In the paper by Aghajanian et al, Clin Cancer Res 2002; 8:2505-11, the recommended phase II dose of velcade was 1.56 mg/m2 twice weekly X 2 weeks, but in the sponsor's summary report page 13, final clinical study report of protocol 98-104A (in module 5), they state "the maximal tolerated dose of PS-341 when administered twice weekly for two weeks ... was determined to be 1.3 mg/m2. Please explain this discrepancy?

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0515
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/23 09:51
USAGE T	00'36
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 23, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and request the following information that is needed to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0514
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/23 09:48
USAGE T	00'38
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet:	**Date:** April 23, 2003
Re: NDA 21-602 VELCADE	

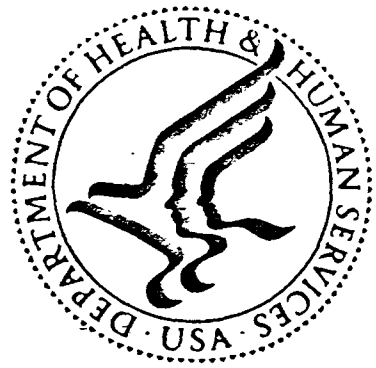
☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached deficiency comments relating to the drug product.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 17, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and request the following information that is needed to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

Please fill in the corresponding information (column 2) of the table below and resubmit to the Agency as soon as possible.

Dose Modifications During Study 025

% patients who started trial at does level 1.3 mg/m2 and received it throughout trial	
% patients who started trial at dose level 1.3 mg/m2 and had one dose level reduction	
% patients who started trial at dose level 1.3 mg/m2 and had two dose level reductions	
% patients who started trial at dose level 1.3 mg/m2 and had a dose held	
% patients who started trial at dose level 1.3 mg/m2 and discontinued for toxicity	
% patients who started trial at dose level 1.0 mg/m2 and received it throughout trial	
% patients who started trial at dose level 1.0 mg/m2 and had one dose level reduction	
% patients who started trial at dose level 1.0 mg/m2 and had a dose held	
% patients who started trial at dose level 1.0 mg/m2 and discontinued for toxicity	
% patients who started trial at dose level 0.7 mg/m2 and received it throughout trial	
% patients who started trial at dose level 0.7 mg/m2 and had a dose held	
% patients who started trial at dose level 0.7 mg/m2 and discontinued for toxicity	

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0498
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/17 11:18
USAGE T	00'39
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 17, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Fax

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Center for Drug Evaluation and Research, HFD-150
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1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 16, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached the Phase 4 commitments from our Clinical Pharmacology and Biopharmaceutics division.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1. As PS-341 is metabolized and eliminated by the liver, you should conduct a pharmacokinetic and pharmacodynamic (PK/PD) study in patients with liver impairment to adequately provide dosing recommendations for this special patient population in the labeling for VELCADE. Please submit the study protocol for Agency review.

2. You should conduct a PK/PD study in patients with various degrees of renal impairment. A study protocol sponsored by CTEP was submitted on January 2, 2003 under _____ to evaluate the pharmacokinetics of PS-341 in patients with advanced malignancies and varying degrees of renal dysfunction. We recommend that you submit the study report and results to the Agency for review as soon as study is completed.

3. As PS-341 is a substrate to both CYP3A4 and 2D6 enzymes, you should conduct PK and PK/PD studies to examine the potential for drug-drug interactions between PS-341 and drugs that are inhibitors and/or inducers of these enzymes. The results of these studies will help to provide proper dosing information in patients with multiple myeloma when VELCADE is coadministered with other drugs that known as inhibitors and/or inducers of 3A4 and 2D6.

4. Please provide your plan and projected completion time for the above recommended studies.

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0494
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/16 13:05
USAGE T	00'42
PGS. SENT	2
RESULT	OK

Fax

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Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 16, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

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If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

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Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 16, 2003
Re: NDA 21-602 VELCADE/Information request	

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Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

For study025, the files conmeds.xpt and cmed_d.xpt seem to have a variable called MED which has the name of the co-medication used in each patient. You also generated a table of common co-medications as part of the submission. According to that table, pamidronate is given to about 145 patients (of 202 total, see table below). The conmed.xpt file shows that only 12 patients received pamidronate. It is possible that the correct data are in another file. Please direct us to the correct file from which the concomitant medication table was generated.

Table 12-27 Commonly (15% of Patients Overall) Used Concomitant Medications (All Patients Treated; N=202)

Medication Preferred Ter	All Treated Patients (N=202) n (%)
Pamidronic acid	145 (72)
Paracetamol	111 (55)
Erythropoietin	93 (46)
Red blood cells	94 (47)
Diphenhydramine	83 (41)
Platelets, human blood	71 (35)
Lorazepam	69 (34)
G-CSF	68 (34)
Ondansetron	65 (32)
Levofloxacin	61 (30)
Multivitamins	58 (29)
Loperamide	55 (27)
Senna	56 (28)
Gabapentin	54 (27)
Prochlorperazine	52 (26)
Sodium chloride	52 (26)
Erythropoietin human	49 (24)
Oxycodone	49 (24)
Acyclovir	47 (23)
Potassium	47 (23)
Fentanyl	44 (22)
Allopurinol	41 (20)
Pyridoxine	40 (20)
Zolpidem	40 (20)
Morphine	36 (18)
Omeprazole	35 (17)
Warfarin	35 (17)
Magnesium sulfate	33 (16)
Oxycocet	32 (16)
Vicodin	32 (16)

