Eileen Bedell, MPH
Richard Labotka, MD
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
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NOV - 6 2017

Re: Docket No. FDA-2017-P-3672

Dear Ms. Bedell and Dr. Labotka:

This letter responds to the citizen petition submitted on behalf of Millennium Pharmaceuticals, Inc. (Millennium) and received by the Food and Drug Administration (FDA or Agency) on June 9, 2017 (Petition).[1] The Petition makes a number of requests relating to Velcade (bortezomib) for Injection, 3.5 milligrams (mg)/vial (NDA 021602) (Velcade), as well as abbreviated new drug applications (ANDAs) and applications submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for bortezomib drug products that rely on Velcade. In particular, the Petition requests that FDA:

1. Refrain from approving any ANDA or 505(b)(2) bortezomib product for any multiple myeloma indication with labeling that omits information regarding the safe and effective conditions of use for the retreatment of relapsed patients;

2. Refrain from approving any ANDA or 505(b)(2) bortezomib product for any mantle cell lymphoma indication with labeling that omits information regarding the safe and effective conditions of use for treatment in previously untreated patients or labeling that adds new language to modify Velcade's current mantle cell lymphoma indication;

3. Seek public comment if FDA is considering allowing an ANDA applicant to revise Velcade's current mantle cell lymphoma indication by adding new language, consistent with FDA's prior action in a similar situation;

4. Identify the active ingredient in Velcade as the mannitol ester of bortezomib;

5. Require Fresenius's 505(b)(2) application ([new drug application (NDA)] 205004) for an injectable bortezomib formulation containing boric acid to be supported with:

    a. preclinical data and, as needed, human clinical 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

[1] On August 13, 2013, FDA received a citizen petition submitted by Millennium (FDA-2013-P-0998) that raised similar issues to some of the issues raised in the current Petition. On January 10, 2014, FDA denied Millennium's 2013 petition without comment on the merits of the arguments raised.

b. 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's, or human clinical data proving that the amount of bortezomib delivered by Fresenius's product is safe and effective; and

6. Require the Fresenius 505(b)(2) application to identify, as described in 21 CFR 314.54(a)(1), each source of information relied on to support approval of its application, including any previously approved product relied on through FDA's inactive ingredient database.[2]

For the reasons explained below, your Petition is denied.

I. BACKGROUND

A. Velcade

Millennium holds NDA 021602 for Velcade, for subcutaneous or intravenous use. FDA originally approved NDA 021602 on May 13, 2003, for the treatment of multiple myeloma patients[3] "who have received at least two prior therapies and have demonstrated disease progression on the last therapy."[4] Since the initial approval, FDA has approved several efficacy supplements that added to and revised the indications and usage section of labeling as well as the dosage and administration section. Currently, Velcade is indicated for "the treatment of patients with multiple myeloma" and "the treatment of patients with mantle cell lymphoma." At issue in the Petition are two labeling changes in particular. First, on August 8, 2014, FDA approved supplement 038 to NDA 021602, which added information to Velcade's approved labeling related to retreatment with Velcade for patients with multiple myeloma.[5] The indication of treatment of patients with multiple myeloma did not change with approval of this supplement. However, revisions were made to the dosing and administration section (as well as other sections, e.g., section 14) of labeling to reflect a single-arm, open label trial to determine the efficacy and safety of retreatment with Velcade in patents with relapsed multiple myeloma. Second, on October 8, 2014, the Agency approved supplement 040 to NDA 021602, which revised the previous indication from "the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy" (i.e., second-line treatment of mantle cell lymphoma) to the current indication for "the treatment of patients with mantle cell lymphoma." To support this labeling change, Millennium conducted a randomized, open-label Phase 3 clinical study in patients with previously untreated mantle cell lymphoma (i.e., first-line treatment of mantle cell lymphoma).[6]

FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book) lists the following 6 remaining periods of exclusivity for Velcade: ODE (Orphan Drug Exclusivity),[7] which expires

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[2] Petition at 2-3.

[3] Multiple myeloma is a form of cancer that occurs due to abnormal and uncontrolled growth of plasma cells in the bone marrow.

[4] Approval Letter, NDA 021602 (May 13, 2003).

[5] Approval Letter, NDA 021612, Supplement 038 (Aug. 8, 2014).

