DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125516

BLA APPROVAL

United Therapeutics Corporation
Attention: Noah Byrd, PhD
Associate Vice President, Regulatory Affairs
55 TW Alexander Drive, P. O. Box 14186
Research Triangle Park, NC 27709

Dear Dr. Byrd:

Please refer to your Biologics License Application (BLA) dated April 11, 2014, received April 11, 2014, submitted under section 351(a) of the Public Health Service Act for Unituxin (dinutuximab).

We acknowledge receipt of your amendments dated April 15, May 5, May 8, May 12, May 15, May 19, May 23, June 2, June 6, June 9, June 13, June 25, June 30, July 7, July 8, July 15, July 16, July 17, July 22, July 28, August 1 (3), August 7, August 8, August 11, August 13, August 14, August 19 (3), August 20 (3), August 21, August 22, August 25, August 26 (2) August 27, August 29, September 2, September 4, September 5, September 11 (2), September 12, September 15 (4) September 18, September 19 (2) September 26, September 29, October 3, October 8, October 9, October 17, October 27, October 30, October 31, November 5, November 14, November 17, November 21, November 25, December 5, and December 15, 2014; and January 7, February 11, February 12, February 16, February 19, February 20 (3), February 23, February 25 (3), February 27, March 2, March 4, and March 9, 2015 (3).

LICENSING

We have approved your BLA for Unituxin (dinutuximab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce Unituxin under your existing Department of Health and Human Services U.S. License No. 1993. Unituxin is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture Unituxin at your facility in Silver Spring, Maryland. The final formulated product will be labeled and packaged at your facility in Research Triangle Park, North Carolina or at (b) (4)

(b) (4). You may label your product with the proprietary name, Unituxin, and will market it in a 17.5 mg/5 mL single-use vial.

DATING PERIOD

The dating period for Unituxin shall be 18 months from the date of manufacture when stored at 2 to 8 °C (36 - 46°F). 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) months 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 Unituxin 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 Unituxin, 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.

We note that your March 9, 2015, submission includes final printed labeling (FPL) for your package insert. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert). 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.

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your February 25, 2015, submission containing final printed carton and container labels.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the Federal Food, Drug, and Cosmetic Act (FDCA). This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 125516. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population

aged 0 through 18 years),
- the estimated demand in the U.S. for the product, and
the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FD&C Act by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for Unituxin (dinutuximab) was not referred to an FDA advisory committee because the safety profile of dinutuximab is acceptable for the treatment of high-risk neuroblastoma and the evaluation of the safety data when used in treatment of high-risk neuroblastoma did not raise significant safety or efficacy issues that were unexpected for a drug in this population.

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.

Because Unituxin (dinutuximab) for this indication has orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the 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 the known serious risks of serious infusion reactions and hypersensitivity, including anaphylaxis; the potential serious risk of an immunogenic response to dinutuximab; and the serious risk of neurologic toxicity, including sensory and motor neuropathy.

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:

2878-1 Conduct a study to compare exposure and safety data from approximately 220 patients who complete treatment with dinutuximab, pooling across dinutuximab lots and by individual lot, with the historical experience observed in approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the risk serious infusion reactions and neuropathy, and the overall safety and tolerability of the marketed product, Unituxin. In addition, assess whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alter the safety and tolerability of dinutuximab.

The timetable you submitted on February 27, 2015 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	September 2015
Study Completion:	June 2016
Final Report Submission:	December 2017

2878-2 Conduct a study to analyze laboratory data including serum complement, IgE, tryptase, histamine, and human anti-chimeric antibody levels obtained in patients with documented Grade 4 allergic reactions or anaphylaxis from a sufficient number of patients with neuroblastoma to allow for improved characterization of these adverse reactions to better inform product labeling. For each case identified, provide a narrative description that includes a summary of the allergic reaction or anaphylaxis adverse reaction, re-challenge information, and an assessment of whether the clinical presentation and laboratory data obtained were consistent with an allergic reaction or an infusion reaction. In addition, submit datasets used for safety analyses of the laboratory data.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Analysis Plan Submission:	April 2016
Final Report Submission:	March 2017

2878-3 Develop and validate an assay with improved sensitivity for the detection of neutralizing antibodies against dinutuximab in the presence of dinutuximab levels that are expected to be present in samples at the time of patient sampling.