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0491
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/16 10:02
USAGE T	00'40
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 16, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown	**From:** Brenda Atkins, CSO for Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 3	**Date:** April 11, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Melody,

Here are our responses to your April 8, 2003 questions sent in reference to our April 7, 2003 CMC comments/questions.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Regards,

/S/

Sean Bradley, R.Ph.
Regulatory Project Manager

We have considered your concerns/questions to us dated April 08, 2003 regarding our CMC comments relayed to you by FAX on April 07, 2003. We have also considered the pre-NDA meeting minutes you cite which are dated November 05, 2002.

We remind you (as per 11/05/02 minutes), that compound 1 does not fit some of the generally accepted criteria to qualify as a starting material. While it's propinquity is acceptable, it is not commercially available except as a custom synthesis for you. It lacks a significant pharmaceutical or non pharmaceutical market. It contributes critical structural features including chirality to the API. However, we understand your science-based approach as well as your willingness to accept a certain level of risk; that risk being controlled by your careful acquisition of adequate data for compound 1.

In order for us to accept as adequate the slightly higher level of risk you propose to adopt, and which will allow you to enjoy the benefits of using compound 1 as a starting material, we feel justified in seeking certain information to document in our review.

We felt that the information we asked for regarding Compound 1, although slightly more than what might be asked for a more conventional starting material, should be easily at hand and requires no further data gathering on your part. If indeed, you do lack this information, it can be argued that you may lack the necessary controls over compound 1.

However, in consideration of your requests, we have taken a look at our April 7 comments regarding compound 1 and have modified them somewhat (see below).

Comment 2 of our April 07 FAX now becomes:

2. [redacted]

The foregoing comment also addresses your concerns regarding comment 7 of our April 07 FAX. **Therefore, comment 7 from our April 07 FAX is now eliminated.**

We understand your concern regarding comment 10 of our April 07 FAX regarding compound 2. This comment arises out of a recent ONDC policy regarding the control of potential TSE (transmissible spongiform encephalopathy) agents derived from animal tissue. This policy extends to [redacted] even if they are used as starting materials. Therefore, please provide the requested information.

Millennium is correct regarding the level of information asked for in comment 12 of our April 07 FAX.

Comment 12 is changed as follows:

12. Please provide information which documents and substantiates that your suppliers of _____ are (and that new ones will be) qualified against the specifications provided in your NDA.

NDA amendment #006 is currently under review. We acknowledge your concerns regarding comments 18 and 19 from our April 07 FAX. Pending our review of this amendment, **we agree to hold our comments 18 and 19 for the time being**. We will advise you if we need these comments addressed in the future.

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0364
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/11 14:46
USAGE T	01'12
PGS. SENT	3
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown	**From:** Brenda Atkins, CSO for Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 3	**Date:** April 11, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Melody,

Here are our responses to your April 8, 2003 questions sent in reference to our April 7, 2003 CMC comments/questions.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 9, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached questions that need to be addressed in order to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

1. Module 5.2.1 notes additional Velcade studies under sponsor of NCI DCTD. Table 3, page 14 shows 7 patients with hypotension grade 3 (requires hospitalization by ECOG but not by CTC tox). Please identify the dose schedule, number of doses and total mg of Velcade received for each patient at the time of onset of the hypotension toxicity, the therapy for the hypotension given to each patient, and the time of occurrence of the hypotension (which cycle of Rx and how many hours after a Velcade dose) and how low the BP went. Provide same data for any grade 3 hypotensive patients in studies -024 and -025 also.

2. You have a number of phase 2 studies with twice weekly dose of 1.5 mg/m2 times two weeks then one week off. How many patients are in this population as of time of report and how many patients were dose-reduced or missed doses in cycles 1 and 2 on this dose-schedule to date of report?

3. For protocol -025, please provide a table showing incidence of: nausea, diarrhea, vomiting, night sweats, anxiety, and total SAEs for each cycle one, two, and three of protocol -025. For anemia, thrombocytopenia and peripheral neuropathy in same study, what is the baseline frequency of each at start of study and identify the increase in frequency and severity for cycles 1, 2, and 3 of Velcade treatment on -025 for each of these AEs? Also provide a listing of the sources (module, page) of submission where the information is located that you are compiling.

4. At what level of frequency or severity of adverse event do you advise investigators to administer any pre-meds with Velcade, given frequencies of 30% or more for nausea, diarrhea, constipation, and anxiety after Velcade 1.3 mg/m2 IV?

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0452
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/09 16:25
USAGE T	00'42
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, Including cover sheet: 2	**Date:** April 9, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Fax

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Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To:	Melody A. Brown	**From:** Sean Bradley, CSO	
Fax:	617-551-3742	**Fax:** 310-827-4590	
Phone:	617-551-4977	**Phone:** 301-594-5770	
Pages, including cover sheet:	3	**Date:** April 7, 2003	
Re:	NDA 21-602 VELCADE/Information request		

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1.

2. Provide the detailed manufacturing information of Compound 1.

3. Provide the GC spectrum of Compound 1 and test conditions to demonstrate adequate quantification of the designated compound and its stereo-isomers as well as other impurities.