[6] Approval Letter, NDA 021612, Supplement 040 (Oct. 8, 2014) and Velcade labeling approved Oct. 8, 2014.

[7] See the Orange Book, available at http://www.accessdata.fda.gov/scripts/cder/ob/. FDA notes that the scope of 3-year exclusivity is not intended to be defined or circumscribed by the exclusivity code listed in the Orange Book. See FDA Response to GL Veron (Docket No. FDA-2010-P-0614) (May 25, 2011) at 22-23 (FDA determined that although the descriptor in the Orange Book stated that Colcrys' exclusivity covered "gout flares," the single clinical trial essential to the approval of Colcrys was for the treatment of acute gout flares, not prophylaxis of gout flares and therefore acute gout flairs was the exclusivity-protected indication).

on April 8, 2022 (including a pediatric extension),[8] I-695 (described in the Orange Book as "revised indication for bortezomib in the treatment of patients with mantle cell lymphoma"), which expires on April 8, 2018 (including a pediatric extension), D-142 (described in the Orange Book as "dose modification guidelines for bortezomib when given in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone"), which expires on April 8, 2018 (including a pediatric extension), D-141 (described in the Orange Book as "dosing information in previously untreated mantle cell lymphoma"), which expires on April 8, 2018 (including a pediatric extension), M-139 described in the Orange Book as "information added to the dosing and administration section of the package insert regarding retreatment with Velcade for patients with multiple myeloma"), which expires on February 8, 2018 (including a pediatric extension), and M-165 (described in the Orange Book as "provides for updates to the pediatric use section based on the pediatric study report entitled, 'A Phase II Pilot Trial of Bortezomib in Combination with Intensive Re-induction therapy in children with relapsed acute lymphoblastic lymphoma (LL)'"), which expires on March 14, 2019 (including a pediatric extension).[9]

B. Legal and Regulatory Background

1. Drug Approval Pathways Under the Federal Food, Drug, and Cosmetic Act

Section 505 of the FD&C Act (21 U.S.C. 355) establishes approval pathways for three categories of drug applications: (1) 505(b)(1) NDAs, (2) 505(b)(2) NDAs, and (3) 505(j) applications (abbreviated new drug applications or ANDAs).

a. 505(b)(1) NDAs: Stand-Alone Approval Pathway

Section 505(b)(1) of the FD&C Act requires that an NDA contain, among other things, "full reports of investigations" to show that the drug for which the applicant is seeking approval is safe and effective.[10] NDAs that are supported entirely by investigations either conducted by or for the applicant or for which the applicant has a right of reference are referred to as *505(b)(1) NDAs* or *stand-alone NDAs*.

b. Abbreviated Application Pathways

The Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Amendments)[11]

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[8] Velcade received this Orphan Drug Exclusivity for the treatment of patients with mantle cell lymphoma who have not received at least 1 prior therapy.

[9] In addition, the following exclusivities have already expired for Velcade: 5-year new chemical entity exclusivity (Orange Book (24th ed. 2004), 3-year exclusivity listed as I-452 (described in the Orange Book as "expanded indication to include treatment of multiple myeloma patients who have received at least 1 prior therapy") (Orange Book (26th ed. 2006)), 3-year exclusivity listed as I-521 (described in the Orange Book as "treatment of patients with mantle cell lymphoma who have received at least 1 year prior therapy") (Orange Book (27th ed. 2007)), 3-year exclusivity listed as I-564 (described in the Orange Book as "treatment of patients with multiple myeloma") (Orange Book (29th ed. 2009)), 3-year exclusivity listed as NR for a new route of administration (subcutaneous) (Orange Book (33rd ed. 2013)), and three 7-year periods of orphan drug exclusivity for "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy" (Orange Book (35th ed. 2015)), "treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy" (Orange Book (24th ed. 2004)), and "treatment of multiple myeloma patients who have received at least one prior therapy" (Orange Book (27th ed. 2007)).

[10] See section 505(b)(1)(A) of the FD&C Act. A 505(b)(1) NDA must also include a full list of the articles used as components of such drug described in the NDA; a full statement of the composition of such drug; a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; samples of the drug as necessary; proposed labeling for the drug; and pediatric assessments (see section 505(b)(1) of the FD&C Act).

