	08/2022
	08/2024
	08/2026
Study Completion:	08/2027
Final Report Submission:	08/2028

3084-5 Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against daclizumab in the presence of daclizumab levels that are expected in samples collected from patients on treatment.

The timetable you submitted on May 19, 2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2017
Final Report Submission:	01/2019

Submit the protocol(s) to your IND 12120 with a cross-reference letter to this BLA. Submit all 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)."

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 SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3084-6 Re-evaluate the acidic charge variant specification for drug substance after 30 lots have been manufactured using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

The timetable you submitted on April 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2019

3084-7 Re-evaluate the acidic charge variant specification for drug product after manufacturing 30 lots using the commercial manufacturing process or 3 years post-approval, whichever is sooner. Provide a final report that includes data, the statistical analysis, and proposed changes to the specifications.

The timetable you submitted on April 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2019

3084-8 Validate a non-reduced (b) (4) method and evaluate the need for its inclusion in the drug substance and drug product specification. Provide a final report that includes the analytical procedure, validation report, any proposed specification acceptance criteria, and the data used to establish the proposed criteria.

The timetable you submitted on April 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2020

3084-9 Conduct microbial spiking studies of the (b) (4) product intermediates in a small-scale study to demonstrate that the product intermediates do not support significant microbial growth under the proposed hold conditions.

The timetable you submitted on April 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 11/2017

3084-10 Provide endotoxin recovery data from two additional drug product lots spiked with Control Standard Endotoxin (CSE).

The timetable you submitted on April 29, 2016, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2016

Submit clinical protocols to your IND 12120 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Zinbryta (daclizumab) to ensure the benefits of the drug outweigh the risks of severe and fatal hepatic injury and serious immune-mediated disorders.

Your proposed REMS must include the following:

Communication Plan: We have determined that a communication plan targeted to healthcare providers who are likely to prescribe Zinbryta (daclizumab) will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about the risks of severe and fatal hepatic injury and serious immune-mediated disorders.

Elements to assure safe use: Pursuant to 505-1(f)(1), we have also determined that Zinbryta can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of severe and fatal hepatic injury and serious immune-mediated disorders listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan are not sufficient to mitigate the serious risks. The elements to assure safe use will ensure that only specially certified prescribers prescribe Zinbryta, that Zinbryta is dispensed only by specially certified pharmacies, that only enrolled and authorized patients receive Zinbryta, that specially certified prescribers submit documentation of periodic monitoring of patients who receive Zinbryta to identify hepatic injury and serious immune-mediated disorders, and that all patients who receive Zinbryta are enrolled in a registry to establish long-term safety and safe use of Zinbryta.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers who prescribe the drug must be specially certified.
- Pharmacies that dispense the drug are specially certified.
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions.
- Each patient using the drug is subject to certain monitoring.
- Each patient using the drug is enrolled in a registry.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the elements to assure safe use (outlined above) that require pharmacies that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions. Include an intervention plan to address any findings of non-compliance with elements to assure safe use and to address any findings that suggest an increase in risk.

Your proposed REMS, submitted on May 27, 2016, and appended to this letter, is approved. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

The REMS assessment plan must include, but is not limited to, the following:

1) REMS Program Utilization Statistics
   a) Patients
      i) Number of newly enrolled and active* (existing) patients
      ii) Number of patients who have discontinued therapy
   b) Prescribers

i) Number of newly enrolled and active* (existing) certified prescribers

c) Pharmacies
   i) Number of newly enrolled and active* (existing) certified pharmacies