4. Provide the melting point for Compound 1.

5.

6. Provide the published references related to the synthesis and isomer identification.

7

8.

9. Please add melting point to the specifications of Compound 2.

10. Compound 2, please provide the species, source countries and processing countries.

11.

12.

13. Please provide reaction completion data for Step 1 and step 3.

14. The mass spectrum of the reference standard (lot 020136) shows

15. Please provide evidence from NMR, MS or HPLC to support the structure claims for Impurity E and F's monomeric and trimeric forms.

16.

17. Provide the melting point for the DS, PS-341.

18. The investigation report for two stability failure drug substance lots (010185, 010187) should be submitted and updated stability information for on going 4 drug substance lots (010201, 020077, 020149 and 020150) should be provided,when available.

19.

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0330
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/07 08:34
USAGE T	01'14
PGS. SENT	3
RESULT	OK

Fax

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Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody A. Brown	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 3	**Date:** April 7, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Sean Bradley R Ph

Fax

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1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 3, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1. Please submit the PK assay validation report for the 21 patients from Study M34100-027.

2. Please provide the data that shows there are no drug-drug interactions which occur between Velcade and gemcitabine.

3. You mention a container closure integrity test (section 3.2 P.2.5 microbiological attributes) but do not give any details of the method used. You also refer to the Stability section (P.8) for information about the method but we cannot find it there either. Please provide a method, including details about the sensitivity of the test, and a summary of the results. You also state this method as part of the post-approval stability protocol.

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0420
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/03 15:30
USAGE T	00'38
PGS. SENT	2
RESULT	OK

Fax

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Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S. **From:** Sean Bradley, CSO

Fax: 617-551-3742 **Fax:** 310-827-4590

Phone: 617-551-8951 **Phone:** 301-594-5770

Pages, including cover sheet: 2 **Date:** April 3, 2003

Re: NDA 21-602 VELCADE/Information request

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To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 3, 2003
Re: NDA 21-602 VELCADE/Information request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached questions that need to be addressed in order to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1. Patient 003-0001
   According to patient data listings for study 25 (Listing 16.2.6.4A and B p 3803 and 3880) this patient had only one bone marrow performed on June 13, 2001. However, the IRC report for that patient lists two more bone marrows- one during cycle 6 and one during cycle 8.

2. Patient 012-0027
   According to patient data listings for study 25 (Listing 16.2.6.4A and B pp 3874 and p 3909) this patient has only one bone marrow aspirate and biopsy performed on November 8, 2001. However, the IRC report for that patient lists one more bone marrow- one at followup.

3. Please account for the apparent discrepancies, and if possible provide all the bone marrow aspiration and biopsy reports for all the CR(blade) patients. As previously mentioned, we would like to review the actual aspirate and biopsy slides, if possible.

4. Patient 014-0015
   According to the patient data listings for study 25 (Listing 16.2.6.2A p 3516) and the IRC worksheets, this patient had only one negative serum immunofixation on February 5, 2002. The previous 4 IF's were all positive for M-protein. Do you have any additional information on subsequent IF tests to justify inclusion as a confirmed CR (blade)?

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0421
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/03 17:49
USAGE T	00'40
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

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Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** April 1, 2003
Re: NDA 21-602 VELCADE	

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Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1. Is there a regulatory meeting history in the submission? If not, could you provide one?

2. The most helpful bone marrow slides we would like to review are the follow-up samples obtained on the following patients: 03-001, 06-002, 12-0027, and 14-0015.

3. On patient 14-0015, can you obtain any further determinations on the serum IF results beyond the last reported determination on cycle 8 on 05Feb02?

4. In patient 06-0010, with IgA M protein, the IgA fell from 20.5 to 1.78 g/L, from baseline to cycle 2, suggesting a large amount of the IgA may have actually been M protein.

5. Why was it not possible to quantitate the M Spike at baseline? If this was an IgA myeloma, how could the M spike go up to 2.6 g/L at cycle 8 if the IgA was only 1.15 g/l?

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0410
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SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	04/01 16:57
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PGS. SENT	2
RESULT	OK

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Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 4	**Date:** March 26, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

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Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

1. For study M34100-027 (Gemcitabine):

   A total of 31 patients were treated at 4 dose levels of PS-341and gemcitabine (in mg/m2): 1.0/500 (3 patients), 1.0/800 (3 patients), 1.0/1000 (15 patients), and 1.3/800 (10 patients). Plasma PS-341 concentration profiles were evaluated on Days 1 and 2 and on Days 8 and 9 of Cycle 1 (Dose 1 and 3) from 17 patients receiving a dose of 1.0mg/m2 and from 5 patients receiving a dose of 1.3 mg/m2 in the presence of gemcitabine.

   Please submit the PK data for these patients.

2. There are multiple missing data points in the BMBx dataset:

Table 1: Bone Marrow results (% Plasma cells) on 7 CR^{Blade} patients from BMBX dataset

PAT#	Baseline	Cycle 3	Cycle 5	Cycle 7	EOS
02-0015	80	5	*	5	5
03-0001	80	*	*	*	*
03-0021	0	*	*	*	*
03-0033	3	2	*	*	*
06-0002	45	*	5		
12-0027	100	*	*	*	*
14-0015	40	*	*	*	*

*missing

Please provide a dataset with all the bone marrow results (Plasma cell %) which were obtained, including both the biopsy and aspirate and central and local readings, or provide the location in the electronic document where these datasets are available.