[11] Public Law 98-417 (1984).

amended the FD&C Act to add section 505(b)(2) and 505(j), as well as other conforming amendments. These provisions describe abbreviated pathways for 505(b)(2) NDAs and ANDAs, respectively. The Hatch-Waxman Amendments reflect Congress's efforts to balance the need to "make available more low cost generic drugs by establishing a generic drug approval procedure" with new incentives for drug development in the form of exclusivity and patent term extensions.[12] These pathways permit sponsors to rely on what is already known about the previously approved drug, which both allows for a speedier market entry than would be possible with a full, stand-alone 505(b)(1) NDA and leads to increased competition.[13]

Like a stand-alone NDA, a 505(b)(2) NDA is submitted under section 505(b)(1) of the FD&C Act, is approved under section 505(c) of the FD&C Act, and must meet both the "full reports" requirement in section 505(b)(1)(A) and the same safety and effectiveness standard as a 505(b)(1) NDA. Unlike a stand-alone NDA, however, in a 505(b)(2) NDA, some or all of the safety and/or effectiveness information relied upon for approval comes from investigations (1) "not conducted by or for the applicant" and (2) "for which the applicant has not obtained a right of reference or use."[14] Thus, the difference between a 505(b)(2) NDA and a stand-alone NDA is the source of the information relied on for approval. Whereas a stand-alone NDA is supported entirely by studies that the sponsor owns or to which it has a right of reference, the 505(b)(2) applicant may rely on sources such as its own studies, published reports of studies to which the applicant has no right of reference, the Agency's findings of safety and/or effectiveness for one or more previously approved drug products (i.e., the listed drug relied upon), or a combination of these sources to support approval.

To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product. Instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD)[15] is safe and effective. Under section 505(j) of the FD&C Act, to rely on a previous finding of safety and effectiveness, an ANDA applicant must demonstrate that, among other things, its generic drug is bioequivalent to the RLD. In addition, a drug product described in an ANDA generally must contain the same active ingredient; conditions of use; route of administration, dosage form, strength; and (with certain permissible differences) labeling as the RLD.[16]

The timing of 505(b)(2) application or ANDA approval depends on, among other things, any patent and exclusivity protection for the listed drug relied upon or RLD, as applicable, and on whether the 505(b)(2) or ANDA applicant challenges those patents or seeks approval for uses covered by that exclusivity.[17] The 505(b)(2) or ANDA applicant must include an appropriate patent certification or statement for each patent that claims the listed drug relied upon or RLD or a method of using the listed drug relied upon or RLD for which the applicant is seeking approval and for which information is required to be filed under section 505(b)(1) or 505(c)(2) of the FD&C Act. For each unexpired patent listed in the Orange Book, the 505(b)(2) or ANDA applicant must submit either a paragraph III certification (indicating that an applicant is not seeking approval until the date on which such patent will expire), a paragraph IV certification (certifying that such patent is invalid or will not be infringed by the manufacture, use, or sale of the drug

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[12] See House Report No. 98-857, part 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647 at 2647-2648.

[13] See *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990); see also *Bristol-Myers Squibb Co. v. Royce Labs., Inc.*, 69 F.3d 1130, 1132-1134 (Fed. Cir. 1995).

[14] See section 505(b)(2) of the FD&C Act.

[15] An RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA" (21 CFR 314.3). RLDs are identified in the Orange Book.[16] See Section 505(j)(2)(A) & (j)(4) of the FD&C Act and 21 CFR 314.94(a).

[16] See Section 505(j)(2)(A) & (j)(4) of the FD&C Act and 21 CFR 314.94(a).

[17] See, e.g., section 505(b)-(c), (j)(2)(A)(vii), (j)(2)(A)(viii), and (j)(5)(B) of the FD&C Act.

product for which the ANDA is submitted), or, with respect to a method of use patent, a statement that the patent does not claim a use for which the 505(b)(2) or ANDA applicant is seeking approval (see section 505(b)(2)(A)(iii)-(iv), 505(b)(2)(B), 505(j)(2)(A)(vii)(III)-(IV) and 505(j)(2)(A)(viii) of the FD&C Act).[18]

2. Exclusivity

a. Three-Year Exclusivity

Under section 505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) of the FD&C Act and § 314.108(b)(4) (21 CFR 314.108(b)(4)), the Agency will recognize a 3-year period of exclusivity for a drug that contains a previously approved active moiety(ies), when the application contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by or on behalf of the applicant that were essential to approval of the application.[19] During this 3-year period, the Agency will not approve a 505(b)(2) NDA or an ANDA for the conditions of approval of the original application.

