DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 10 2014

Vivek Kadambi, Ph.D., Vice President, Drug Safety Evaluation
Melody Brown, Vice President, Regulatory Affairs
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

Re: Docket No. FDA-2013-P-0998

Dear Dr. Kadambi and Ms. Brown:

The Food and Drug Administration (FDA or the Agency) is responding to your citizen petition dated August 12, 2013 (Petition). Your petition concerns Fresenius Kabi USA's (Fresenius's) 505(b)(2) application (new drug application (NDA) 205004) for an injectable bortezomib formulation containing boric acid and requests that we

1. require Fresenius to support its 505(b)(2) application with certain data and

2. require 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, and to require Fresenius to withdraw and resubmit its 505(b)(2) application with additional references 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.

We have carefully considered the Petition. For the reasons stated below, the Petition is denied without comment on whether we will take the actions you request.

I. BACKGROUND

A. Bortezomib Products

On May 13, 2003, Millennium Pharmaceuticals, Inc. (Millennium) obtained approval for Velcade (bortezomib) for Injection, 3.5 milligrams (mg)/vial (NDA 021602) (Velcade). Velcade is indicated for the treatment of patients with multiple myeloma and for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Velcade was initially approved for intravenous administration, and on January 23, 2012, it was approved for a subcutaneous route of administration.

B. Section 505(q) of the FD&C Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA), which was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs the manner in which these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on a petition not later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason.

II. DISCUSSION

In the Petition, you request that FDA require:

1. Fresenius's 505(b)(2) application (NDA 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 (bortezomib), 3.5 mg/vial (NDA 021602) 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, require Fresenius to withdraw and resubmit its application with the additional references.

(Petition at 2).

You state that you believe 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 (Petition at 1). You claim that the boric acid in the

Fresenius product is presumptively unsafe (Petition at 8). You assert that 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 (Id.). Moreover, you believe that this supposed unqualified standard of safety can be met in this case only with data from preclinical and human testing conducted by Fresenius because 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 (Id.). You also believe that the intended patient populations already have treatment options that have been demonstrated to be safe and effective based on well-controlled human studies (Petition at 10). Furthermore, you believe that Fresenius's proposed product seemingly would expose patients to levels of boron that exceed the permitted daily exposure (Petition at 11). In addition, you state that 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 (Petition at 22).

In support of your requests, you also state that 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, or raise significant safety concerns if it delivers more bortezomib than Velcade because there are associated dose-limiting toxicities (Petition at 14). For those reasons, you believe that 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 (Id.). You claim that bioequivalence must be shown in both of the approved routes of administration (intravenous injection and subcutaneous injection) (Petition at 15). You claim that FDA should not waive *in vivo* human bioequivalence testing for the Fresenius product because it does not contain the same ingredients as Velcade and thus does not qualify for a waiver under FDA's parenteral waiver regulation (Petition at 18). You state that there is also no basis to grant a bioequivalence waiver to Fresenius's formulation based on previous experience (Petition at 19). You also state that the chemical characteristics of bortezomib are complex and do not support a bioequivalence waiver (Id.).

Lastly, you state that 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 but failed to reference the drug product associated with that finding (Petition at 25).

As described in section I.B of this response, section 505(q)(1)(F) of the FD&C Act requires FDA to take final Agency action on the Petition within 150 days of submission. Therefore, we must take action on the Petition at this time. For the reasons explained below, we deny without comment the specific requests in your Petition regarding the approvability of any specific 505(b)(2) application.

FDA has made no final determination on whether to approve or not approve any 505(b)(2) application for an injectable bortezomib formulation. Therefore, we must determine whether it would be appropriate for us to take final Agency action on the approvability of a specific aspect of an application for such a bortezomib product before taking final action on the approvability of a 505(b)(2) application as a whole. To make this determination, we believe it is appropriate to

evaluate the statutory and regulatory provisions governing the content and review of 505(b)(2) applications in connection with the statutory provision of section 505(q) governing the time frame for action on the Petition.

The FD&C Act and FDA regulations establish procedural protections for applicants in the context of application review. Section 505 of the FD&C Act and FDA's regulations at 21 CFR part 314 describe certain procedures by which the Agency reviews an NDA or abbreviated new drug application (ANDA) and notifies an applicant if it determines that an application is approved (21 CFR 314.105) or may not be approved (section 505(c) and (j) of the FD&C Act, 21 CFR 314.125 and 314.127), or identifies the deficiencies in the application and the steps an applicant may take to respond to the deficiencies (21 CFR 314.110). In addition, the statute and regulations describe a specific process through which an applicant whose application the Agency has found does not meet the requirements for approval may challenge the Agency's determination (section 505(c)(1)(B) and (d) of the FD&C Act; 21 CFR 314.200). Under this process, the Agency will give the applicant notice of an opportunity for a hearing on whether the application is approvable, with a specific time frame and process, should the applicant request such a hearing (Id.). These procedures ensure that applicants have an adequate opportunity to challenge a finding by the Agency that a product does not meet the requirements for approval.

There is no evidence that in enacting section 505(q) of the FD&C Act, Congress intended to bypass the application review process or to lessen an ANDA or NDA applicant's procedural rights by requiring that the Agency make decisions that constitute final Agency action regarding the approvability of certain aspects of pending applications on a piecemeal basis outside of the process established under the FD&C Act and regulations.[1] Therefore, we do not interpret section 505(q) to require that the Agency render a final Agency decision within the statutory deadline on the approvability of a specific aspect of any 505(b)(2) application for an injectable bortezomib formulation when a final decision on the approvability of any such application has not yet been made.[2] Accordingly, we are denying without comment your requests on the specific requirements for approval of any 505(b)(2) application for an injectable bortezomib formulation.

[1] In other citizen petition responses, we have responded to requests related to general standards for approval (e.g., bioequivalence criteria for generic drug products) that may pertain to one or more pending drug applications without commenting on the approvability of any particular aspect of a specific pending application. We believe that this approach of describing our general policies or standards for approval of a drug application (beyond that described in this response) would not be appropriate in this case because the Petition's requests focus on narrow issues of whether a specific drug product proposed in a 505(b)(2) application should contain certain data that is dependent on the specific drug product's formulation before we have reached a final decision on whether to approve or not approve any such 505(b)(2) application. We will continue to evaluate each citizen petition on a case-by-case basis on the appropriateness of responding to requests regarding any pending application.

[2] Under applicable statutory and regulatory provisions, we are generally prohibited from disclosing any determinations regarding the filing or approvability of any pending 505(b)(2) application before we have reached a final decision on whether to approve or not approve the application.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research