MILLENNIUM®

Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, Massachusetts 02139
617.679.7000
www.millennium.com

August 12, 2013

By Hand Delivery

Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

Millennium Pharmaceuticals, Inc. ("Millennium") submits this petition under Section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 CFR 10.30 and 21 CFR part 314, among other provisions of law. Millennium markets VELCADE® (bortezomib) for Injection, a first-in-class proteasome inhibitor approved to treat multiple myeloma and relapsed mantle cell lymphoma. The Food and Drug Administration ("FDA") recently accepted for filing a New Drug Application ("NDA") submitted by Fresenius Kabi USA ("Fresenius") for a bortezomib product that relies, at least in part, on FDA's findings of safety and effectiveness for VELCADE (bortezomib) for Injection.

Unlike VELCADE (bortezomib) for Injection, which contains bortezomib and mannitol, Fresenius proposes delivering bortezomib in an injectable formulation containing boric acid and glycine. As detailed below, the potential toxicity of boric acid has limited its use in injectable drug products. Given the differences between VELCADE (bortezomib) for Injection and Fresenius's proposed product, potential safety and efficacy differences must be carefully investigated. Indeed, as a matter of law and science, Fresenius was required to submit an NDA instead of an Abbreviated New Drug Application ("ANDA") to address the clinical implications of its proposed product.

However, based on a review of publicly available sources, such as clinicaltrials.gov, Trialtrove, and the EU Clinical Trials Register, Millennium has been unable to find any indication that Fresenius has conducted any human testing with its proposed bortezomib product; not even a comparative bioavailability study or a local injection site reaction study could be found. Millennium has extensive experience with the bortezomib molecule, including with different routes of administration and alternative formulations. With the benefit of that experience, Millennium believes there are reasonable and meaningful scientific questions raised by the Fresenius product that cannot be answered based solely on analytical testing, animal data, literature, and a general reference to VELCADE.

Millennium therefore submits this petition to ensure that Fresenius's proposed formulation of bortezomib is not approved for use *before* it has been sufficiently tested in human subjects and shown to be safe and effective. The risks are simply too great in this instance to allow Fresenius to rely on supposition and assumptions to meet its burden of proof, when well-established tests would definitively answer whether the proposed product is (or is not) safe and effective. Such tests include the same types of human studies that FDA indicated Millennium would need to conduct when it conferred with FDA about a new bortezomib formulation Millennium proposed to develop for the U.S. market, and some of the same studies Millennium conducted to assess the safety and efficacy of VELCADE for subcutaneous administration.

ACTION REQUESTED

Millennium respectfully requests that the Commissioner require:

(1) Fresenius's 505(b)(2) application (NDA No. 205004) for an injectable bortezomib formulation containing boric acid to be supported with:

(a) human bioequivalence data from multiple-dose testing in patients using intravenous administration and subcutaneous administration proving that Fresenius's proposed product is bioequivalent to VELCADE when administered intravenously and subcutaneously, or human clinical data proving that the amount of bortezomib delivered by Fresenius's proposed product is safe and effective, and

(b) preclinical data proving that the use of boric acid in the proposed product is safe for intravenous and subcutaneous injection in the intended patient populations; and

(c) additional human clinical data, as needed, to resolve any potential risks identified based on the data accumulated and observations made in the preclinical and human bioequivalence studies of the Fresenius product.

(2) Fresenius to reference in its 505(b)(2) application each source of information relied on to support its proposed product, including the safety of boric acid. If Fresenius does not own or otherwise have a right of reference to the data needed to demonstrate that its proposed use of boric acid is safe and additional listed drugs must be referenced, the Commissioner must require Fresenius to withdraw and resubmit its application with the additional references.

STATEMENT OF GROUNDS

I. Background

VELCADE (bortezomib) for Injection is approved to treat patients with multiple myeloma and certain patients with mantle cell lymphoma. Bortezomib is a first-in-class proteasome inhibitor, which inhibits the 26S proteasome. The 26S proteasome regulates protein degradation, and its inhibition can lead to cell death.

Multiple myeloma and mantle cell lymphoma are potentially fatal cancers of the blood for which there is no known cure. VELCADE was the first treatment in more than a decade to be approved for patients with multiple myeloma and has a demonstrated sustained survival benefit. In particular, VELCADE in combination with melphalan and prednisone has been shown to provide a statistically significant survival benefit versus melphalan and prednisone alone in patients with previously untreated multiple myeloma, as well as a statistically significant improvement in time to progression ("TTP").[1] Similarly, a pivotal study in relapsed multiple myeloma found that patients taking VELCADE had statistically significant improvement in TTP and overall survival versus dexamethasone.[2]

Although initially approved only for intravenous administration, VELCADE subsequently received approval for subcutaneous administration as well. The subcutaneous and intravenous routes of administration differ with respect to pharmacokinetics and adverse events.[3] Millennium's supplemental NDA for approval of subcutaneous administration of VELCADE was supported by a randomized non-inferiority study with 222 patients comparing the intravenous route versus the subcutaneous route in patients with relapsed multiple myeloma.[4] The parameters compared included overall response rate after 12 weeks and 24 weeks of treatment, progression-free survival, one-year overall survival, and safety and tolerability of the two routes of administration.

VELCADE is administered in multiple, lengthy treatment cycles, and patients generally are exposed to the product for extended periods of time. In patients with previously untreated multiple myeloma, for example, VELCADE is administered for nine six-week treatment cycles (*i.e.*, 54 weeks). For patients with relapsed multiple myeloma and mantle cell lymphoma, VELCADE is administered in up to eight three-week cycles with dosing twice weekly for two weeks, followed by a ten-day rest period. For extended therapy of more than eight cycles,

---

[1] VELCADE Package Insert (Oct. 26, 2012) at 21-23 (Clinical Studies).

[2] *Id.* at 24-27 (Clinical Studies).

[3] *Id.* at 11-12 (Adverse Reactions) and 19 (Clinical Pharmacology).

[4] Supplemental New Drug Application 021602-0S27 (March 23, 2011).

VELCADE may be administered using the same schedule or with dosing once weekly for four weeks followed by a 13-day rest period.

Among other properties, the bortezomib molecule has relatively low solubility in water.[5] Developing a viable and stable formulation of the drug was difficult. The VELCADE formulation, which is sufficiently stable for commercialization and is easily reconstituted, is based on mannitol. The mannitol component forms an ester with bortezomib in the lyophilized product and, upon reconstitution, the mannitol ester and bortezomib exist in a state of equilibrium.[6] Mannitol, a sugar alcohol, is a commonly used bulking agent in lyophilized formulations and consequently has a proven safety record through most routes of administration, including intravenous and subcutaneous injection.

Fresenius recently submitted a 505(b)(2) application for a proposed bortezomib formulation that, according to Fresenius, does not contain mannitol.[7] Rather, Fresenius's proposed product includes other ingredients, such as boric acid and glycine. In particular, Fresenius has stated that its formulation contains boric acid in excess of 15:1 relative to bortezomib, and a related patent application indicates that the boric acid may form an anhydride structure with bortezomib.[8]

Boric acid is considered to be moderately acutely toxic due to acute effects, including dermal toxicity and skin irritation.[9] FDA's inactive ingredient database does not list boric acid for subcutaneous administration; however, the database does list boric acid for use in an intravenous injection at a maximum potency of 0.319%.[10] As reflected in the inactive ingredient database, there does not appear to be any previous FDA experience with boric acid for subcutaneous administration. Additionally, as detailed below, Millennium is aware of only a few intravenous products that include boric acid, and all of those products contain the active ingredient sodium thiosulfate.[11] Furthermore, those products were approved for an imminently life threatening condition (acute cyanide poisoning) based on case reports and anecdotal

---

[5] *See* VELCADE Package Insert (Oct. 26, 2012) at 18 (Description).