Similarly, FDA will recognize 3-year exclusivity when a supplement to an NDA is approved and the supplement contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by or on behalf of the applicant that were essential to approval of the supplement. When a supplement meets the criteria set forth in these provisions, FDA "may not make the approval of an application . . . for a change approved in the supplement effective before the expiration of three years . . . ." (see sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act and § 314.108(b)(5) (21 CFR 314.108(b)(5))). Although the statute and regulations use different words to describe 3-year exclusivity for an original NDA (i.e., "conditions of approval") and a supplement to an NDA (i.e., "change approved in the supplement"), FDA has taken a consistent approach to both types of applications in determining their eligibility for 3-year exclusivity and the scope of that exclusivity.[20]

b. Orphan Drug Exclusivity

The Orphan Drug Act (Public Law 97-414) was enacted in 1983 and added sections 525 to 528 to the FD&C Act (21 U.S.C. 360aa-360dd). In enacting the Orphan Drug Act, Congress sought to promote the development of drugs for rare diseases and conditions that would not otherwise be developed and approved, including drugs that are potentially safer or more effective than already approved drugs for such diseases or conditions. Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is generally so limited that the cost of developing the drugs makes a profit by the developer unlikely.[21] Accordingly, as amended, the Orphan Drug Act provides various incentives, including tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, formal protocol assistance to sponsors of drugs for rare diseases, and a 7-year exclusivity period during which FDA may not approve another sponsor's application "for such drug for such disease or condition," subject to certain conditions.[22] The scope of orphan drug exclusivity "protects only the

[18] If an ANDA includes a statement that the patent does not claim a use for which the ANDA applicant is seeking approval, then the ANDA must be accompanied by labeling that includes a corresponding labeling carve-out of that protected use. See 21 CFR 314.94(a)(8)(iv).

[19] A 5-year exclusivity period is provided for a drug with "no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under [section 505(b)]." Section 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act. See also 21 CFR 314.108.

[20] See *Otsuka Pharmaceutical Co. v. Price*, No. 16-5229 (D.C. Cir. Aug. 29, 2017).

[21] See Orphan Drug Regulations, Notice of Proposed Rulemaking, Docket No. 85N-0483, 56 FR 3338 (Jan. 29, 1991).

[22] See sections 525 to 528 of the FD&C Act and section 227 of the Public Health Service Act (42 U.S.C. 236); see also 21 CFR part 316.

approved indication or use of a designated drug."[23] FDA has issued regulations implementing its Orphan Drug Act authority.[24]

To be eligible for 7-year orphan drug exclusivity, a sponsor must participate in a two-step process that includes designation and approval. A sponsor must first submit a request for designation of its drug for a rare disease or condition that includes, among other things, a scientific rationale to establish a medically plausible basis for the use of the drug for the rare disease or condition identified.[25] To obtain orphan drug exclusivity, the sponsor must then obtain approval of the drug for the rare disease or condition for which orphan designation was granted. Orphan drug exclusivity begins on the date that the marketing application is approved and precludes approval for 7 years of the same drug (same active moiety) for the same orphan indication for which the drug has been designated and approved, i.e., for "such drug for such disease or condition."[26] Orphan drug exclusivity is limited in its scope and protects against approval only of the same drug[27] for the same indication. It does not preclude approval of the same drug for which orphan drug exclusivity was granted for a different, non-protected indication.

3. *"Same Labeling" Requirement for Products Approved in ANDAs and Permissible Carve-Outs*

Section 505(j)(2)(A)(i) of the FD&C Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Also, section 505(j)(2)(A)(v) of the FD&C Act requires that an ANDA contain:

> information to show that the labeling proposed for the new [generic] drug is the same as the labeling approved for the listed drug . . . except for changes required because of differences approved under a petition filed under [section 505(j)(2)(C) of the FD&C Act] or because the new [generic] drug and the listed drug are produced or distributed by different manufacturers.[28]

A parallel provision appears in section 505(j)(4)(G) of the FD&C Act.[29]

Although the requirements set forth in section 505(j)(2)(A)(v) and 505(j)(4)(G) are known as the "same labeling" requirements, they do not require that a generic drug's labeling be identical to that of the listed drug it references in every respect. Instead, these provisions reflect, among other things, Congress's intent that the generic drug be safe and effective for each condition of use prescribed, recommended, or suggested

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[23] 21 CFR 316.31(b).