In addition, we would like to arrange to review the actual aspirate and biopsy slides from the CR(Blade) patients.

ESPONSE

missing *

ows	REC_ID	CNO	PATNO	EVENT_ID	PAG_NAME	CYCLE	DAY	RESP_CD	ASSES_DT	PRGDS_CD	STABL_CD
1	97655201	001	001	C3D1	RESPC3D1	3	1	.	09/11/2001	2	.
2	100704401	001	001	C5D1	RESPC5D1	5	1	.	10/23/2001	2	2
	00826401	001	001	C7D1	RESPC3D1	7	1	.	12/04/2001	2	.
	04962901	001	001	EOS	RESPONSE	.	.	.	01/03/2002	.	.
5	97499601	001	002	C3D1	RESPC3D1	3	1	.	09/25/2001	2	.
6	105079501	001	002	C5D1	RESPC5D1	5	1	.	11/06/2001	2	2
7	117345101	001	002	C7D1	RESPC3D1	7	1	.	12/18/2001	2	.
8	117391601	001	002	EOS	RESPONSE	.	.	.	01/28/2002	.	.
9	127382501	001	003	C3D1	RESPC3D1	3	1	.		.	.
10	112754001	001	003	C4D1	RESPC3D1	4	1	.	10/30/2001	1	.
11	112778601	001	003	EOS	RESPONSE	.	.	.	11/20/2001	.	.
12	114189101	001	004	C3D1	RESPC3D1	3	1	.	10/16/2001	2	.
13	114275901	001	004	C5D1	RSPC5D15	5	1	.	11/27/2001	.	.
14	114641201	001	004	C7D1	RSPC7D15	7	1	.	01/08/2002	.	.
15	114665501	001	004	EOS	RESPONSE	.	.	.	01/29/2002	.	.
16	105718701	001	005	C3D1	RESPC3D1	3	1	.	10/23/2001	2	.
17	127388101	001	005	C5D1	RSPC5D15	5	1	.	12/04/2001	.	.
18	114110701	001	005	C7D1	RSPC7D15	7	1	.	01/15/2002	.	.
19	114147301	001	005	EOS	RESPONSE	.	.	.	02/27/2002	.	.
20	113181601	001	006	EOS	RESPONSE	.	.	.	.	.	.
21	104991601	001	007	C3D1	RESPC3D1	3	1	.	11/13/2001	2	.
22	113361401	001	007	EOS	RESPONSE	.	.	.	12/07/2001	.	.
23	104790501	001	008	C3D1	RESPC3D1	3	1	.	12/11/2001	1	.
24	108464401	001	008	C5D1	RSPC5D15	5	1	.	01/22/2002	.	.
	14090901	001	008	C7D1	RSPC7D15	7	1	.	03/05/2002	.	.
	17137301	001	008	EOS	RESPONSE	.	.	.	04/17/2002	.	.
27	96490401	002	001	C3D1	RESPC3D1	3	1	.	07/24/2001	2	.
28	98260201	002	001	C5D1	RESPC5D1	5	1	.	09/07/2001	2	2
29	101971601	002	001	C7D1	RESPC3D1	7	1	.	10/19/2001	2	.
30	105072001	002	001	EOS	RESPONSE	.	.	.	11/28/2001	.	.
31	115540201	002	004	EOS	RESPONSE	.	.	.	09/10/2001	.	.
32	118877101	002	005	C3D1	RESPC3D1	3	1	.	09/25/2001	1	.
33	118880001	002	005	EOS	RESPONSE	.	.	.	11/14/2001	.	.
34	122324001	002	006	C3D1	RESPC3D1	3	1	.	09/28/2001	1	.
35	122824601	002	006	C5D1	RSPC5D15	5	1	.	11/16/2001	.	.
36	122877801	002	006	EOS	RESPONSE	.	.	.	01/29/2002	.	.
37	120188001	002	007	C3D1	RESPC3D1	3	1	.	09/24/2001	1	.
38	120226301	002	007	C5D1	RSPC5D15	5	1	.	11/06/2001	.	.
39	120289301	002	007	C7D1	RSPC7D15	7	1	.	01/07/2002	.	.
40	120364801	002	007	EOS	RESPONSE	.	.	.	02/21/2002	.	.
41	119376701	002	008	C3D1	RESPC3D1	3	1	.	10/01/2001	2	.
42	119398401	002	008	EOS	RESPONSE	.	.	.	10/24/2001	.	.
43	121834501	002	009	C3D1	RESPC3D1	3	1	.	10/12/2001	2	.
44	127923501	002	009	C5D1	RSPC5D15	5	1	.	11/30/2001	.	.
45	122094801	002	009	C7D1	RSPC7D15	7	1	.	01/15/2002	.	.
46	122195101	002	009	EOS	RESPONSE	.	.	.	03/18/2002	.	.
	11980401	002	010	C3D1	RESPC3D1	3	1	.	10/08/2001	1	.
	22146101	002	010	EOS	RESPONSE	.	.	.	11/21/2001	.	.
49	115328301	002	011	C3D1	RESPC3D1	3	1	.	10/09/2001	2	.
50	118578201	002	011	C5D1	RSPC5D15	5	1	.	11/20/2001	.	.
51	115582601	002	011	C7D1	RSPC7D15	7	1	.	01/04/2002	.	.

