DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT # 1

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 September 21, 2010, requesting changes to FDA's April 27, 2010, Written Request for pediatric studies for Velcade® (bortezomib) for Injection.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on April 27, 2010, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *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. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

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 <u>the</u> ages <u>of</u> 1 and 21 <u>years</u> 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). ~~It is recommended, though not required, that the study have a stratified two-stage design~~. 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 ~~stage~~ Block 1 therapy, and the four month event-free survival; to describe the toxicity of the regimen; to evaluate pharmacokinetics by sparse PK sampling ~~in a minimum of 15 patients in each stratum to describe bortezomib PK in the combination regimen~~.

- *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.

- *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 ~~60~~ 30 patients ~~in total, including at least 30 patients enrolled in stratum 1 and 30 patients~~ are to be enrolled in ~~stratum 2~~ 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. A minimum of 15 patients in each age group of 2-11 years and 12-16 years ~~should~~ must be sampled for pharmacokinetics through approaches such as sparse sampling unless stopped early due to lack of effect.

- *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. The studies must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate ~~of~~ for CL and Vd for bortezomib in the 2-11 years and

12-16 years age groups. 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.

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

The study will use a stratified two-stage phase 2 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 ~~potentially~~ be potentially enrolled ~~with at least~~. A total of 30 patients will be enrolled in ~~s~~Stage 1. Decision boundaries may be used to assess CR2 with respect to the null hypothesis at the end of ~~s~~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.

Timeframe for submitting reports of the study(ies): Reports of the above studies must be submitted to the Agency on or before ~~September 1~~ February 3, 201~~3~~6. 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.

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 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 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, 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 Allison Adams-McLean, Regulatory Project Manager, at 301-796-3996.

Sincerely,

{See appended electronic signature page}

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

Attachment: Word Copy of Initial April 27, 2010 Written Request

WRITTEN REQUEST

NDA 21602

Millennium Pharmaceuticals, Inc.
Attention: Margarita Aguilera, M.S.
Senior Director Regulatory Affairs
35 Landsdowne Street
Cambridge, Massachusetts 02139

Dear Ms. Aguilera:

Reference is made to your October 21, 2009, Proposed Pediatric Study Request for Velcade® for Injection.

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 following study:

- *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. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

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 ages 1 and 21 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). It is recommended, though not required, that the study 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 stage 1 therapy, and the four month event-free survival; to describe the toxicity of the regimen; to evaluate pharmacokinetics by sparse PK sampling in a minimum of 15 patients in each stratum to describe bortezomib PK in the combination regimen

- *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 10 patients per each age group (2-11 and 12-16) will be enrolled in each of strata 1 and 2.

- *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 60 patients in total, including at least 30 patients enrolled in stratum 1 and 30 patients enrolled in stratum 2. A minimum of 15 patients in each stratum should be sampled for pharmacokinetics through approaches such as sparse sampling.

- *Study endpoints:*

Phase 1 Studies:

3. Determine the maximum tolerated dose (MTD), dose-limiting and other toxicities in pediatric patients with cancer.
4. 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. The studies must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of CL and Vd for bortezomib in each age group (2-11, 12-16, and 17-21 years of age). 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 enrolled with at least 30 patients for each stage. Decision boundaries may be used to assess CR2 with respect to the null hypothesis at the end of each stage and also to decide whether to enroll 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 September 1, 2013. 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) should 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, approvable, not approvable); 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/cder/pediatric/index.htm

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 Allison Adams-McLean, Regulatory Project Manager, at 301-796-3996.

Sincerely,

{See appended electronic signature page}

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

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

/s/

RICHARD PAZDUR
01/26/2011