DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021602

**WRITTEN REQUEST - AMENDMENT #2**

Millennium Pharmaceuticals, Inc.
Attention: Eileen Bedell, M.P.H.
Director Regulatory Affairs
35 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Bedell:

Please refer to your correspondence dated May 20, 2011, and December 20, 2011, requesting changes to FDA's January 26, 2011 Written Request (WR) for VELCADE (bortezomib) for Injection.

We have reviewed your proposed changes and are amending the below-listed section of the Written Request (Text added is underlined. Text deleted is ~~strikethrough~~.). All other terms stated in our Written Request issued on January 26, 2011, remain the same. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Requests dated April 27, 2010 and January 26, 2011.

***Age group in which the study will be performed*:**

Phase 1 Studies: Patients 1 to 18 years of age.
Phase 2 Study: Patients of age 1 to 21 years are eligible; however, a minimum of 5 patients in the 12-16 age group and 25 in the 2-11 age group will be enrolled ~~10 patients per each age group (2-11 and 12-16) will be enrolled in each of strata 1 and 2~~.

Although the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g) states "including neonates in appropriate cases" as one of the pediatric age groups for pediatric studies, the proposed trial includes children no younger than 2 years of age. Neonates would not be an appropriate group for inclusion for two reasons: 1) the proposed trial's eligibility criteria require that pediatric patients must have relapsed disease following first complete remission; and, 2) the treatment of infants with leukemia differs from the treatment of older children in which the proposed backbone therapy is appropriate.

***Number of patients to be studied:***

Phase 1 Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives. Phase 2 Study: At least 30 patients are to be enrolled in Stage 1. If the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries and the

adverse event profile is favorable according to the protocol stopping rules, 30 additional patients will be enrolled in Stage 2.

All Studies: Pharmacokinetic data should be appropriately analyzed using methods such as nonlinear mixed effects modeling. A minimum of 20 patients in each age group of 2-11 and 12-16 years must be sampled for pharmacokinetics ~~unless AALL07P1 is stopped earlier due to lack of effect or safety.~~ To enable this analysis, data from this Phase 2 study may be combined with PK data collected in other pediatric studies of VELCADE. The data from the relevant studies must then be used to explore the exposure-response relationship for safety and effectiveness endpoints.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated April 27, 2010, as amended by this letter and by a previous amendment dated January 26, 2011, must be submitted to the Agency on or before February 3, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

*{See appended electronic signature page}*

Gregory H. Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

**WRITTEN REQUEST - AMENDMENT #2**

NDA 021602

Millennium Pharmaceuticals, Inc.
Attention: Eileen Bedell, M.P.H.
Director Regulatory Affairs
35 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Bedell:

Please refer to your correspondence dated May 20, 2011, and December 20, 2011, requesting changes to FDA's January 26, 2011 Written Request (WR) for VELCADE (bortezomib) for Injection.

This study investigates the potential use of bortezomib in the treatment of pediatric patients with acute lymphocytic leukemia (ALL).

To obtain needed pediatric information on bortezomib, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

***Type of study(ies)*:**

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities.

Phase 1 Studies: Studies, including pharmacokinetics, that define age appropriate dosing in pediatric patients.

Phase 2 Study: A non-randomized, drug activity, safety and pharmacokinetic trial in children with acute lymphocytic leukemia (ALL) in first relapse, assessing the activity of the addition of bortezomib to multi-agent re-induction chemotherapy, limited to those patients with first relapse of pre-B ALL between the ages of 1 and 21 years and considered to be in "early" relapse, defined as relapse within 18 months of diagnosis (stratum 1) or relapse 18-36 months from diagnosis (stratum 2). The study will have a stratified two-stage design. Patients enrolled in Stage 1 should be evaluated at the end of the stage for second complete response (CR2). The decision to enroll additional patients in the study, in Stage 2, should depend on whether the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries.

***Indication(s) to be studied:***

Phase 1 Studies: Relapsed or refractory solid tumors and/or leukemias.
Phase 2 Study: Pre-B-cell ALL in first relapse.