BMBX 7 SPNSR CR (BLADE)

Rows	PATID	REC_ID	PNO	EVENT_ID	CYCLE	BX_CD	ASSES_DT	ADEQ_CD	CELL_CD	PLASPCT	PLASUNIT
1	002015	123059701	M34100025_C	C3D1	3	1	10/23/2001	1	1	5	%
2	002015	123114101	M34100025_C	C5D1	5	2	.	.	.	.	%
3	002015	123207801	M34100025_C	C7D1	7	1	01/23/2002	1	1	5	%
4	002015	123302901	M34100025_C	EOS	.	1	03/28/2002	1	2	5	%
5	002015	122956301	M34100025_C	SCREENIN	.	1	09/07/2001	1	1	80	%
6	003001	91457901	M34100025_C	C3D1	3	2	.	.	.	.	%
7	003001	106246501	M34100025_C	C5D1	5	2	.	.	.	.	%
8	003001	106808201	M34100025_C	C7D1	7	2	.	.	.	.	%
9	003001	106385501	M34100025_C	EOS	.	2	.	.	.	.	%
10	003001	97398301	M34100025_C	SCREENIN	.	1	06/13/2001	1	2	80	%
11	003021	109524201	M34100025_C	C3D1	3	1	10/09/2001	1	2	.	%
12	003021	109575701	M34100025_C	C5D1	5	1	11/20/2001	2	.	.	%
13	003021	109659901	M34100025_C	C7D1	7	2	.	.	.	.	%
14	003021	109685001	M34100025_C	EOS	.	2	.	.	.	.	%
15	003021	109492801	M34100025_C	SCREENIN	.	1	08/21/2001	2	3	0	%
16	003033	113825701	M34100025_C	C3D1	3	1	12/21/2001	1	2	2	%
17	003033	113866701	M34100025_C	C5D1	5	2	.	.	.	.	%
18	003033	113906001	M34100025_C	C7D1	7	1	03/18/2002	1	2	.	%
19	003033	113922601	M34100025_C	EOS	.	2	.	.	.	.	%
20	003033	113792501	M34100025_C	SCREENIN	.	1	10/31/2001	1	3	3	%
21	006002	91588301	M34100025_C	C3D1	3	2	.	.	.	.	
22	006002	91605001	M34100025_C	C5D1	5	1	07/12/2001	1	2	5	%
23	006002	91045101	M34100025_C	SCREENIN	.	1	04/10/2001	1	2	45	%
24	012027	110870301	M34100025_C	C3D1	3	2	.	.	.	.	%
25	012027	112030001	M34100025_C	C5D1	5	2	.	.	.	.	%
26	012027	113435401	M34100025_C	EOS	.	2	.	.	.	.	%
27	012027	110823701	M34100025_C	SCREENIN	.	1	11/08/2001	1	1	100	%
28	014005	91844001	M34100025_C	C3D1	3	2	.	.	.	.	%
29	014005	100660501	M34100025_C	C5D1	5	2	.	.	.	.	%
30	01400[illegible]	[illegible]424001	M34100025_C	C7D1	7	2	.	.	.		%

****
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TX/RX NO	0387
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	03/26 08:25
USAGE T	01'20
PGS. SENT	4
RESULT	OK

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Pages, including cover sheet: 4	**Date:** March 26, 2003
Re: NDA 21-602 VELCADE	

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Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

1. The dataset RESPONSE.xpt appears to be missing entries in the column marked RES_CD. Please resubmit this dataset or indicate where we can find this information.

2. Pat # 03-001: Urine IF cycle 6 - kappa and lambda IF's are both positive although the monoclonal band IFwas negative. The myeloma secreted IGA kappa and sometimes lambda. What is the explanation for the presence of the Kappa and Lambda IF bands in cycle 6? Please justify inclusion as a CR (Blade).

3. Pat # 03-0033: Study 025 entry criteria state that patients are to be "Relapsed following a response to standard first-line chemotherapy (e.g., VAD or MP) or first-line high-dose chemotherapy..." From the PRIQRTHR dataset, this patient has received DECADRON, PREDNISONE, and BIAXIN, but not VAD or MP. Please justify eligibility. The skeletal survey on cycle 4 appears to show a 30% increase in the area of one of the target lesions and a 24% increase in the area of another target lesion, however the response assessment commented that these changes represented 'technical variation' and not PD. What were the objective criteria for determination of progressive disease on skeletal survey? Were any further films obtained to confirm SD on this pt? This pt was taking low dose prednisone 20 mg QOD tapered to 15 QOD on 11/08/01 then to 10 QOD on 12/29/01 for indication 'myeloma.' Could this dose have contributed to the response?

4. Pat # 12-0027: Although the urine IF's are negative, this pt showed 24 hour urine M protein of 14 mg on cycle 2 and 377 mg on cycle 5, according to the IRC data form. The IRC reviewer A comments stated that the data are 'incomplete and contradictory.' The Dataset UPRO_D1 appears to be missing EVENT_IDs C2REST and C5 REST. Please provide explanation for missing and inconsistent data and justification for inclusion as a CR (Blade).