[6] *Id.*

[7] Letter from L. Sung, Baker & Hostetler LLP, regarding NDA No. 205004 (Feb. 5, 2013) ("Notice Letter") at 19. (Relevant pages at Tab 1).

[8] *See* World Intellectual Property Association, International Application No. WO 2012/047845 A1 at 9 (Published April 12, 2012) ("WO 2012/047845 A1"). (Tab 2).

[9] EPA RED FACTS: Boric Acid, EPA-738-F-93-006 (Sept. 1993). (Tab 3).

[10] *Inactive Ingredient Search for Approved Drug Products, available at http://www.accessdata.fda.gov/scripts/cder/iig/ (search term = "boric acid")* ("The 'maximum potency' field specifies the maximum amount of inactive ingredient for each route/dosage form containing that ingredient.").

[11] Other approved injectable products that use boron-based inactive ingredients, as noted *infra*, similarly are limited to single or short courses of therapy.

evidence, and not on the basis of any clinical safety and effectiveness studies, let alone a well-controlled study.

II. Legal Framework

Under the FDCA, every new drug product must be demonstrated to be safe and effective. To meet that burden, a generic applicant who submits an ANDA need only show that its product is the same as a previously approved reference product.[12] By demonstrating sameness, FDA's finding of safety and effectiveness for the reference product is presumed to apply to the generic product. However, the burden of proof is much greater for an applicant, such as Fresenius, who submits an NDA. Under an NDA, the applicant must demonstrate that its product is safe and effective with clinical data. The applicant may generate its own clinical data, or in the case of a 505(b)(2) application, the applicant may, where appropriate, rely in part on data that it otherwise would not have a right to reference.

FDA has stated that a 505(b)(2) applicant may rely on published literature or FDA's finding of safety and effectiveness for a previously approved product.[13] To the extent there are differences between the proposed and reference products, the 505(b)(2) applicant must bridge the differences to provide an adequate scientific basis to rely on the reference product's clinical data. At a minimum, bridging studies typically include an assessment of comparative bioavailability or a showing of bioequivalence, which means the products have a similar rate and extent of drug absorption. However, even bioequivalent products may have different profiles, such as different safety risks, due to formulation differences. Thus, a 505(b)(2) applicant must provide its own studies to support any changes from the reference product. As FDA explained:

> The 505(b)(2) application must include data and information (including bioavailability and/or comparative bioavailability studies) sufficient to establish that it is appropriate for the applicant to rely on the Agency's finding of safety and effectiveness for the listed drug. To the extent that the listed drug and the drug proposed in the 505(b)(2) application differ, the 505(b)(2) application must include sufficient data, including clinical or nonclinical data, as appropriate (21 CFR 314.54(a)), to

[12] FDCA 505(j)(2)(A) (requiring a generic product to have the same active ingredient, route of administration, dosage form, strength, and, with minor exceptions, labeling as the reference product).

[13] Guidance for Industry: Applications Covered by Section 505(b)(2) (Draft Oct. 1999) ("FDA Draft 505(b)(2) Guidance").

> demonstrate that the proposed drug meets the statutory approval standard for safety and effectiveness.[14]

Accordingly, Fresenius's 505(b)(2) application must include data proving, for each proposed route of administration, that: (1) its product, particularly the use of boric acid, is safe for the intended patient populations, and (2) its product is bioequivalent to VELCADE (bortezomib) for Injection based on *in vivo* human testing or, absent a showing of bioequivalence, is safe and effective based on human clinical studies.[15, 16]

III. Fresenius's Proposed Product Containing Boric Acid is Presumptively *Unsafe*

A. FDA Regulations Recognize the Sensitivity and Safety Risks of Parenteral Formulations

Bortezomib, a dipeptide boronic acid, is a difficult molecule to hold within a stable, pharmaceutically acceptable formulation. Central to the VELCADE (bortezomib) for Injection formulation is mannitol, a sugar alcohol that forms a mannitol boronic ester when formulated with bortezomib in the solid, lyophilized state. Among other things, the mannitol boronic acid ester inhibits the formation of the anhydride form of bortezomib, trimeric boroxine, and increases solubility. When reconstituted for administration to the patient, the mannitol ester exists in equilibrium with monomeric boronic acid.[17]

Fresenius has chosen to modify the VELCADE formulation by substituting boric acid and glycine in place of mannitol.[18] In particular, Fresenius has stated that its product contains

---

[14] FDA Petition Response, Docket Nos. 2004P-0231, 2003P-0176, 2004P-0171, 2004N-0355 (May 30, 2006); *see also* 21 CFR 314.54(a) (a 505(b)(2) application "need contain only that information needed to support the modification(s) of the listed drug").

[15] As a 505(b)(2) applicant, Fresenius also is subject to other limitations. For example, FDA regulations provide that a 505(b)(2) application may not be submitted for a product that is not bioequivalent to the reference listed drug because either the rate or extent of absorption of the active ingredient is less than that of the reference drug. 21 CFR 314.54(b). In that case, the product would require a full 505(b)(1) application.

[16] Additionally, FDA must ensure that the data submitted in support of Fresenius's application is accurate and reliable. Recently, FDA issued a Warning Letter to a Fresenius Kabi facility in Kalyani, India that manufactures oncolytic active pharmaceutical ingredients ("APIs"). Warning Letter to M. Henriksson at Fresenius Kabi AG, WL: 320-13-20 (July 1, 2013). As detailed in the Warning Letter, the facility engaged in practices that raise "serious concerns regarding the integrity and reliability of the data generated at [Fresenius's] Kalyani plant." Warning Letter at 1. For example, the facility combined batches of APIs that failed to meet impurity test specifications with other API batches that passed specifications, in order to meet the final impurity test specifications. To the extent that Fresenius's application is supported with data from its Kalyani facility, FDA should require Fresenius to resubmit that data from sources that are not associated with data integrity and manipulation issues.

[17] VELCADE Package Insert at 18 (Description). The reconstituted mannitol ester-boronic acid solution is stable for up to eight hours at room temperature. *Id.* at 5-6 (Dosage and Administration).

[18] Notice Letter at 19.

boric acid in excess of 15:1 relative to bortezomib. A patent application prepared by Fresenius indicates that the boric acid may form an anhydride structure with bortezomib.[19]

As explained below, the inactive ingredients in a parenteral formulation can have significant safety consequences. Here the issue is two-fold: First, the safety of the boric acid-bortezomib compound formed within the Fresenius product has never previously been qualified or evaluated by FDA; second, the safety of boric acid itself has not been established in the injectable routes of administration at the levels proposed by Fresenius.

For good reason, FDA applies a rigorous scientific and legal standard to the substitution of inactive ingredients in parenteral formulations. According to the agency, it will "presume any inactive ingredient in an applicant's proposed drug product different from that in the reference listed drug to be unsafe ...."[20] This is based on the long-held view that each parenteral drug formulation has its own internal dynamic, such that a change to any one ingredient, or even to the concentration of an ingredient, can yield a new dynamic with unique properties and, in particular, unique safety issues. The agency explained this in detail in the course of issuing a rule that carefully restricts changes to parenteral drug products for purposes of staying within the framework for generic drugs:

> The agency intends to place more stringent limitations on the variations permitted in the inactive ingredients in the formulation of parenteral ... drug products than on other dosage forms. This is because each parenteral ... drug product represents an individual pharmaceutical system with its own characteristics and requirements. In the formulation of parenteral drug products, certain added substances are used to maintain solubility, stability, sterility, and to increase patient comfort (i.e., by adjusting toxicity and reducing tissue irritation). Added substances selected for parenteral drug products must be known to be of the highest quality, must be known to not interfere with the therapeutic effectiveness of the product and must be known to be nontoxic in the quantities used.[21]

The Fresenius boric acid product goes well beyond what FDA would permit for a generic drug.[22] Boric acid is a moderately acutely toxic substance. It is not a preservative, a buffer, or an

---

[19] WO 2012/047845 A1 at 9.