[24] See 21 CFR part 316.

[25] See section 526 of the FD&C Act (21 U.S.C. 360bb); see also § 316.20.

[26] See section 527(a) of the FD&C Act (21 U.S.C. 360cc) (providing that FDA "may not approve another application . . . for such drug *for such disease or condition* . . . until the expiration of seven years") (emphasis added); § 316.31(b) ("Orphan-drug exclusive approval protects only the approved indication or use of a designated drug."). The regulation also describes certain situations not relevant here when an application for the same drug for the same indication can be approved during the period of orphan drug exclusivity (see § 316.31(a)).

[27] Note that a drug that is clinically superior to a previously approved drug with the same active moiety for the same indication is not considered to be the "same drug." See 21 CFR 316.3(b)(14) (defining "same drug").

[28] See also 21 CFR 314.92(a)(1), 314.94(a)(4)(i), 314.94(a)(8)(iv), 314.127(a)(2), and 314.127(a)(7).

[29] Section 505(j)(4)(G) of the FD&C Act provides that FDA shall approve an ANDA unless, among other things, "the information submitted in the application is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for [the listed drug] except for changes required because of differences approved under [an ANDA suitability petition] or because the drug and the listed drug are produced or distributed by different manufacturers."

in the generic drug labeling without requiring that an ANDA be approved for each condition of use for which the listed drug is approved. In describing the Hatch-Waxman Amendments, Congress explicitly acknowledged that "the bill permits an ANDA to be approved for less than all of the indications for which the listed drug has been approved."[30]

In interpreting the statutory exception to the same labeling requirement, which allows certain labeling differences due to the fact that the proposed ANDA and the listed drug are "produced or distributed by different manufacturers," the regulations at § 314.92(a)(1) (21 CFR 314.92(a)(1)) explicitly state that a proposed generic drug product must have the same conditions of use as the listed drug, except that "conditions of use for which approval cannot be granted *because of exclusivity* or an existing patent may be omitted" (emphasis added). Section 314.94(a)(8)(iv) (21 CFR 314.94(a)(8)(iv)) sets forth some examples of permissible differences in labeling that may result because the generic drug product and listed drug are produced or distributed by different manufacturers. Permissible differences include, but are not limited to:

> [D]ifferences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or *omission of an indication or other aspect of labeling protected by patent or accorded exclusivity* under section 505(j)(5)(F) of the [FD&C Act].[31]

The regulations at § 314.127(a)(7) (21 CFR 314.127(a)(7)) further provide that, to approve an ANDA containing proposed labeling that omits "aspects of the listed drug's labeling [because those aspects] are *protected by patent, or by exclusivity*," we must find that the "differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use" (emphasis added). These provisions thus specifically affirm that ANDA applicants may carve out from their proposed labeling any patent- or exclusivity-protected conditions of use and obtain approval for the remaining non-protected conditions of use as long as the ANDA remains safe and effective for the remaining non-protected conditions of use.

Relevant case law affirms an ANDA applicant's ability to carve out protected labeling without violating the "same labeling" requirement. For example, in *Bristol-Myers Squibb Co. v. Shalala,* 91 F.3d 1493 (D.C. Cir. 1996), the D.C. Circuit ruled that "the statute expresses the legislature's concern that the new generic be safe and effective for each indication that will appear on its label; whether the label for the new generic lists every indication approved for use of the pioneer is a matter of indifference."[32] Similarly, in *Sigma-Tau*

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[30] H.R. Rep. No. 98-857, pt.1, at 2; see also id. at 21 ("The [ANDA] applicant need not seek approval for all of the indications for which the listed drug has been approved.").