5. Pat # 14-0015: Response criteria for CR (IF+) require 100% reduction in UPEPs. Urine paraproteins remained positive at 133, 124, 106, and 88 on cycles 2,4,6 and 8 although Urine IFE results were negative. Please provide an explanation for this discrepancy and justify the inclusion of this patient as a CR (IF+). The IRC worksheets did not comment on this.

6. Pat # 03-0005: The urine paraprotein was 10 on cycle 4, and 1815 on cycle 7, please justify the inclusion of this patient as a CR (IF+). Response criteria for CR (IF+) require 100% reduction in UPEPs, for a minimum of 6 weeks.

7. Pat 03-0015: Have you confirmed with the investigator to be certain that urine IFE results are not available from cycle 5?

8. PAT 03-00019: This patient never lost urine paraprotein, although they had 2 consecutive evaluations without measurable serum paraprotein. IRC notes record the best response as a PR. Please justify the inclusion of this patient as a CR (IF+).

9. Pat 06-0022: This patient had only 3 determinations of urine paraprotein, which was 'unable to calculate ' on the last determination only. IRC notes record the best response as a PR. Please justify the inclusion of this patient as a CR (IF+).

10. Pat 14-0006: This patient had a minimum urine protein of 5 mg/24 h on cycle #2. IRC notes record the best response as a PR. Please justify the inclusion of this patient as a CR (IF+).

****
*** TX REPORT ***
****

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TX/RX NO	0381
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	03/24 16:25
USAGE T	00'51
PGS. SENT	2
RESULT	OK

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Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** March 24, 2003
Re: NDA 21-602 VELCADE	

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[illegible] 301-594-5770 or BradleyS@CDER.FDA.GOV.

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To: Melody Brown	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** March 19, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Melody,

Regarding the two lots of Velcade that were manufactured at [redacted], release testing at Quintiles may proceed for these two batches. However, the expiry and/or retest date for these 2 batches will be from the original date of manufacture and NOT the re-release test date.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Regards,

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

****
*** TX REPORT ***
****

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TX/RX NO	0367
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	03/19 10:49
USAGE T	00'29
PGS. SENT	1
RESULT	OK

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If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

From the CDER Electronic Document Room Staff

Central Document Room (HFD-94)
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

To Contact: Melody A Brown Fax: 617-551-3742 Phone: 617-551-4977

Re: Firm: Millennium Application: NDA 21602 Letter Date: 3/17/03

RESUBMISSION REQUIRED

	1. Document(s) submitted in non archival format (MS Word, etc.) – documents other than draft labeling text, should only be submitted in PDF format described in the guidance(s).
	2. Labeling was submitted in MS Word format as described in the guidance, but without a corresponding PDF rendition - labeling should be submitted in PDF format. Draft labeling text may also be submitted in MS Word format, but all labeling submitted in word processing format should be accompanied in the submission by a ~~PDF~~ rendition.
	3. Data set(s) submitted in non archival format(s) – SAS transport V5 as per SAS TS-140 (XPORT) is the format specified by the guidance.
	4. Other - **Avoid duplicate electronic media**

RESUBMISSION NOT REQUIRED

Your electronic records may have been delayed for the following reasons, but No further action is necessary at this time. Please address these issues in future submissions.

✔	1. Electronic Submission submitted to wrong address – If electronic components are included, submit entire submission (paper and electronic components) only to the CDR (see address above).
	2. Duplicate copies of electronic media submitted - Submit only 1 set of electronic media, submitting a duplicate copy of electronic media may delay review and is unecessary.
	3. Electronic Table of Contents, e356h form and/or eCover Letter) not submitted - Including electronic PDF renditions of these paper documents, will help speed up the document room process.
✔	4. Other – **Do not send electronic media to any HFD Division. Insert electronic media only in archival copy**

For assistance or questions contact:

Office of Information Management – Ken Edmunds

Email (preferred) ESUB@CDER.FDA.GOV **Phone: 301-827-7706**

For Electronic Submission Guidance documents see:

http://www.fda.gov/cder/regulatory/ersr/default.htm

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** March 14, 2003
Re: Velcade (bortezomib) Meeting Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer your January 21, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELCADE™ (bortezomib) for Injection.

Please review and respond to the attached questions and information requests regarding this application.

If you have any questions regarding this transmission, please contact me at 301-594-5770.

Regards,

Sean Bradley, R.Ph.
/S/
Regulatory Project Manager

A) In section 2.4.2.6 'Safety Pharmacology Studies' on page 11, you assert that "Using an ex vivo perfused heart preparation, hearts from PS-341 treated mice showed no difference in heart rate and force of contraction compared with untreated controls indicating there was no direct effect of PS-341 on the heart (Tab Sum 2.6.3.4). (31; 32) " Unfortunately, you have only provided abstracts of these studies. Given that these studies are integral to your hypothesis that "PS-341 does not show direct effects on the heart or peripheral vascular systems", we request that you provide full study reports or provide a detailed explanation of why you are not capable of providing these documents.