[20] 54 FR 28872, 28884 (July 10, 1989); *see also* 21 CFR 314.127(a)(8)(ii)(B).

[21] 54 FR at 28883-84; *see also* 21 CFR 201.100 (requiring certain added substances and their concentrations be listed on the label of parenteral drug products).

[22] *See* 21 CFR 314.127(a)(8)(ii)(B).

antioxidant. And, the information required to affirmatively demonstrate that the product is safe and effective cannot be submitted or reviewed within the confines for the ANDA statute. Thus, Fresenius had no choice but to seek approval under an NDA.

As an NDA applicant, the burden is on Fresenius to demonstrate that its product is safe in each proposed route of administration. As noted above, the boric acid in the Fresenius product is *presumptively unsafe.* As a matter of law and science, this presumption can be overcome only by a persuasive demonstration that the proposed use of boric acid "does not affect the safety ... of the drug product."[23] For the reasons described below, Millennium believes this unqualified standard of safety can be met in this case only with data from preclinical and human testing conducted by Fresenius.

B. Boric Acid is Not a Typical Injectable Ingredient, and The Paucity of Data and Prior Experience with Boric Acid for Injection Do Not Support Fresenius's Proposed Formulation

Fresenius cannot rely on experience with boric acid as an inactive ingredient in other approved drug products to meet its burden to establish the safety of its proposed product. FDA lists previous approvals of inactive ingredients in its inactive ingredient database. To be relevant, a previous approval would have to be in the same route of administration and at the same or higher potency level as proposed by Fresenius. As FDA has explained:

> For new drug development purposes, once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and *may require* a less extensive review the next time it is included in a new drug product.[24]

According to FDA's inactive ingredient database, there have been no previous approvals of boric acid for subcutaneous use at any potency level.[25] Thus, previous experience does not support the conclusion that boric acid would be safe for subcutaneous use.

---

[23] *Id.*

[24] Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions at question 3, *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm (emphasis added); *see also* 57 FR 17950, 17969-70 (April 28, 1992) ("the inquiry is not whether each [ingredient] is commonly used or known; instead, the inquiry is whether the [ingredients] in the proposed drug product are safe under the conditions prescribed, recommended, or suggested in the labeling.").

[25] *See* Inactive Ingredient Search for Approved Drug Products, *available at* http://www.accessdata.fda.gov/scripts/cder/iig/ (search term = "boric acid").

Boric acid has a history as an eye wash (*e.g.*, against chemical exposure), as a household chemical (*e.g.*, in insect poison), and as an inactive ingredient when used on the skin and in/around the eyes. Thus, the inactive ingredient database includes listings for boric acid for ophthalmic and topical administration. These listings, however, have little relevance to Fresenius's proposed product. The only listing of an injectable route of administration for boric acid is for intravenous injection at a maximum potency of 0.319%.[26] While it is unclear what the maximum potency represents (*i.e.*, weight/weight or weight/volume) and how it correlates to Fresenius's proposed product, one thing is clear: boric acid typically is not used for parenteral dosing to patients. In fact, to the best of Millennium's knowledge, the only approved injectable products containing boric acid are sodium thiosulfate products for intravenous injection for the treatment of cyanide poisoning.[27]

In particular, sodium thiosulfate is indicated for sequential use with sodium nitrite to treat acute cyanide poisoning that is judged to be imminently life-threatening. According to its package insert, the currently marketed Hope Pharmaceuticals products contain 2.8 mg boric acid per mL. The dose is 50 mL, which would make the total amount of boric acid administered per dose of sodium thiosulfate 140 mg. Typically, only one dose is needed, although an additional one-half dose may be administered if needed.

Although the currently marketed sodium thiosulfate products may contain more boric acid than Fresenius's proposed product (based on a single injection of Fresenius's proposed formulation containing a 15:1 ratio of boric acid to bortezomib), the products must be compared in light of their risk-benefit profiles. Sodium thiosulfate is approved to treat acute cyanide poisoning that is imminently life-threatening (cyanide poisoning can cause death within minutes to hours of exposure). Sodium thiosulfate products are rarely used and, even when needed, they generally require only a single dose. Under those conditions, the known or potential toxicity of boric acid in an injectable format may be considered acceptable. In contrast, bortezomib is administered for an extended period of time (*e.g.*, nine six-week cycles for the treatment of previously untreated multiple myeloma) and patients would be exposed to a greater overall amount of boric acid with Fresenius's product than with sodium thiosulfate. Additionally, multiple myeloma and mantle cell lymphoma patients often have other co-morbidities, such as renal impairment, which may make them more sensitive to boric acid toxicity.

---

[26] *Id.* ("The 'maximum potency' field specifies the maximum amount of inactive ingredient for each route/dosage form containing that ingredient.").

[27] FDA has approved three NDAs for sodium thiosulfate products; however, two of these NDAs merely cover different packaging arrangements of the same product. *See* NDA 20166 (sodium thiosulfate injection, 250 mg/mL) (U.S. Army) (discontinued); NDA 201444 Nithiodote (sodium nitrite injection USP and sodium thiosulfate injection USP for intravenous infusion) (Hope Pharmaceuticals); NDA 203923 (sodium thiosulfate intravenous solution 12.5 gm/50 mL (250 mg/mL)) (Hope Pharmaceuticals). Hope Pharmaceuticals' NDA 201444 provides for the copackaging of vials of sodium nitrite and sodium thiosulfate, while Hope Pharmaceuticals' NDA 203923 provides for the marketing of the sodium thiosulfate vials without sodium nitrite.

The boric acid associated with the sodium thiosulfate products also has a limited safety database because the products apparently were approved without clinical safety trials. As stated in the package insert for NDA 20144, "There have been no human studies to prospectively and systematically evaluate the safety of sodium thiosulfate or sodium nitrite in humans. Available human safety information is based largely on anecdotal case reports and case series of limited scope."[28] Thus, to Millennium's knowledge, the lone set of injectable drug products containing boric acid was approved only for intravenous injection, not for subcutaneous injection, and apparently without human studies evaluating safety. Fresenius's proposed product is significantly different from the sodium thiosulfate products, with respect to active ingredient, route of administration, and indication. To base the safety of Fresenius's proposed use of boric acid on the sodium thiosulfate products, which were approved for an imminently life-threatening condition based on case reports, would subject patients to unnecessary and unknown risks. The inactive ingredient database reference in this instance cannot be extrapolated to a product administered intravenously or subcutaneously for multi-cycle oncology therapy.[29]

In addition to boric acid, FDA's inactive ingredient database lists other boron-containing ingredients, such as sodium borate. However, these other ingredients also are of little relevance for qualifying boric acid for the uses envisioned by Fresenius. There are a number of listings of sodium borate but, as with nearly all of the boric acid listings, they are for ophthalmic, auricular, and topical use. The database lists a tetrafluoroborate ingredient and methyl boronic acid for intravenous administration with a maximum potency of 0.1% and 0.2%, respectively. These ingredients appear to be associated with kits used to prepare technetium TC 99 Sestamibi injections for myocardial imaging, such as Cardiolite and Cardiotec. The package insert for Cardiotec, which is no longer marketed, indicates that the product contained only 2 mg of methyl boronic acid. Similarly, the package inserts for Cardiolite and related generic products indicate that the products contain only 1 mg of the tetrafluoroborate ingredient. Thus, the amount of boron in those products is much lower than in Fresenius's proposed product, and, unlike VELCADE, they are considered single use products.[30]

Ultimately, there is no reason to introduce new safety risks associated with Fresenius's proposed product because the intended patient populations already have treatment options that have been demonstrated to be safe and effective based on well-controlled human studies. To accept a greater safety risk, or even a less well-characterized risk profile for a bortezomib

---

[28] Nithiodote Package Insert (Jan. 14, 2011) at Section 14 (Clinical Studies).