***Objectives:***

Phase 1 Studies: To determine the maximum tolerated dose and/or pharmacokinetics.
Phase 2 Study: To estimate the rate of second complete response (CR2) achieved in each of the two strata at the end of Block 1 therapy, and the four month event-free survival; to describe the toxicity of the regimen; to evaluate pharmacokinetics by sparse PK sampling.

***Age group in which the study will be performed*:**

Phase 1 Studies: Patients 1 to 18 years of age.
Phase 2 Study: Patients of age 1 to 21 years are eligible; however, a minimum of 5 patients in the 12-16 age group and 25 in the 2-11 age group will be enrolled.

Although the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a(g) states "including neonates in appropriate cases" as one of the pediatric age groups for pediatric studies, the proposed trial includes children no younger than 2 years of age. Neonates would not be an appropriate group for inclusion for two reasons: 1) the proposed trial's eligibility criteria require that pediatric patients must have relapsed disease following first complete remission; and, 2) the treatment of infants with leukemia differs from the treatment of older children in which the proposed backbone therapy is appropriate.

***Number of patients to be studied:***

Phase 1 Studies: The number of patients entered must be sufficient to achieve Phase 1 objectives. Phase 2 Study: At least 30 patients are to be enrolled in Stage 1. If the number of patients with CR2 at the end of Stage 1 meets the pre-specified decision boundaries and the adverse event profile is favorable according to the protocol stopping rules, 30 additional patients will be enrolled in Stage 2.

***Study endpoints:***

Phase 1 Studies:

1. Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer.
2. Assess patients for responses to therapy and duration of responses.

Phase 2 Study:

1. To determine the toxicities of bortezomib when administered in combination with intensive re-induction chemotherapy in patients with relapsed ALL

2. To estimate for patients in strata 1 and 2 with pre-B ALL, the rate of re-induction of CR and the 4 month EFS (as an indication of potential transplant eligibility) for this regimen

All Studies: Pharmacokinetic data should be appropriately analyzed using methods such as nonlinear mixed effects modeling. A minimum of 20 patients in each age group of 2-11 and 12-16 years must be sampled for pharmacokinetics. To enable this analysis, data from this Phase 2 study may be combined with PK data collected in other pediatric studies of VELCADE. The data from the relevant studies must then be used to explore the exposure-response relationship for safety and effectiveness endpoints.

***Drug information***

- *dosage form*
  Bortezomib for injection will be provided in the marketed formulation.
- *route of administration*
  Intravenous
- *regimen*
  Phase 1 Studies: Bortezomib 1-1.7 $mg/m^2$ on days 1, 4, 8, and 11 every 3 weeks.
  Phase 2 Study: Bortezomib 1.3 $mg/m^2$ will be given on days 1, 4, 8, and 11 during the first 35 days of treatment, then again on days 1, 4, and 8 of the second 35 day treatment block, for a total of 7 injections.

***Drug specific safety concerns*:**

In adults receiving bortezomib on a similar schedule cycled every three weeks, neurologic toxicity (peripheral sensory neuropathy) is usually cumulative and dose-limiting. Ileus has also been observed. Provide safety information on these and other toxicities encountered.

***Statistical information, including power of study and statistical assessments:***

The study will use a stratified two-stage phase II design to test the null hypothesis that adding bortezomib to the AALL01P2 backbone gives an overall (across strata) CR2 response rate of 67%. CR2 response will be assessed at the end of Stage 1 and, if necessary, again at Stage 2. The power of a global one-sample test against the alternative hypothesis that the CR2 response is 79% is at least 80% assuming a one-sided alpha of 10%. A total of 60 patients will be potentially enrolled. A total of 30 patients will be enrolled in Stage 1. Decision boundaries may be used to assess CR2 with respect to the null hypothesis at the end of Stage 1 and also to decide whether to enroll 30 additional patients in Stage 2. The overall CR2 rate must be estimated at the end of the study with an appropriate 2-sided 95% confidence interval. Descriptive statistics will be provided for CR2 responses by stratum.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that bortezomib is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports and datasets (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before February 3, 2016. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

*Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of

the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Amy Baird, Regulatory Project Manager, at (301) 796-4969.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

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/s/

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GREGORY H REAMAN
11/13/2012