The timetable you submitted on, March 9, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission:	October 2015

2878-4 To conduct a study to assess the neutralizing anti-drug antibody responses to dinutuximab with a validated assay capable of sensitively detecting neutralizing antibody responses in the presence of dinutuximab levels that are expected to be present in the blood at the time of patient sampling. The clinical impact of the neutralizing antibody response should be evaluated in at least 300 patients to include an interim report analyzing data from Studies DIV-NB-302, DIV-NB-303 and DIV-NB-201 and a final report analyzing data from Study NANT2011-04.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Interim Report Submission:	September 2016
Final Report Submission:	June 2019

2878-5 To conduct a 5-month repeat-dose juvenile animal toxicology study in cynomolgus monkeys that will measure the chronic toxicity of dinutuximab, particularly its effects on the central and peripheral nervous system. Administration of dinutuximab should be reflective of the clinical administration schedule. Incorporate an evaluation of the effect of treatment on the proximal and distal nerves, and evaluation of the C1 level of the spinal cord in this study and include 7-8 slices for histopathological assessment of the brain. Evaluate the potential for long-term effects on nociception and pain threshold at the end of an appropriate recovery period.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	January 2017
Final Report Submission:	May 2018

Submit the protocol(s) to your IND 110494, 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 NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2878-6 Conduct a study to re-assess drug substance and drug product specifications based on additional clinical experience with material manufactured using the commercial process and/or additional characterization data on product critical quality attributes. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2017

2878-7 Manufacture, qualify, and implement a new reference standard and enter the reference standard into a requalification program. The reference standard qualification and requalification protocols and the qualification report for the new reference standard will be submitted in a prior approval supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: December 2015
Final Report Submission: December 2015

2878-8 Develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the dinutuximab drug substance release program. The anti-HCP antiserum will be evaluated using two-dimensional SDS-PAGE and Western Blot analysis of proteins from the production cell line or a representative cell line for the determination of the percent of potential HCP impurities that are recognized by this antiserum. The analytical procedure, validation report, reproductions of an appropriately stained two-dimensional gel and the corresponding western blot, the analysis of the approximate percent of HCP coverage, the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be submitted in a prior approval supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: October 2015

2878-9 Validate an assay for the detection of dinutuximab (b) (4) and implement this assay in the drug substance and drug product release and stability specifications. The analytical procedure, validation report, the proposed specification acceptance criterion, and the data used to set the acceptance criterion will be provided in a prior approval supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final report submission: April 2016

2878-10 Establish and qualify a Working Cell Bank (WCB) to be used for production of dinutuximab. Qualification of the WCB will include safety testing, an evaluation of the growth of WCB cultures relative to the growth of Master Cell Bank (MCB) cultures, testing of end of production cells generated from the commercial scale process, and a comparability assessment that includes the first three lots manufactured from the WCB using the commercial process. One lot manufactured using the commercial process will be placed on a stability protocol and the data will be submitted in the subsequent BLA annual reports. The WCB qualification report will be submitted in a prior approval supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2016

2878-11 Conduct studies to further characterize the Unituxin master cell bank (MCB) and to confirm the monoclonality of the MCB.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	June 2015
Study Completion:	December 2015
Final Report Submission:	January 2016

2878-12 Conduct validation studies to confirm acceptable product quality and shipper performance during shipping of dinutuximab drug product. This should include consideration for worst case shipping routes, including routes to testing sites. The study will include monitoring of temperature during the shipment, testing of pre- and post-shipping samples for drug product quality [e.g., opalescence, protein

concentration, purity by SEC-HPLC, cSDS (reduced and non-reduced), cIEF, WCX, sub-visible particulates, and potency of dinutuximab], and confirmation that the commercial shipping configuration minimizes physical damage to drug product containers.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2015

2878-13 Conduct a leachable study of drug product through the end of shelf-life under recommended storage conditions. Testing will be performed at 0, 3, 6, 12, 24, and 36 month time points. This should include consideration for the detection of extractables observed in drug substance and drug product extractable studies. The analysis of leachables should include organic nonvolatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS) and semivolatile (e.g., GC-MS) species and metals (e.g., ICP-MS). Study results will be updated annually in the BLA Annual Report until the final PMC study report is submitted.