[29] *Cf.* Letter from J. Woodcock to G. May (EKR Therapeutics, Inc.) regarding Docket No. FDA-2008-P-0621 at 9 (May 29, 2009) (extrapolating the inactive ingredient database to "commonly used and well understood" inactive ingredients in concentrations well below the levels identified in the database).

[30] Millennium also is aware of three vaccine products for intramuscular injection that contain very small amounts of sodium borate. Vaqta, Gardasil, and Comvax all contain 35 *mcg* of sodium borate. Additionally, Anascorp, a scorpion antivenom, contains trace amounts (< 1 mg/vial) of borates as an impurity.

product, Fresenius would need to show greater efficacy relative to that of VELCADE. Although the risks from boric acid may be acceptable in certain situations, such as the treatment of acute cyanide poisoning (an imminently life-threatening condition), FDA should not approve Fresenius's proposed product unless and until the product is shown in human studies to be as safe as VELCADE. There is no justification to expose patients to additional safety risks when there are no corresponding additional benefits associated with Fresenius's proposed product.

C. Fresenius's Proposed Product Seemingly Would Expose Patients to Levels of Boron that Exceed the Permitted Daily Exposure

The U.S. Environmental Protection Agency ("EPA") considers boric acid to be moderately acutely toxic due to acute effects, including dermal toxicity and skin irritation.[31] The effect of new ingredients in Fresenius's proposed product when administered by injection to the intended patient populations in this instance is unknown. To investigate the potential safety issues, Millennium analyzed the permitted daily exposure ("PDE") limit for boric acid in boron equivalents (the boron element is associated with toxicity). Generally, PDE is the maximum acceptable intake per day of residual solvent in pharmaceutical product, and it is commonly used to evaluate toxicity. The PDE calculation is described in a guidance document developed by the International Conference on Harmonisation ("ICH") and adopted by FDA.[32] Based on the calculations described below, patients who would be administered Fresenius's proposed product containing boric acid would be exposed to about twice the PDE limit for boron.

---

[31] EPA RED FACTS: Boric Acid, EPA-738-F-93-006 (Sept. 1993).

[32] ICH Q3C, Impurities: Residual Solvents, ("ICH Guidance") (Dec. 1997). According to the ICH Guidance, "PDE is derived from the NOEL [no-observed-effect level], or the LOEL [lowest-observed effect level] in the most relevant animal study as follows: PDE = NOEL x Weight Adjustment / F1 x F2 x F3 x F4 x F5." As described in that guidance, the modifying factors include F1 = A factor to account for extrapolation between species; F2 = A factor of 10 to account for variability between individuals; F3 = A variable factor to account for toxicity studies of short-term exposure; F4 = A factor that may be applied in cases of severe toxicity, *e.g.*, non-genotoxic carcinogenicity, neurotoxicity or teratogenicity; and F5 = A variable factor that may be applied if the no-effect level was not established.

Millennium calculated the PDE for boron using EPA's no observed adverse effect level (NOAEL) of 8.8 mg/kg. According to EPA, the oral NOAEL of 8.8 mg/kg/day boron equivalents came from two-year and 38-week dog studies.[33] Using the NOAEL value of 8.8 mg/kg, the PDE calculation for boron is:

$$PDE = \frac{8.8\ mg/kg * 50\ kg}{(2)(10)(5)(1)(1)} = \mathbf{4.4\ mg\ boron/day}$$

where:

F1 = 2 (dog to human)
F2 = 10 (individual variability)
F3 = 5 (study duration)
F4 = 1 (severe toxicity)
F5 = 1 (NOEL established).

To approximate the amount of boron that would be administered to a patient per dose of Fresenius's proposed product, Millennium focused on the size of the target populations because bortezomib is dosed based on body surface area ("BSA"). According to the National Cancer Institute, patients with multiple myeloma or mantle cell lymphoma are predominantly male and tend to be in their late sixties at the time of diagnosis.[34] While estimates of BSA vary, data from the U.S. Centers for Disease Control and Prevention ("CDC") report that a 60-69 year-old American male in the 50th percentile for height and weight has a height of 69.0 inches and a weight of 194.1 pounds, which equates to a BSA of 2.07 m^2.[35] Additionally, a 60-69 year-old American male in the 85th percentile for height and weight has a height of 71.9 inches and a weight of 238.1 pounds, which equates to a BSA of 2.34 m^2.

Bortezomib is dosed at 1.3 mg/m^2. Accordingly, male patients in the 50th percentile would receive 2.69 mg of bortezomib, while male patients in the 85th percentile would receive 3.04 mg of bortezomib. Fresenius has indicated that its proposed formulation contains boric acid in excess of 15:1 relative to bortezomib. (Millennium presumes that the ratio is in mass units.) Accordingly, 50th percentile male patients would receive at least 40.35 mg of boric acid, and 85th

---

[33] *See* U.S. EPA Integrated Risk Information System, Boron and Compounds; CASRN 7440-42-8 (Aug. 5, 2004) at 10 *available at* http://www.epa.gov/iris/subst/0410.htm. (Tab 4).

[34] National Cancer Institute, Surveillance Epidemiology and End Results Stat Fact Sheets: Myeloma ("From 2006-2010, the median age at diagnosis for myeloma was 69 years of age.") (Tab 5); National Cancer Institute, Surveillance Epidemiology and End Results Stat Fact Sheets: B-cell Non-Hodgkin Lymphoma ("From 2006-2010, the median age at diagnosis for B-cell non-Hodgkin lymphoma was 67 years of age.") (Tab 6).

[35] McDowell *et al.*, National Center for Health Statistics, Centers for Disease Control and Prevention, "Anthropometric Reference Data for Children and Adults: United States, 2003-2006," National Health Statistics Reports No. 10, at 10, 16 (Oct. 22, 2008) (Tab 7). BSA was calculated by using the following standard nomogram: BSA (m 2) = $\sqrt{}$[(height (in.) * weight (lbs.))/3131]. *See* Mosteller, "Simplified Calculation of Body-Surface Area," *New Eng. J. Med.* 317(17):1098 (Oct. 22, 1987) (Tab 8).

percentile male patients would receive at least 45.60 mg of boric acid. Converting the boric acid to boron equivalents, the 50th and 85th percentile male patients would receive 7.06 mg and 7.98 mg of boron, respectively.[36]

In addition to the boron from the boric acid, patients would also receive boron from other sources, such as the bortezomib molecule itself. Male patients in the 50th percentile would receive about 0.08 mg boron per dose of bortezomib, while male patients in the 85th percentile would receive about 0.09 mg boron per dose of bortezomib.[37] Additionally, boron is in food, and patients would be exposed to boron from their diet. In the United States, the average daily boron from diet is approximately 1 mg boron per day.[38] Adding the boron from the bortezomib and diet to the boron from Fresenius's proposed product, the total approximate boron exposure for male patients in the 50th percentile would be 8.14 mg boron. The total approximate boron exposure for patients in the 85th percentile would be 9.07 mg boron.

Based on these calculations, patients receiving a single dose of Fresenius's proposed product would be exposed to about a two-fold higher amount of boron than the calculated PDE for boron.[39] Furthermore, bortezomib is administered to patients in multiple, lengthy treatment cycles. For example, the recommended duration of bortezomib use in patients with newly diagnosed multiple myeloma is nine six-week treatment cycles (54-week treatment plan). Consequently, patients would be repeatedly exposed to this excessive level of boric acid throughout their treatment. The persistent exposure to boron in excess of the PDE level, without data to support such exposure through intravenous and subcutaneous administration, would create a significant and unnecessary safety risk.

