DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022468 **NDA ACCELERATED APPROVAL**

Allos Therapeutics, Inc.
Attention: Linnea Tanner, M.S., R.A.C.
Senior Director, Regulatory Affairs
11080 Circle Point Road, Suite 200
Westminster, CO 80020

Dear Ms. Tanner:

Please refer to your new drug application (NDA) dated March 23, 2009, received March 24, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FOLOTYN™ (pralatrexate injection) 20 mg/1 mL and 40 mg/2 mL.

We acknowledge receipt of your submissions dated April 20, April 27, May 12, May 14, May 27, May 28, June 3, June 18, June 19, June 29, July 1, July 14, July 23, July 31, August 20, August 21, August 26, August 28, September 1, September 4, September 9, September 10, September 18, September 20, September 21, September 22, and September 24, 2009.

This new drug application provides for the use of FOLOTYN™ (pralatrexate injection) for the treatment of patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).

We completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.510), effective on the date of this letter, for use as recommended in the enclosed labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the package insert) submitted September 22, 2009. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 022468**."

CARTON AND IMMEDIATE CONTAINER LABELS

The final printed labeling (FPL) must be identical to the submitted labeling (immediate container and carton labels submitted September 24, 2009. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA.* Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 022468**." Approval of this submission by FDA is not required before the labeling is used.

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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 21 CFR 31.510 (SUBPART H)

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled trials to verify and describe clinical benefit. We remind you of the following post marketing requirements specified in your submission dated September 20, 2009. Submit clinical protocols for at least two trials to confirm the clinical benefit of treatment with FOLOTYN™ (pralatrexate injection). These requirements, along with any completion dates, are listed below.

1547-1 A randomized trial of maintenance treatment with pralatrexate in previously untreated patients with PTCL who have demonstrated a response to CHOP or a CHOP-like regimen.

Description of trial: This will be a Phase 3 multi-center, randomized clinical trial of sequential FOLOTYN versus observation in patients with newly diagnosed aggressive peripheral T-cell lymphoma who have responded following initial treatment with CHOP-based chemotherapy. The primary endpoint will be progression-free survival (PFS). The trial will also be sized to detect a realistic difference in survival. Patients will be enrolled prior to initiation of the CHOP-based regimen. Patients responding (CR or PR) after CHOP-based treatment will then be randomized 2:1 to FOLOTYN versus observation.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: December 23, 2009
Trial Completion Date: December 31, 2016
Final Report Submission Date: June 30, 2017

1547-2 A randomized trial comparing pralatrexate in combination with systemic bexarotene versus systemic bexarotene alone in patients with cutaneous T-cell lymphoma (CTCL) who are refractory to at least one prior systemic therapy.

Description of trial: This will be a Phase 3 multi-center, randomized clinical trial in patients with CTCL. The primary endpoint will be progression-free survival (PFS). Response rate will be a secondary endpoint. Prior to initiation of the Phase 3 trial, a Phase 1 trial will be conducted to determine the maximum tolerated dose (MTD) of the combination.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Protocol Submission Date for Phase 1 Trial: November 15, 2009
Phase 1 Trial Completion Date: August 31, 2011
Final Phase 3 Protocol Submission Date: September 30, 2011
Phase 3 Trial Completion Date: March 31, 2015
Phase 3 Trial Final Report Submission Date: September 30, 2015

Submit final reports and datasets to this NDA as a supplemental application. For administrative purposes, all submissions relating to these postmarketing requirements must be clearly designated "**Subpart H Postmarketing Requirements**."

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 a signal of a serious risk of altered drug levels resulting from organ impairment.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess this serious risk.

Finally, we have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of altered drug levels resulting from organ impairment.

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

1547-3 A clinical pharmacokinetic trial in patients with renal impairment to include patients with severe renal impairment.

Description of trial: This will be a Phase 1 clinical trial to evaluate the pharmacokinetics of pralatrexate in relapsed/refractory lymphoma patients (B-cell, T-cell, and Hodgkin's Lymphoma) with mild to severe renal impairment. Three cohorts (N=6 per cohort) will be enrolled in this study for a total of 18 patients. Cohorts will be based on the severity of renal impairment, i.e., cohort A = severely impaired (Creatinine clearance Cockroft-Gault (CrCl C-G) < 30 mL/min), cohort B = moderately impaired (CrCl C-G = 30-50 mL/min), and cohort C = mildly impaired patients (CrCl C-G = 50-80 mL/min). The pralatrexate dose for cohorts A and B will be determined based on the pharmacokinetics experience from the PROPEL study. Cohort C will be dosed at the recommended dose (30 mg/m^2) since patients with mild renal impairment were included in the PROPEL trial. Patients will undergo extensive plasma and urine collections following the first dose of FOLOTYN.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: January 31, 2010
Trial Completion Date: June 30, 2012
Final Report Submission Date: January 31, 2013

1547-4 Completion of the planned mass balance trial. Contingent on FDA review of the mass balance results, a clinical pharmacokinetic trial in patients with hepatic impairment may be required.

Description of trial: This is an ongoing Phase 1 mass balance clinical trial to evaluate the excretion and metabolic profile of pralatrexate. Patients will receive a fixed dose of 225 mg radio-labeled pralatrexate. Patients will undergo intense sampling of blood, urine, feces, expired air, and other incidental excreta as needed for up to 7 days. Analysis of the samples will be done by liquid scintillation counting for mass balance determination and HPLC for metabolite profiling. Pralatrexate diastereomer concentrations in plasma and urine will be determined in parallel using a validated LC-MS/MS method.

The timetable you submitted on September 20, 2009, states that you will conduct this trial according to the following timetable:

Final Protocol Submission Date: October 29, 2008
Trial Completion Date: June 30, 2010
Final Report Submission Date: December 31, 2010

Submit the protocols to your IND 52,604 with cross-reference letters to this NDA. Submit all final reports and datasets to your NDA. 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2(vii). 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

In addition, we note your following postmarketing commitment, specified in your submissions dated September 20, and September 22, 2009, that are not a condition of the accelerated approval. This commitment is listed below:

5. Perform *in vitro* studies to determine if transporters are involved in the elimination of pralatrexate.

   Description of study: This will be an *in vitro* study to determine whether pralatrexate is a substrate for the organic anion transporter (OAT) family, including but not limited to OAT1 and OAT3, and whether drugs that interfere with or compete for these transporters (e.g., acyclovir, probenecid, NSAIDS) have an effect on pralatrexate transport

   Study Start Date: December 1, 2009
   Study Completion Date: January 31, 2011
   Final Report Submission Date: July 31, 2011

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. 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 trials, number of patients entered into each trial. All submissions, including supplements, relating to this postmarketing commitment must be prominently labeled "**Postmarketing Commitment Protocol**", "**Postmarketing Commitment Final Report**", or "**Postmarketing Commitment Correspondence**."

In addition, as required by 21 CFR 314.550, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to:

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

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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/default.htm.

If you have any questions, call Milinda Vialpando, Regulatory Project Manager, at (301) 796-1444.

Sincerely,

{See appended electronic signature page}

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