[31] (emphasis added). We note that although the regulation provides removal of an aspect of labeling protected by exclusivity under section 505(j)(5)(F) of the FD&C Act as an example of a permissible difference due to difference in manufacturer, FDA has never interpreted this example as the only permissible exclusivity-based carve-out. On the contrary, FDA has consistently permitted labeling carve-outs based on orphan drug exclusivity protection as well. See, e.g., ANDA labeling approvals for levoleucovorin (carving out labeling protected by both 3-year exclusivity and orphan drug exclusivity), temozolomide (carving out labeling protected by both 3-year exclusivity and orphan drug exclusivity), tacrolimus (carving out labeling protected by orphan drug exclusivity), aripiprazole (carving out labeling protected by both 3-year exclusivity and orphan drug exclusivity), and rosuvastatin (carving out labeling protected by both 3-year exclusivity and orphan drug exclusivity). In addition, section 505A(o) of the FD&C Act, as amended by the FDA Reauthorization Act of 2017, authorizes FDA to approve an ANDA or a 505(b)(2) NDA that carves out from labeling a pediatric indication or other aspect of labeling related to pediatric use that is protected by patent(s), 3-year exclusivity, or orphan drug exclusivity of the relied-upon listed drug, while retaining pediatric information necessary for safe use of the drug.

[32] *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996). See also *Spectrum Pharm., Inc. v. Burwell*, 824 F.3d 1062, 1066 (D.C. Cir. 2016) (explaining that D.C. Circuit has "approved FDA's general approach to labeling carve-outs as

Pharmaceuticals, Inc. v. Schwetz, 288 F.3d 141 (4th Cir. 2002), the Fourth Circuit upheld the right of an ANDA applicant to carve out an indication protected by orphan drug exclusivity as a permissible difference due to a difference in manufacturer.[33] Sigma-Tau Pharmaceuticals, Inc. (Sigma-Tau) argued that FDA was obligated to look beyond the labeling an ANDA applicant proposed to use in determining whether a generic drug would violate an innovator's orphan drug exclusivity. The court observed that orphan drug exclusivity is "disease-specific, not drug-specific," and noted that if FDA adopted Sigma-Tau's argument, this could mean that once the Agency approves an orphan drug for a protected indication, "generic competitors might be prohibited from entering the market for almost any use."[34] The court further stated that Sigma-Tau's argument would extend exclusivity beyond what Congress intended and "frustrate the longstanding practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses."[35] The court reasoned that "[Sigma-Tau's theory] to bar the approval of generic drugs, even for unprotected indications . . . [would add] a huge evidentiary hurdle to the generic drug approval process [and] would be profoundly anti-competitive."[36] Accordingly, the court rejected Sigma-Tau's argument and concluded that the statutory scheme permitted an ANDA applicant to carve out the orphan-protected indication at issue.

Consistent with 21 CFR 314.94(a)(8) and 21 CFR 314.127(a)(7), the Agency may approve an ANDA with labeling that differs from the listed drug labeling because aspects of the listed drug labeling are protected by exclusivity.[37]

Thus, the statute, regulations, and applicable case law permit the omission of an indication or other aspect of labeling protected by a listed patent or applicable exclusivity, including orphan drug exclusivity, as an acceptable difference between the proposed generic drug and the RLD that are produced or distributed by different manufacturers if the omission does not render the proposed generic drug less safe or effective than the RLD for the non-protected conditions of use that remain in the labeling.[38]

II. DISCUSSION

The Petition states that FDA should not approve ANDAs or 505(b)(2) applications for bortezomib drug products with labeling that omits protected information regarding retreatment with Velcade of patients with multiple myeloma, as well as first-line treatment for mantle cell lymphoma.[39] The Petition contends that FDA may not approve applications that propose to carve out the exclusivity-protected information because omitting this information would render the products less safe or effective for the remaining, non-protected conditions of use.[40] The Petition also contends that FDA lacks the authority to allow sponsors to carve out protected information about first-line treatment for mantle cell lymphoma because "FDA's carve-out

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an acceptable interpretation of the [FD&C Act]" and upholding FDA's approval of a generic drug with an indication protected by orphan exclusivity carved out).

[33] *Sigma-Tau Pharms., Inc. v. Schwetz*, 288 F.3d 141, 148, n. 3 (4th Cir. 2002).

[34] Id. at 147.

[35] Id. (citations omitted).

[36] Id.

[37] Such differences may include, but are not limited to, omissions of words or phrases from the RLD's labeling and minor attendant changes to ensure that the language of the labeling reads properly. See March 24, 2016, Response to J. Rodenberg, Teva Pharmaceuticals, re: Docket No. FDA-2015-P-3980 at 14-15.