In sum, Fresenius must overcome – *with evidence* – the presumption that its proposed product is unsafe. Boric acid has known toxic effects, and Fresenius's product will repeatedly expose patients to levels of boric acid exceeding the PDE level. Fresenius must provide a complete nonclinical data package to qualify the level of boric acid in its proposed product,

---

[36] The conversion was accomplished by multiplying the amount of boric acid by the ratio of the molecular weight of boron to boric acid (10.8/61.84 = 0.175).

[37] The amount of boron from bortezomib was calculated by multiplying the bortezomib dose by the ratio of molecular weight of boron to bortezomib (10.8 /384.2 = 0.028).

[38] Dinca *et al.*, "Boron in Human Nutrition and its Regulations Use," *Journal of Nutritional Therapeutics* 2:22-29 (2013). (Tab 9).

[39] Millennium used the PDE method because it is described in a guidance document adopted by FDA; however, Millennium is aware that the PDE calculation is not the only method to assess tolerability limits. For example, the European Food Safety Authority has established a tolerable upper level for boron intake of 10 mg boron/adult person/day. Dinca, *supra,* note 36, at 24, 26. Additionally, the World Health Organization (WHO) and the Japanese National Institute for Health Sciences have established tolerable daily intakes for boron of 0.17 mg boron/kg/day and 0.13 mg boron/kg/day, respectively. WHO, "Boron in drinking-water," WHO/HSE/WSH/09.012 at 14 (2009) (Tab 10); Hasegawa *et al.*, "Safety assessment of boron by application of new uncertainty factors and their subdivision," *Regul. Toxicol. Pharmacol.* 65 (1):108-14 (Feb. 2013) (Tab 11).

including toxicology studies in one or more relevant animal species.[40] Finally, as discussed in detail below, Fresenius must provide data from human testing.[41]

IV. Fresenius Must Sufficiently Test its Product in Human Subjects

Fresenius's proposed product raises important scientific and regulatory issues that cannot be answered without human bioequivalence data showing that the product provides an equivalent amount of bortezomib to patients as VELCADE. VELCADE is approved to treat potentially fatal cancers, and Fresenius's proposed formulation would raise significant efficacy issues if it delivers a sub-therapeutic dose of bortezomib. Fresenius's proposed formulation also would raise significant safety concerns if it delivers more bortezomib than VELCADE because there are associated dose-limiting toxicities (*e.g.*, grade 3 diarrhea). Accordingly, Fresenius must conduct *in vivo* human testing to establish that its proposed product is bioequivalent to VELCADE under all of the approved conditions of use. Depending on the information developed during bioequivalence testing and the required preclinical testing of the formulation, Fresenius also may need to conduct an original clinical study of its formulation to ensure that it is safe and effective for the intended patient populations.

A. Fresenius Must Conduct *In Vivo* Human Bioequivalence Testing

Generally, bioequivalence means the same rate and extent of drug absorption and is established through *in vivo* human studies that measure drug concentration in the blood.[42] In particular, bioequivalence is demonstrated when the area under the plasma concentration time curve ("AUC") and maximum drug concentration ("C_{max}") for the proposed product are equivalent to the reference product.

Fresenius must show that its product is safe and effective. Instead of proving safety and effectiveness through independent clinical tests, Fresenius may be seeking to rely solely on FDA's finding of safety and effectiveness for VELCADE. Establishing that Fresenius's proposed product provides an equivalent release of bortezomib compared to VELCADE is an

---

[40] *See* Guidance for Industry: Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients at 1, 4-8 (May 2005) ("FDA's Excipient Guidance") (recommending studies to support approval of "new excipients," *i.e.*, those that "are not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration").

[41] Moreover, Fresenius must also demonstrate that its proposed product has sufficient stability for commercialization, as Millennium has done for VELCADE. The stability of Fresenius's reconstituted product should be approximately the same as VELCADE; otherwise, it could cause confusion among healthcare providers. For example, even if Fresenius's product is labeled for use within four hours after reconstitution, healthcare providers may use Fresenius's product up to eight hours after reconstitution because they would be familiar with VELCADE's stability profile.

[42] 21 CFR 320.1(e) and 320.24(b).

essential condition for reliance on VELCADE. Indeed, FDA's draft guidance regarding 505(b)(2) applications specifically states that such applications should include a bioequivalence study comparing the proposed product to the reference product.[43] Bioequivalence provides a scientific bridge between the proposed and reference products. If Fresenius cannot show bioequivalence, then Fresenius would have to support its proposed product with independent safety and efficacy clinical studies showing that the level of bortezomib released by the product is safe and effective.

Additionally, the human *in vivo* bioequivalence testing will provide important information regarding the safety of Fresenius's proposed use of boric acid. The presumption that VELCADE's clinical data would support the approval of Fresenius's proposed product is justified only if Fresenius's proposed product has the same inactive ingredients in the same concentration as VELCADE (except for differences in preservative, buffer, or antioxidant). As described above, Fresenius's proposed product falls well outside this presumption. In short, Fresenius must conduct studies showing that the product differences (*e.g.*, boric acid) are safe.

B. Bioequivalence Must be Shown in Both Routes of Administration and With Multiple-Doses

In vivo human bioequivalence testing is needed to ensure that Fresenius's proposed product performs the same as VELCADE under bortezomib's complex conditions of use. In particular, VELCADE is approved for two different routes of administration: intravenous injection and subcutaneous injection. The effect of Fresenius's proposed formulation must be understood with respect to both of the approved routes of administration.

The different routes of administration involve different physiological factors and display different pharmacokinetics. In contrast to intravenous delivery, subcutaneous delivery involves injecting the drug into the interstitial tissue beneath the surface of the skin. The drug must then pass through the extracellular matrix and be absorbed into the circulatory system through capillaries or the lymphatic system. Absorption can be affected by many different factors, including the drug product's formulation. The time needed to absorb a subcutaneous drug would affect its bioavailability. A drug delivered subcutaneously can become trapped in the extracellular matrix, which also would affect bioavailability. Accordingly, a drug product could perform differently depending on its formulation and method of administration.

Indeed, VELCADE exhibits different pharmacokinetics for each route of administration. Both routes of administration for VELCADE have been demonstrated to be safe and effective and provide comparable systemic exposure. However, the subcutaneous route provides a lower maximum drug concentration (*i.e.*, C_{max}) than the intravenous route. And, the time to maximum

[43] FDA Draft 505(b)(2) Guidance at 8.

drug concentration (*i.e.*, T_{max}) for the subcutaneous route is longer than for the intravenous route, which reflects the subcutaneous absorption process. According to one publication: "as would be expected, C_{max} was lower and T_{max} longer with subcutaneous than with intravenous administration, bortezomib systemic exposure was equivalent between groups."[44]

Fresenius's proposed product has the potential to affect bioavailability, and the effects could differ depending on whether it is administered subcutaneously or intravenously. Establishing that Fresenius's proposed product is bioequivalent to VELCADE in one route of administration would not automatically ensure that it is bioequivalent in the other route of administration. Thus, Fresenius must test its product in both routes of administration to ensure that the product is bioequivalent to VELCADE.

Additionally, bortezomib exhibits time-dependent kinetics, and Fresenius's proposed product must be tested in an *in vivo* human study to ensure bioequivalence during the complex dosing cycles. To treat newly diagnosed multiple myeloma, VELCADE is administered in combination with oral melphalan and oral prednisone for nine six-week treatment cycles. In cycles one to four, VELCADE is administered twice weekly, while it is administered once weekly in cycles five to nine. To treat relapsed multiple myeloma and mantle cell lymphoma, VELCADE is administered in up to eight three-week cycles with dosing twice weekly for two weeks, followed by a ten-day rest period. For extended therapy of more than eight cycles, VELCADE may be administered using the same schedule or with dosing once weekly for four weeks, followed by a 13-day rest period. Patients received an average of 22 doses of VELCADE in the Phase 3 randomized prospective study comparing the treatment of relapsed refractory multiple myeloma patients with VELCADE to treatment with dexamethasone.