2) REMS Program Infrastructure and Performance
   a) Percent of prescriber responses attesting to patient compliance with required monitoring
   b) Percent of patients whose physician attested as being complaint with the required monitoring
   c) Number of patients not enrolled in the REMS program/ registry who were dispensed medication
   d) Number of enrolled patients who were not authorized in the REMS program who were dispensed medication
   e) Number of pharmacies who dispensed drug to non-authorized patients
   f) Number of Zinbryta REMS Program patient status forms received within 25 days of the due date (day 115)
   g) Number of Zinbryta REMS Program patient status forms not received within 25 days (day 115) of the due date
   h) Number of Zinbryta REMS Program patient status forms not received within 55 days (day 145) of the due date and resulting patient de-enrollments
   i) From audited pharmacies only, provide the number of Zinbryta shipments sent to patients during the time authorization to dispense was lost
   j) Number of Zinbryta REMS Program patient status forms outstanding at the end of the reporting period
   k) Number of Zinbryta REMS Program patient status forms for discontinued patients submitted during the reporting period
   l) Number of outstanding Zinbryta REMS Program patient status forms for discontinued patients during the reporting period
   m) Number of certified prescribers that were decertified from the Zinbryta REMS program during the reporting period
   n) Number of patients unenrolled from the Zinbryta REMS program during the reporting period due to noncompliance with REMS requirements
   o) Number of certified pharmacies that were decertified from the Zinbryta REMS program during the reporting period due to noncompliance with REMS requirements
   p) Number of non-certified pharmacies that received shipments during the assessment period
      i) Number of shipments to institutional/inpatient healthcare facilities (including long-term care, rehabilitation, skilled nursing facilities, nursing homes, etc.)
      ii) Number of shipments to locations other than institutional/inpatient healthcare facilities (i.e., other non-certified retail, mail order, or specialty pharmacies)
   q) Number of patients receiving delivery of product at a healthcare facility from a certified pharmacy during the assessment period
      i) Of the patients above, number that have an adverse event reported within 90 days of the shipment date
      ii) Disposition of product to include date shipped, date received, date injected, or date returned to original shipping source, whenever possible

3) Knowledge (beginning with the 12-month assessment)
   a) Patient understanding of serious risks and safe use conditions for Zinbryta
   b) Prescriber understanding of serious risks, safe use conditions, and proper patient selection for Zinbryta

4) Safety surveillance
   a) Number of Zinbryta REMS Program patient status forms that reported an event of severe or fatal hepatic injury or a serious immune mediated disorder and resulting prescription disposition (discontinued, continued)
   b) Adverse event assessments of severe and fatal hepatic injury and serious immune mediated disorders

5) An assessment of the extent to which the elements to assure safe use of the REMS are meeting the goals of the REMS and whether the goals or elements should be modified

*For the purposes of the REMS assessment, active prescribers, pharmacies, or patients are those that have prescribed, dispensed, or received at least one prescription for Zinbryta during the assessment period.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any of goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;
b) A determination of the implications of a change in the benefit-risk profile for the current REMS;
c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.
d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.
e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.
f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the

proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761029 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761029 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 761029/SECONDARY TRACKING NUMBER
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761029/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA761029/SECONDARY TRACKING NUMBER
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABEL CHANGES SUBMITTED IN SUPPLEMENT XXX

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761029/SECONDARY TRACKING NUMBER
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR BLA 761029

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

If you do not submit electronically, please send 5 copies of REMS-related submissions.

ENHANCED PHARMACOVIGILANCE

We request that you provide expedited reporting of cases that include multiorgan involvement that could be consistent with Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). For each of the cases, please indicate which of the Regiscar criteria for DRESS are fulfilled. For cases of skin rash that include another component of the Regiscar criteria but do not fulfill the criteria for DRESS, please provide a justification for why those cases do not meet the Regiscar criteria for DRESS. If information is missing regarding any of the criteria, please make every attempt to obtain the missing information.

We also request that you provide semi-annual reports that include a cumulative analysis of each of these events with comparison to the expected background rates. Please submit the expedited reports and the semiannual reports to the Division of Neurology Products.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ("the Program"). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Robert Temple, M.D.
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
REMS

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

/s/

ROBERT TEMPLE
05/27/2016