DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

Our STN: BL 125019/156

SUPPLEMENT APPROVAL

September 3, 2009

Spectrum Pharmaceuticals, Inc.
Attention: Kimberly Bollache
Associate Director, Clinical Regulatory
157 Technology Drive
Irvine, CA 92618

Dear Ms. Bollache:

Your request to supplement your biologics license application for Zevalin (ibritumomab tiuxetan) to include a new indication for the treatment of previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy has been approved.

This fulfills your postmarketing commitment number 1 of the February 19, 2002, STN BL 125019/0 approval letter:

> "1. To verify the clinical benefit and further assess the safety and efficacy of Zevalin radioimmunotherapy in patients with chemotherapy relapsed or refractory follicular non-Hodgkin's lymphoma (NHL). This will be assessed in a randomized, multicenter study to establish the net clinical benefit of the Zevalin therapeutic regimen used in combination with Rituxan as compared to Rituxan therapy alone. For this study, the primary efficacy variable will be event-free survival defined as absence of disease progression, initiation of additional lymphoma therapy, or death from any cause. Uniform criteria will be used to define when additional anti-lymphoma treatment is initiated including the presence of disease-related symptoms, threatened end-organ function, cytopenias secondary to NHL, massive bulk disease, or steady disease progression over at least 6 months without meeting the definition of progressive disease. The final protocol will be submitted to CBER by May 30, 2002. Completion of subject accrual and the study are anticipated by November 30, 2004 and May 30, 2006, respectively. A final clinical study report will be submitted to CBER by August 30, 2006."

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 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)).

Since Zevalin (ibritumomab tiuxetan) was approved on February 19, 2002, we have become aware of the potential for the occurrence of myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and other secondary cancers arising in patients who received Zevalin (ibritumomab tiuxetan). During review of this supplement, two new cases of AML and one new case of pancreatic cancer were revealed. Therefore, we consider this information to be "new safety information" as defined in FDAAA.

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 known serious risk of myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and other secondary cancers arising in patients who received Zevalin (ibritumomab tiuxetan).

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 these serious risks.

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 myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and other secondary cancers arising in patients who received Zevalin (ibritumomab tiuxetan). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

1. Continued long-term monitoring of subjects enrolled in the SAG 304820 clinical trial to determine the incidence of myelodysplastic syndrome (MDS), acute myelogenous leukemia (AML) and other secondary cancers.

We acknowledge your August 18, 2008, submission to STN BL 125019/151 which contained pre-BLA meeting briefing material, including the final protocol for SAG 304820. The timetable you submitted on May 5, 2009, states that you will conduct this trial according to the following timetable:

- **Interim Report Submission:** **by August 15, 2009**
  by August 15, 2010
  by August 15, 2011

- **Final Report Submission: by August 15, 2012**

Submit all interim and final report(s) to your BLA 125019. Use the following designators to prominently label all submissions, including supplements, relating to these postmarketing studies and clinical trials 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 OF SECTION 506B

We also acknowledge your written commitment as described in your letter of May 5, 2009 and as outlined below:

2. Submit the results of the final analysis of overall survival (OS) from trial SAG 304820, entitled **"**Efficacy and safety of subsequent treatment with 90-ibritumomab tiuxetan versus no further treatment in patients with stage III or IV follicular NHL having achieved partial or complete remission after first line chemotherapy. A prospective, multicenter, randomized phase III clinical trial." The report will include both the analysis results and the primary datasets used to generate the final analysis, in electronic, SAS-compatible format.

   - **Trial Completion: by February 28, 2012**
   - **Final Report Submission: by February 28, 2013**

We request that you submit clinical protocols to your IND, with a cross-reference letter to this BLA, STN BL 125019. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment - Final Report**
- **Postmarketing Correspondence**
- **Annual Status Report of Postmarketing Commitments**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing commitments for this product. The status report for each commitment should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical trials, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the milestone schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing commitments on our Web site (see http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf **)** for further information.

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

We note your September 1, 2009 submission included final content of labeling [CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the enclosed labeling text. Within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

You may submit draft copies of the proposed introductory advertising and promotional labeling with a cover letter requesting advisory comments to the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising and Communication, 5901-B Ammendale Road, Beltsville, MD 20705-1266. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by a FDA Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This information will be included in your biologics license application file.

Sincerely,

/Patricia Keegan, M.D./
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research