The intricate dosing cycles affect pharmacokinetics because bortezomib accumulates in the body during the cycles. In other words, the multiple-dose pharmacokinetics of bortezomib are nonlinear. As FDA explained:

> In conclusion, bortezomib accumulates upon twice weekly administration; the mean AUC of bortezomib was 3.7- to 4.2-fold higher on Day 11 than on Day 1 during Cycle 1 ($p \leq 0.05$). Bortezomib exhibits time-dependent kinetics; the mean AUC of bortezomib was 2- to 3-fold higher on Day 1/Cycle 3 than on Day 1/Cycle 1 ($p \leq 0.05$). The maximum proteasome inhibition was comparable between the 1.0 mg/m^2 and 1.3 mg/m^2 doses across days and cycles, ranging from 70-84%. The incidence of adverse

[44] Moreau *et al.*, "Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomized, phase 3, non-inferiority study," *Lancet Oncol.* 12:431-40 at 438 (2011). (Tab 12).

events was 2- to 5-fold higher following the 1.3 mg/m^2 dose than the 1.0 mg/m^2 dose.[45]

Consistent with FDA's conclusion, a publication describing a study of bortezomib states that "a noteworthy finding of this study is that the pharmacokinetics of bortezomib displayed time-dependent changes, characterized by an approximately fourfold decrease in systemic plasma clearance and resultant increases in systemic plasma exposure and terminal half-life following repeat dose administration in relation to the first dose of the first treatment cycle."[46] To ensure that Fresenius's proposed product is equivalent to VELCADE during the cyclic dosing regimen, Fresenius must conduct a multiple-dose trial that measures pharmacokinetic parameters at various time points in the treatment cycle.

Furthermore, Fresenius must conduct its testing in patients and not healthy subjects because bortezomib is a toxic chemotherapeutic compound. Indeed, FDA has recommended multiple-dose bioequivalence studies in patients for other chemotherapeutic agents. For example, altretamine is a cytotoxic antineoplastic compound indicated for the treatment of certain types of ovarian cancer. Altretamine is administered in 28-day cycles, and FDA recommended a multiple-dose, two-way crossover study in patients undergoing treatment to establish bioequivalence.[47] In particular, FDA recommended that the treatment cycle be divided into two periods and that pharmacokinetic sampling take place on day five of each period, as well as on the last three days of each period to ensure steady-state blood plasma/serum levels.

Similarly, FDA recommended a multiple-dose, two-way crossover bioequivalence study in patients for etoposide, which is a chemotherapeutic agent indicated for the treatment of small cell lung cancer. FDA recommended that pharmacokinetic sampling take place on day five of the treatment cycle and that the two study periods be conducted in two consecutive cycles.[48]

For the reasons described above, Fresenius must conduct a multiple-dose *in vivo* pharmacokinetic study in patients using both routes of administration to establish whether Fresenius's proposed product provides an equivalent amount of bortezomib as VELCADE under real-world conditions.

---

[45] FDA Summary Basis of Approval for VELCADE NDA 21-602/S-10, Clinical Pharmacology Review at 15 (2006) (emphasis added), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021602_s010_velcade.pdf.

[46] Reece *et al.* "Pharmacokinetic and pharmacodynamic study of two doses of bortezomib in patients with relapsed multiple myeloma," *Cancer Chemother. Pharmacol.* 67:57-67 at 65 (2011). (Tab 13).

[47] FDA Draft Bioequivalence Guidance on Altretamine (April 2010).

[48] FDA Draft Bioequivalence Guidance on Etoposide (Aug. 2010).

C. FDA Should Not Waive *In Vivo* Human Bioequivalence Testing for the Fresenius Product

Although bioequivalence is typically demonstrated through *in vivo* human testing, FDA may waive the requirement for *in vivo* human evidence of bioequivalence where bioequivalence is considered self-evident based on the underlying science. Under FDA's regulation, bioequivalence may be considered self-evident for a parenteral solution when the proposed product "[c]ontains the same active and inactive ingredients in the same concentrations" as the reference product.[49] The requirement that the proposed product have the same ingredients as the reference product represents a reasoned scientific determination by FDA regarding the circumstances in which a waiver is acceptable. Fresenius's proposed product does not contain the same ingredients as VELCADE, and thus does not qualify for a waiver under FDA's parenteral waiver regulation.

In addition to considering a bioequivalence waiver for parenteral products where warranted under FDA's parenteral waiver regulation (which is not applicable to Fresenius's product), FDA also has indicated that it has general authority to grant a proposed parenteral solution a bioequivalence waiver even when the proposed product does not have the same ingredients as the reference product.[50] For example, in a citizen petition matter involving the drug nicardipine HCl, FDA granted a bioequivalence waiver to a proposed parenteral product that did not have the same ingredients as the reference product.[51] In the nicardipine matter, a 505(b)(2) application referenced Cardene I.V. (nicardipine HCl). However, the 505(b)(2) product differed from Cardene I.V. in two ways. The 505(b)(2) product contained sodium chloride as a tonicity adjusting agent, while Cardene I.V. contained sorbitol. Additionally, the 505(b)(2) product contained benzoic acid as a buffering agent instead of the citric acid monohydrate used in Cardene I.V. FDA granted the 505(b)(2) product an *in vivo* human bioequivalence waiver despite the ingredient differences. FDA indicated that the waiver was based on FDA's previous experience and knowledge regarding the new ingredients and their impact on injectable formulations. In particular, FDA concluded, and Millennium agrees, that benzoic acid and sodium chloride are commonly used excipients and well understood.[52, 53]

---

[49] 21 CFR 320.22(b)(1)(i).

[50] Letter from J. Woodcock to G. May (EKR Therapeutics, Inc.) regarding Docket No. FDA-2008-P-0621 (May 29, 2009) ("FDA Nicardipine Response"); *see also* 21 CFR 320.22(e).

[51] FDA Nicardipine Response at 11.

[52] *Id.* at 9.

[53] It is interesting to note that shortly after approval, the 505(b)(2) product evidenced formulation problems and had to be recalled due to excessive impurities. *See* FDA Enforcement Report 09-03 (Jan. 21, 2009), Recall No. D-167-2009 (nicardipine HCl injection).

In contrast to the nicardipine situation, boric acid is not a typical ingredient for an injectable product, and there is very little FDA and patient experience to support a bioequivalence waiver. Millennium is aware of only a few injectable products that contain boric acid (*i.e.*, the sodium thiosulfate products) and is not aware of any product for subcutaneous injection that contains boric acid. Sodium thiosulfate is indicated for use with sodium nitrite to treat acute cyanide poisoning that is judged to be imminently life-threatening. It is not a widely used drug, and apparently was approved based on individual case studies, or anecdotal evidence, not on a clinical study.[54] There is no FDA or patient experience regarding the effect of boric acid on bortezomib formulations, very little experience regarding how boric acid affects intravenous formulations, and apparently no experience regarding how boric acid affects subcutaneous formulations. Accordingly, there is no basis to grant a bioequivalence waiver to Fresenius's formulation based on previous experience.