[38] A 505(b)(2) application is not required to have the same labeling as the listed drug relied upon. Therefore, a 505(b)(2) application can omit aspects of labeling that are included in the listed drug relied upon and that are protected by exclusivity so long as the 505(b)(2) application can be approved with that information omitted from its labeling.

[39] Petition at 7, 12.

[40] Id. at 5-16.

authority and precedent make clear that the agency will permit only omissions and minor attendant changes" to approved labeling.[41] Additionally, the Petition requests that FDA seek public comment on this issue.[42]

In addition, the Petition asks FDA to identify the active ingredient in Velcade as the mannitol ester of bortezomib.[43] The Petition also raises concerns with respect to Fresenius Kabi USA's (Fresenius's) proposed bortezomib drug product, asks FDA to require certain testing to support the safety and efficacy of the proposed drug product, and asks FDA to require Fresenius to identify each source of information relied on to support approval of its application, including any previously approved product relied on through FDA's Inactive Ingredient Database.[44]

We address each of these arguments below.

A. Protected Information About Retreatment of Multiple Myeloma Patients Who Had Previously Received Bortezomib May Be Carved Out Without Causing Bortezomib Drug Products To Be Less Safe or Effective for the Remaining, Non-Protected Conditions of Use.

On August 8, 2014, the Agency approved supplement 038 to NDA 021602, which added information to Velcade's prescribing information (PI) related to retreating relapsed multiple myeloma patients who had previously been treated with Velcade.[45] Prior to the approval of this supplement, the Velcade PI contained information pertaining to the relapsed multiple myeloma patient population, but did not contain information specific to relapsed patients who had previously received Velcade.[46] This supplement qualified for 3-year exclusivity described in the Orange Book as "information added to the dosing and administration section of the package insert regarding retreatment with Velcade for patients with multiple myeloma."[47]

The Petition states that "Millennium is concerned that an ANDA or 505(b)(2) applicant seeking to market for multiple myeloma may seek to omit the protected safety and efficacy information regarding retreatment."[48] According to the Petition, the protected information regarding retreatment with Velcade includes information about the use of Velcade in combination with dexamethasone.[49] The Petition states that this information on combination use with dexamethasone provides "important information that could improve the effectiveness of retreatment."[50] Further, the protected retreatment information states that the patient "may retreat starting at the last tolerated dose."[51] If this information were omitted, the Petition asserts, patients would receive treatment according to the non-protected information for the general population of relapsed multiple myeloma patients that would remain in product labeling.[52] The Petition asserts that "VELCADE's labeling provides that the starting dose for the general population of relapsed

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[41] Id. at 7
[42] Id. at 8.
[43] Id. at 16-19.
[44] Id. at 19-29.
[45] See NDA 021602 Supplement 038, approved Aug. 8, 2014.
[46] Petition at 12.
[47] See Orange Book, Patent and Exclusivity Data for NDA 021602, available at https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=021602&Appl_type=N.
[48] Petition at 11.
[49] Id. at 14.
[50] Id.
[51] Id. at 13.
[52] Id.

multiple myeloma patients is 1.3 [milligrams (mg)]/ m^2/dose," which could be higher than the last tolerated dose for some patients being retreated with Velcade.[53] The Petition further states that "[a]dministering the higher dose, which was not previously tolerated by the patient, would be less safe for that patient."[54] The Petition also raises concerns about the omission of protected information related to cumulative toxicities associated with retreatment, the timing of initiating retreatment with Velcade, and the number of cycles that are appropriate for retreatment with Velcade.[55] Thus, the Petition asserts that the omission of protected retreatment information "would raise safety and efficacy issues and should not be permitted."[56]

1. Bortezomib Drug Product Labeling May Omit Protected Information About Combination Use With Dexamethasone Without Adversely Affecting Efficacy for the Remaining Conditions of Use.