The timetable you submitted on February 25, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: January 2016
Study Completion: March 2019
Final Report Submission: July 2019

2878-14 Conduct a study to verify (b) (4) lifetimes at commercial scale using a validation protocol to evaluate (b) (4) capability and cleaning procedures throughout the intended lifetime of the (b) (4)

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2015
Study Completion: November 2017
Final Report Submission: December 2017

2878-15 Conduct a study to further investigate the root cause for (b) (4) observed in drug product stored under recommended conditions and to perform a risk assessment based on the root cause, the levels of (b) (4) observed, and the potential effects on safety and efficacy of dinutuximab. Appropriate corrective and preventative actions will be implemented based on the results of the root cause investigation and risk assessment. The root cause investigation, risk assessment reports, and proposed corrective and preventive actions will be submitted as a prior approval supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: March 2016

2878-16 Conduct a study to confirm validation of the SEC-HPLC assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: March 2016
Final Report Submission: June 2016

2878-17 Conduct a study to confirm validation of the cSDS reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 2016
Final Report Submission: July 2016

2878-18 Conduct a study to confirm validation of the cSDS non-reduced assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: April 2016
Final Report Submission: July 2016

2878-19 Conduct a study to confirm validation of the cIEF assay. Validation reports will be updated to include evaluations of accuracy, precision, specificity, quantitation limit, linearity and range with respect to the purity and the product related impurities included in the final drug substance and drug product release and stability specifications.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Protocol Submission: June 2016
Final Report Submission: December 2016

2878-20 Develop, validate/qualify and implement an osmolality assay for the drug product release specifications. The analytical procedure, qualification report, proposed acceptance criterion, and data used to set the proposed acceptance criterion should be submitted as a Changes Being Effected in 30 Days (CBE-30) supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: May 2015

2878-21 Conduct a study to confirm compatibility of drug product with intravenous infusion (IV) bags and IV administration sets of different materials of construction. The compatibility study will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

2878-22 Conduct a study to confirm compatibility of the drug product with the use of an in-line filter during administration. These studies will include monitoring samples for protein concentration, purity by SEC-HPLC, cIEF, sub-visible particulates, and potency. The final report will be submitted as a Prior Approval Supplement.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: November 2015

2878-23 Conduct a study to re-evaluate dinutuximab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. Provide the final report, the corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2017

2878-24 Conduct a study to re-evaluate dinutuximab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis, and the statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2017

2878-25 To determine whether endotoxin masking occurs in vivo, conduct a comparison study between the LAL kinetic chromogenic test and the rabbit pyrogen test for drug product that has been spiked with an endotoxin standard and then held prior to testing.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: July 2015

2878-26 Conduct a study, including analyses, to understand the mechanism of endotoxin masking in the drug product. Explore alternative test methods and develop a more suitable endotoxin release test for the drug product. Study results will be updated annually in the BLA Annual Report until the final PMC study report is submitted.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2018

2878-27 Conduct a study to validate the dye ingress test using dinutuximab drug product vials. The validation study should identify the range of breach sizes detectable by the assay. The positive control used for the dye ingress test should be based on the validation study data.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: June 2015

2878-28 Conduct a study, including the bioburden method qualification analyses, for the [redacted] (b) (4) using 2 additional batches and for the bulk drug substance using 3 different drug substance lots. Submit the results.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: April 2015

2878-29 Conduct a study to determine the final established [redacted] (b) (4) after trending the data from 10 drug substance batches.

The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:

Final Report Submission: December 2015

Submit clinical protocols to your IND 110494 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**."

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

WATCH-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 within two weeks of receipt of this communication.

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, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

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

/s/

GINA M DAVIS
03/10/2015

RICHARD PAZDUR
03/10/2015