Additionally, the chemical characteristics of bortezomib are complex and do not support a bioequivalence waiver. With respect to VELCADE, bortezomib exists in three different inter-converting molecular forms.[55] The drug substance exists in its cyclic anhydride form as a trimeric boroxine. In the lyophilized drug product, bortezomib forms a mannitol ester. The mannitol ester and the monomeric boronic acid, bortezomib, exist in equilibrium in the reconstituted drug product. With respect to Fresenius's proposed formulation, a related patent application indicates that the boric acid ingredient may form an anhydride structure with bortezomib.[56] The interaction of boric acid and Fresenius's other ingredients, such as glycine, with bortezomib may also affect the bioavailability of the product. Again, Fresenius has the burden to demonstrate that the aforementioned intermolecular interactions do not affect bioavailability and that its proposed product is safe and effective. Fresenius cannot meet that burden through supposition. An adequate, well-designed *in vivo* bioequivalence study is essential to understanding whether the Fresenius product indeed releases the same amount of bortezomib at the same rate as VELCADE.

In addition to ensuring effectiveness, there are significant safety reasons not to waive the *in vivo* human testing requirement. Bortezomib has been described as having a narrow therapeutic index, which means that there is a small window between an effective dose and a toxic dose.[57] The dose limiting toxicities associated with bortezomib may be severe and include

---

[54] Nithiodote Package Insert (Jan. 14, 2011) at Section 14 (Clinical Studies).

[55] VELCADE Package Insert (Oct. 26, 2012) at 18 (Description).

[56] WO 2012/047845 A1 at 9.

[57] Lu *et al.*, "Investigation of Drug-Drug Interaction Potential of Bortezomib In Vivo in Female Sprague-Dawley Rats and In Vitro in Human Liver Microsomes," *Drug Metabolism and Disposition* 34:702-708 at 702 ("Like many other cancer drugs, bortezomib is a cytotoxic agent with a narrow therapeutic index.") (Tab 14).

several Grade 3 or higher adverse events.[58] To the extent that Fresenius's proposed product provides more bortezomib than VELCADE, it could result in an inferior side effect profile compared to VELCADE in terms of frequency or severity of adverse events, including serious adverse events. It also could result in new and unexpected adverse events not observed with VELCADE. Accordingly, it is critical that Fresenius's proposed product actually be proven bioequivalent to VELCADE through *in vivo* human testing *via* both proposed routes of administration, rather than being granted a waiver based on a theoretical presumption of bioequivalence.

In addition to bortezomib toxicity, *in vivo* human testing also would provide important information regarding the safety of the new ingredients, such as boric acid, in Fresenius's proposed formulation. As detailed above, Fresenius's proposed use of boric acid in an injectable product raises significant safety issues that must be adequately addressed within the context of bortezomib's conditions of use. For example, VELCADE is proven to be safe and effective for both intravenous and subcutaneous routes of administration. However, a different formulation than VELCADE could result in new adverse events, or adverse events with different frequency or severity of known adverse events, in one or both proposed routes of administration. When administered intravenously, Fresenius's product could cause inflammation of the vein (*i.e.*, phlebitis). Similarly, when administered subcutaneously, Fresenius's product could irritate the injection site and cause induration, sloughing, or abscesses. Millennium's clinical study involving the subcutaneous route of administration showed a small underlying risk of local reaction associated with the subcutaneous route of administration (6% of the subcutaneous patients reported a local reaction), and Fresenius's proposed product could exacerbate that risk. The burden is on Fresenius to demonstrate that its proposed product is safe for both routes of administration. Millennium submits that *in vivo* human pharmacokinetic testing will provide critical safety information and is necessary to satisfy that burden.

In fact, as noted above, FDA indicated that Millennium would need to conduct an *in vivo* human pharmacokinetic study when Millennium discussed with FDA the path for obtaining approval for a new bortezomib formulation that Millennium considered in 2009. Specifically, the study discussed with FDA was a multiple-dose, randomized, two-way crossover study in patients who complete two cycles of protocol-specified treatments and pharmacokinetic assessments. Due to within-patient variability, Millennium requested that bioequivalence be established if the 90% confidence intervals for AUC and C_{max} would be expected to be contained in the 70% to 143% range. However, FDA rejected the request and stated that the 90% confidence interval for AUC and C_{max} should be contained in the standard range of 80% to 125%.[59] Millennium's proposed formulation would have been subject to *in vivo* human

[58] *See, e.g.*, FDA Summary Basis of Approval for VELCADE NDA 21-602, Medical Review at 14 (May 9, 2003) ("At weekly single doses above 1.5 mg/m^2, orthostatic hypotension and diarrhea were dose-limiting.").

[59] IND materials on file with FDA (Oct. – Nov. 2009).

pharmacokinetic testing even though Millennium's proposed new ingredients were widely used as components in many drug products approved before 2009.

Similar to Millennium's proposed formulation change, and particularly as previous experience with bortezomib demonstrated that simply changing the route of administration from intravenous to subcutaneous without any change in formulation resulted in a different toxicity profile, FDA must require Fresenius to support its proposed product with an *in vivo* human pharmacokinetic study.

D. Fresenius Must Show that Its Use of Boric Acid for Injection is Safe

In addition to the *in vivo* human bioequivalence testing, Fresenius must conduct the necessary foundational testing to ensure that its proposed product, particularly the use of boric acid, is safe. Fresenius's safety evaluation must include preclinical testing addressing the potential safety issues raised by the specific conditions of use proposed for Fresenius's product, such as the routes of administration and duration of treatment. If there are any unresolved risks regarding the safety of Fresenius's proposed product after the preclinical and human bioequivalence testing, Fresenius may need to conduct additional human clinical studies to demonstrate the safety of its proposed product.

The boric acid in Fresenius's proposed formulation is considered a "new excipient" because, as detailed above, the boric acid is not qualified by existing safety data with respect to the proposed routes of administration.[60] Accordingly, Fresenius must conduct the necessary studies to qualify its proposed use of boric acid as safe for both intravenous and subcutaneous administration. Under FDA's guidance document governing the types of nonclinical studies needed for the safety evaluation of new excipients, Fresenius's application should be supported with safety pharmacology testing on vital organ systems (*e.g.*, central nervous system, cardiovascular system, and respiratory system).[61]

Additionally, Fresenius should conduct the necessary toxicity studies to establish the safety of boric acid for long-term use by injection because bortezomib is dosed in lengthy treatment cycles (*e.g.*, there is a 54-week treatment plan for newly diagnosed multiple myeloma).[62] Millennium is aware of nonclinical safety studies on boric acid in the literature,

---

[60] *See* FDA's Excipient Guidance at 1.

[61] *Id.* at 4 ("We recommend that all potential new excipients be appropriately evaluated for pharmacological activity using a battery of standard tests (see ICH guidance S7A.")); ICH Guidance for Industry: S7A Safety Pharmacology Studies for Human Pharmaceuticals at 6 (July 2001).

[62] *See id.* at 6-7.

including sub-chronic, chronic, and carcinogenicity studies.[63] However, those studies do not seem to have been conducted *via* Fresenius's proposed routes of administration, *i.e.*, intravenous and subcutaneous injection. Consequently, Fresenius should conduct additional toxicity studies to fully assess the safety of boric acid for long-term use *via* the intended routes of administration of bortezomib.

Also, it is critical that Fresenius support its proposed product with toxicology tests that address safety risks specific to injectable products. For example, FDA recommends that the safety evaluation of new excipients for subcutaneous administration include an analysis of the plasma concentration of creatinine kinase at the intended excipient concentration to provide information on potential muscle damage.[64] Additionally, FDA recommends an evaluation of protein binding in relation to local site tolerability and an *in vitro* hemolysis study for intravenous products to determine hemolytic potential.[65]

In addition to the preclinical and human bioequivalence testing, FDA should require Fresenius to conduct additional human clinical testing to establish the safety of its product if there are any unresolved risks after the preclinical and human bioequivalence testing. In particular, boric acid is considered to be moderately acutely toxic due to effects such as dermal toxicity and skin irritation.[66] A human skin tolerability study or other human trial assessing systemic toxicity may be needed to establish that Fresenius's proposed product does not raise unnecessary safety risks and is as safe for patients as VELCADE. Furthermore, as boric acid is a boron-based compound like bortezomib, FDA must ensure that Fresenius's use of boric acid does not interfere with bortezomib's activity. Indeed, the scientific literature indicates that boric acid has its own chemotherapeutic activity and even may have a similar mechanism of action as bortezomib – increasing caspase-3 activity to promote cell apoptosis.[67] The use of boric acid potentially could be synergistic with bortezomib, which would result in an excessively potent bortezomib formulation. The boric acid also may compete with the bortezomib *in vivo*, which could make the formulation less effective. To adequately address these issues, Fresenius may need to conduct additional human clinical testing with its proposed formulation.