B) In addition, please clarify (1) the time of actual sacrifice versus the "planned or protocol defined" time of sacrifice, (2) a tabular and case-by-case summary of the clinical signs and symptoms evident immediately preceding sacrifice, and (3) a proposed cause of death for all deaths (moribund or preterminal sacrifices) in the following studies (found in section 4.2.1.3):

- 6837-113: PS-341: Cardiovascular Effects after Intravenous Administration in Telemetered Cynomolgus Monkeys
- G465502A: Cardiotoxicity of PS-341 (NSC- D681239) in the Monkey
- KLAW-191: A study to determine the effects of PS-341 on cardiovascular function after intravenous administration to anesthetized cynomolgus monkeys.

C) The summary of safety pharmacology indicates a study in which "telemetered monkeys were administered PS-341 IV at 0.1 and 32 days later at 0.3 mg/ kg (1.2 and 3.6 mg/ m2)." We have been unable to identify a study within the safety pharmacology data which matches these study parameters. Therefore, we request that you provide a specific citation for this claim from within the submitted materials or, that you provide a full report for this study.

D) We note the following publication from the "open literature": Complementary whole genome technologies reveal the cellular response to proteosome inhibition by PS-341; PNAS, 99(3), 1461-1466. This material was not included in your submission to the Agency. We request that you provide an explanation as to why this information was not included in your submission, and whether any other data or study reports of a similar nature are known or available to you. You may wish to refer to the following publication, Petricoin, et. al., Nature Genetics, 32, 474 - 479 (01 Dec 2002), which states that, "If it is likely that such data would be viewed as a valuable component of the pharmacology database of the new drug or biologic, then they should be submitted [to the FDA]. [Moreover] it is most likely that genomic and proteomic data, if considered useful for explaining the mechanism of drug or biologic action, will also be helpful in enhancing our understanding of the effects reported in animal studies."

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0360
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	03/17 15:57
USAGE T	00'48
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** March 14, 2003
Re: Velcade (bortezomib) Meeting Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer your January 21, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VELCADE™ (bortezomib) for Injection.

Please review and respond to the attached questions and information requests regarding this application.

If you have any questions regarding this transmission, please contact me at 301-594-5770.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 23	**Date:** March 14, 2003
Re: Velcade (bortezomib) Meeting Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your questions for discussion for our upcoming Type-A meeting to regarding protocol M34101-039 for Velcade.

Attached are the FDA answer to your questions. You have the option of canceling our upcoming meeting if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, or reach agreement on, such changes at the meeting. Any modifications to the development plan, for which you would like FDA feedback, should be submitted as a new meeting request.

In addition we attached comments regarding protocol #———

If you have any questions regarding this transmission, please contact me at 301-594-5770.

Thank you,

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

Questions for Discussion: Velcade studies #[redacted] and #[redacted]

1. Does the Agency agree with our proposal for non-inferiority on TTP as the primary endpoint, with the option to claim superiority if achieved?

   No, superiority in TTP should remain the primary objective of study 039. To be acceptable as an endpoint for non-inferiority, the beneficial effect of the active control must have been established (see question #3). We may be able to accept similarity in survival, RR and TTP, if you can demonstrate superiority in the disease-specific clinical benefit endpoints of skeletal events and infections, but this would be a review issue.

2. Does the Agency agree with our proposal to use survival as the clinical benefit endpoint using the same methodology as for TTP?

   No. Superiority in survival would be an acceptable clinical benefit endpoint. In the absence of superiority in TTP or survival confirmation of clinical benefit would be a review issue.

3. Does the Agency agree with the selected margins for the non-inferiority analysis of TTP and survival?

   No. We are not convinced that the effect of dexamethasone on time to progression or survival has been adequately established in multiple myeloma, especially since the TTP endpoint in 039 has not been used in previous trials.

4. We have taken a 'conservative' approach regarding survival of patients who received dexamethasone and then are crossed-over to Velcade. Patients can receive dexamethasone for varying lengths of time including very short time frames before being switched to Velcade. We are not censoring them for the survival analysis after they are switched to Velcade. Does the Agency agree with this approach?

   We agree that the primary survival analysis should be on the ITT principle, and patients who cross over should not be censored.

The following are statistical comments from the Agency regarding non-inferiority design:

1. Both TTP and survival endpoint (time to event) should be analyzed based on hazard ratio.

2. The control effect in this case can not be assessed. The assumption that median TTP in "placebo arm"=0 is highly questionable.

3. The calculation of margin is questionable. In the fixed margin non-inferiority hypotheses, the margin should be calculated based on the control effect only. If the margin selection is also

dependent on the assumption of the SE of the treatment effect, the fixed margin hypotheses are not valid because the hypotheses involve a data dependent variable (SE).

4. If both TTP and survival will lead to efficacy claim, alpha adjustment is necessary.

5. We recommend using the method proposed in [1] for this non-inferiority design.

Comments regarding protocol #[redacted]

1. We agree to your proposed CR criteria, not requiring Bone Marrow biopsy or IFE. However, we would like for you to encourage use of these tests where available to fulfill the Blade criteria for CR, and make this a secondary endpoint.

2. Why do you require that "Dexamethasone will be held whenever the corresponding VELCADE dose is held" (section 3.3.7).

3. We suggest you attempt to provide some kind of follow-up for survival, and make this part of the safety analysis secondary endpoint. Presumably you could ask the physicians to agree to fill out a form listing the date and cause of death up to 5 years following study entry.