---

[63] *See, e.g.*, EPA, "Report of the Food Quality Protection Act (FQPA) Tolerance Reassessment Eligibility Decision (TRED) for Boric Acid/Sodium Borate Salts" (7508P) (July 2006). (Tab 15).

[64] *Id.* at 8.

[65] *Id.*

[66] EPA RED FACTS: Boric Acid, EPA-738-F-93-006 (Sept. 1993).

[67] Carper *et al.*, "Boric acid induces apoptosis in the prostate cancer cell line DU-145 via a caspase 3 dependent mechanism," *The FASEB Journal* 20:A194 (2006) ("The results indicate that boric acid is capable of inducing apoptosis in a human prostate cancer cell line.") (Abstract at Tab 16).

V. Fresenius Must Withdraw its 505(b)(2) Application if the Application Failed to Contain the Necessary Reference to a Previous Approval

For the reasons stated above, it would be inappropriate for FDA to rely on the previous approval of boric acid (*i.e.*, FDA's inactive ingredient database) to establish the safety of Fresenius's proposed product. However, even if Fresenius thought it could rely on the agency's prior approval of boric acid in another drug product, Fresenius was required to include a reference to the previous approval in its application. Absent such a reference, the Fresenius 505(b)(2) NDA would lack essential information to support the safety of boric acid as used in the proposed product.

A 505(b)(2) application must identify "those portions of the application that rely on information the applicant does not own or to which the applicant does not have a right of reference (for example, for reproductive toxicity studies)."[68] To the extent data generated with respect to another product is being relied on to support Fresenius's proposed product (particularly the safety of boric acid), Fresenius is required to reference that product in its application. The failure to do so would render the application incomplete on its face.

Moreover, in this instance, Fresenius cannot sidestep the requirement of identifying a listed drug to support the safety of boric acid merely by citing to the agency's inactive ingredient database. The database includes information on inactive ingredients that are present in previously approved drug products, and thus reflects FDA's finding of safety for previously approved drugs. To be listed in the database, there must have been some demonstration that the inactive ingredient is safe under the conditions identified in the database (*e.g.*, route of administration and potency level). Indeed, with respect to an ingredient listed in the database, FDA has stated that "a sponsor could consider it safe for use in a similar manner for a similar type of product."[69] Clearly, FDA would be relying on its finding of safety for a previously approved product if it used the database to support the safety of Fresenius's product, and Fresenius would have to reference the previously approved product.

FDA has indicated that certain information may be so widely known or common that reliance on the information would not require a reference in a 505(b)(2) application.[70] Indeed, information regarding some inactive ingredients is so widely known that it would not require a reference to any previously approved product. For example, the inactive ingredient, stearic acid,

---

[68] FDA Draft 505(b)(2) Guidance at 7.

[69] Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions (Question 3), *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm.

[70] FDA Draft 505(b)(2) Guidance at 2.

is widely used and has 21 listings for oral administration in the inactive ingredient database.[71] However, that is not the situation with respect to boric acid for use by injection.

Boric acid is rarely used in injectable products, and there is no general information or knowledge regarding boric acid that could be used to support Fresenius's application. In contrast to the 21 listings for stearic acid, the inactive ingredient database contains no listing for the subcutaneous use of boric acid and only one listing for the intravenous use of boric acid. As there is no general body of knowledge regarding the use of boric acid in injectable formulations, reliance on the inactive ingredient database essentially would be reliance on FDA's finding of safety and effectiveness for the previously approved drug associated with the database listing. Thus, such reliance would require a 505(b)(2) reference to the previously approved drug associated with the database listing.[72] To the best of our knowledge, the only products that use boric acid for intravenous administration are the sodium thiosulfate products discussed above. And, according to FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("*Orange Book*"), the Hope Pharmaceutical products are the only currently marketed sodium thiosulfate products.[73] Consequently, it seems that Fresenius would have to reference one of Hope Pharmaceutical's sodium thiosulfate NDAs if FDA were to rely on the inactive ingredient database to substantiate the safety of boric acid in Fresenius's formulation for intravenous use.

Furthermore, Fresenius could not simply amend its application to include a reference to the sodium thiosulfate product. The FDCA prohibits a 505(b)(2) applicant from amending its application to reference a new listed drug.[74] As FDA explained: "a 505(b)(2) applicant may not amend or supplement a 505(b)(2) application to seek approval of a drug that relies on the Agency's finding of safety and/or effectiveness for a drug that is different from the drug identified in a previous submission of the application."[75] Thus, Fresenius would have to withdraw its application and resubmit the application with the appropriate reference.

---

[71] *See* Inactive Ingredient Search for Approved Drug Products, *available at* http://www.accessdata.fda.gov/scripts/cder/iig/ (search term = "stearic acid").

[72] *See* 21 CFR 314.54(a)(1)(ii).

[73] The 0.319 % maximum potency level listing for boric acid in an injectable intravenous drug seems to predate the approval of NDA 201444, and Millennium presumes that the basis for the current maximum potency level is the sodium thiosulfate product described in US Army NDA 20166. *See, e.g.,* Inactive Ingredient Database Data File (Sept. 20, 2010), *available at* http://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm.

[74] FDCA 505(b)(4)(A).

[75] Letter from J. Woodcock to M. Aikman (Osmotica Pharmaceutical Corp.) regarding Docket No. FDA-2008-P-0329 at 16 n.30 (Nov. 25, 2008).

VI. Conclusion

In summary, Fresenius's proposed product contains boric acid, which is considered moderately acutely toxic and is rarely used in injectable products. Under FDA's legal framework, Fresenius's product is presumed to be unsafe. The burden is on Fresenius, as an NDA applicant, to provide sufficient data to demonstrate that its proposed product is safe and effective in each proposed route of administration for the proposed patient populations. For all of the above reasons, Fresenius can meet its burden only with appropriate *in vivo* human and preclinical testing. Without such data, FDA should not approve Fresenius's proposed product. In addition, FDA must find the Fresenius NDA incomplete on its face if Fresenius relied to any extent on a prior finding of safety for boric acid, such as FDA's inactive ingredient database, but failed to reference the drug product associated with that finding.

If FDA has any questions regarding this citizen petition, Millennium requests that FDA contact:

Melissa Anderson
Associate Director, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139
(617) 444-2209
melissa.anderson@mpi.com

Thank you for your attention to this important matter.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusions under 21 CFR 25.31.

ECONOMIC IMPACT

Pursuant to 21 CFR 10.30(b), an economic impact statement will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable

to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 5, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Millennium Pharmaceuticals, Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Vivek Kadambi, Ph.D.
Vice President, Drug Safety Evaluation

Melody Brown
Vice President, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

cc: Ann Farrell, M.D.
Director, Division of Hematology Products

Laurie Bartlett Keating
Senior Vice President and General Counsel
Millennium Pharmaceuticals, Inc.

David M. Fox
Gary L. Veron
Hogan Lovells US LLP

Melissa Anderson
Associate Director, Regulatory Affairs
Millennium Pharmaceuticals, inc.

130078