4. We are concerned that the design of the study 039 may not provide the most sensitive assay of the efficacy of Velcade. Ideally a 3-arm trial would have provided the most information.

   Since your proposed trial design already uses a lottery system to allocate Velcade, we suggest you consider modifying it into a randomized phase 2 design:

   - Patients who are not intolerant of dexamethasone would be randomized into an add-on trial of dexamethasone alone vs. dexamethasone plus Velcade.

   - Patients who progress or fail to respond after several cycles of dexamethasone would be eligible to cross over to receive Velcade.

   - Patients who are intolerant of dexamethasone would be treated with Velcade. These patients would not be randomized.

****
*** TX REPORT ***
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TRANSMISSION OK

TX/RX NO	0220
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	03/14 17:47
USAGE T	01'20
PGS. SENT	3
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

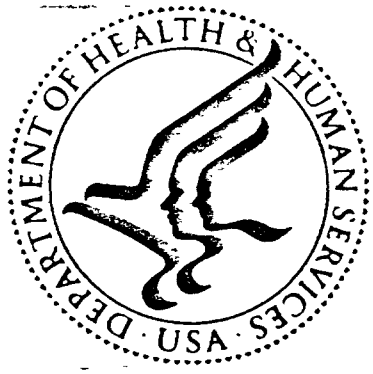
To: Tanya Lewis, MS	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 13	**Date:** March 14, 2003
Re: Velcade (bortezomib) Meeting Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your questions for discussion for our upcoming Type-A meeting to regarding protocol M34101-039 for Velcade.

Attached are the FDA answer to your questions. You have the option of canceling our upcoming meeting if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, or reach agreement on, such changes at the meeting. Any modifications to the

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 1	**Date:** February 28, 2003
Re: Velcade/Meeting Request	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

This fax serves as a notice that your request for a Type-A Guidance meeting to discuss your M34101-039 study protocol for Velcade has been granted. The meeting is scheduled for March 19, 2003 at 3:30, PM, EST. The meeting will take place in Conference Room C located on the 3rd floor of the Woodmont Office Complex-2, 1451 Rockville Pike in Rockville Maryland. FDA attendees will be:

Please note the following:

- Send questions and a list of firm attendees on diskette in MS WORD 97 or via e-mail
- There can be no presentations due to time constraints

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0110
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	02/28 16:03
USAGE T	00'36
PGS. SENT	1
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.
From: Sean Bradley, CSO

Fax: 617-551-3742
Fax: 310-827-4590

Phone: 617-551-8951
Phone: 301-594-5770

Pages, including cover sheet: 1
Date: February 28, 2003

Re: Velcade Meeting Request

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

This fax serves as a notice that your request for a Type-A Guidance meeting to discuss your M34101-039 study protocol for Velcade has been granted. The meeting is scheduled for March 19, 2003 at 3:30, PM, EST. The meeting will take place in Conference Room C located on the 3rd floor of the Woodmont Office Complex-2, 1451 Rockville Pike in Rockville Maryland. FDA attendees will be:

Please note the following:

- Send questions and a list of

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** February 26, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Melody,

Please refer to your February 21, 2003 meeting request to discuss CMC issues for your pending Velcade (bortezomib) for Injection NDA, #21-602.

Attached are our responses to your questions.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager

****
*** TX REPORT ***
****

TRANSMISSION OK

TX/RX NO	0287
CONNECTION TEL	916175513742
SUBADDRESS	
CONNECTION ID	MILLENNIUM INC.
ST. TIME	02/26 08:24
USAGE T	00'37
PGS. SENT	2
RESULT	OK

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Melody Brown	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-4977	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** February 26, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Melody,

Please refer to your February 21, 2003 meeting request to discuss CMC issues for your pending Velcade (bortezomib) for Injection NDA, #21-602.

Attached are our responses to your questions.

If you have any questions, ...

1. The changes in bottle washing described should be reported in appropriate detail as an amendment to the NDA in review; NOT in an annual report. Please note that the impact of any such change on the approvability of your drug product is a review issue.

2. Please provide an amendment by February 28, with a complete and up to date list of all manufacturing, packaging, testing and other manufacturing site changes. We further urge the applicant to minimize such changes as they can impact negatively on the timing of review and inspection activities during the review process.

3. Please provide your specific stability update format questions in writing.

Fax

DIVISION OF ONCOLOGY DRUG PRODUCTS
Center for Drug Evaluation and Research, HFD-150
Woodmont II Building
1451 Rockville Pike, Rockville, MD 20852

To: Tanya Lewis, M.S.	**From:** Sean Bradley, CSO
Fax: 617-551-3742	**Fax:** 310-827-4590
Phone: 617-551-8951	**Phone:** 301-594-5770
Pages, including cover sheet: 2	**Date:** February 21, 2003
Re: NDA 21-602 VELCADE	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

Please refer to your New Drug Application submitted to the Agency December 31, 2002 for your drug product Velcade (bortezomib) for Injection.

We are currently reviewing your application and have attached questions that need to be addressed in order to continue our review.

If you have any questions, please contact me at 301-594-5770 or BradleyS@CDER.FDA.GOV.

Sean Bradley, R.Ph.

/S/

Regulatory Project Manager