As explained in section I.B.3, an ANDA application may carve out aspects of the RLD labeling protected by exclusivity if the differences do not render the proposed drug product less safe or effective than the RLD for the remaining non-protected conditions of use. Similarly, a 505(b)(2) application may carve out aspects of the labeling for the listed drug relied upon if the 505(b)(2) application can be approved as safe and effective under the conditions of use described in its labeling with the protected information omitted from labeling. Regarding the protected retreatment information about the use of bortezomib in combination with dexamethasone, FDA disagrees with the Petition's assertion that omitting the protected information would adversely affect the efficacy of 505(b)(2) and ANDA bortezomib drug products for the treatment of relapsed multiple myeloma patients. The clinical trial that formed the basis for approval for retreatment of patients with multiple myeloma ("Retreatment Study") was a single arm phase 2 study which enrolled a total of 130 patients.[57] The use of dexamethasone in combination with Velcade was allowed "at the investigator's discretion and per the investigator's standard of care."[58] Further, the study was not designed to answer efficacy and safety questions with regard to the addition of dexamethasone. Consistent with this, the clinical studies section of the Velcade PI discussing retreatment does not include information on safety or response rates separately for those who received bortezomib monotherapy and those who received the bortezomib and dexamethasone combination. Thus, the omission of the protected information about combined use with dexamethasone from an ANDA would not render the product less safe and effective for the remaining conditions of use, and a 505(b)(2) NDA could be approved as safe and effective under the conditions of use described in its labeling.

Further, even after the protected information is carved out, some information about the use of bortezomib and dexamethasone for relapsed multiple myeloma patients will remain in the labeling of bortezomib drug products. For example, information from the SUMMIT trial, where patients were treated with bortezomib and where dexamethasone could be added for patients with less than optimal response, would still be described in Sections 6.1 and 14 of the Velcade PI and would not need to be excluded from the labeling of bortezomib drug products relying on Velcade.

2. The Omission of Protected Retreatment Information Will Not Result in Unsafe Dosing of Bortezomib or Otherwise Render Bortezomib Drug Products Less Safe or Effective for the Remaining Conditions of Use.

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[53] Id.
[54] Id.
[55] Id. at 14.
[56] Id. at 11.
[57] See Velcade PI, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021602s043lbl.pdf.
[58] A prospective international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. M.T, Petrucci. 2013, British Journal of Hematology.

FDA has also determined that the dosing of ANDA or 505(b)(2) application bortezomib drug products relying on Velcade will not be less safe or effective if the protected retreatment information is omitted. The information regarding treatment of patients with relapsed multiple myeloma is not protected by exclusivity. Only information describing the Retreatment Study is protected by the 3-year exclusivity described in the Orange Book as "information added to the dosing and administration section of the package insert regarding retreatment with Velcade for patients with multiple myeloma." The retreatment information described in the Velcade PI is necessarily based on the single-arm trial conducted by Millennium of retreatment with Velcade in relapsed multiple myeloma patients.

According to the Petition, relevant protected information includes the following statement in the Dosage and Administration section of the Velcade PI:

> VELCADE retreatment may be considered for patients with multiple myeloma who had previously responded to treatment with VELCADE and who have relapsed at least 6 months after completing prior VELCADE treatment. Treatment may be started at the last tolerated dose.[59]

The Petition also indicates that protected retreatment information includes the description of adverse reactions associated with retreatment with Velcade and provides that "patients should receive retreatment 'for a maximum of 8 cycles.'"[60]

FDA does not agree that carving out the protected retreatment information would result in the administration of an unsafe dose of bortezomib to relapsed patients who had previously received bortezomib therapy for multiple myeloma, as the Petition suggests.[61] The Velcade PI also describes a number of non-protected studies of bortezomib in relapsed patient populations, such as the SUMMIT trial discussed above and a prospective phase 3 randomized, stratified, open-label study in relapsed multiple myeloma patients comparing Velcade and dexamethasone.[62] The schedule of administration and dose levels in the Retreatment Study are consistent with those used in non-protected relapsed multiple myeloma studies, which were described in the PI before approval of the supplement describing the Retreatment Study and will continue to be described in the PI for ANDA or 505(b)(2) bortezomib drug products after any protected retreatment information is carved out. The majority of patients in the Retreatment Study received the standard dose (1.3 mg/m^2) of bortezomib, and the study did not evaluate any new dose levels that had not been previously studied and that will not continue to be described in the PI. Further, the dose modification guidelines for toxicity employed in the Retreatment Study are consistent with those used in non-protected studies of relapsed multiple myeloma patients that were described in the PI before approval of the supplement describing the Retreatment Study and will continue to be described in the PI for ANDA or 505(b)(2) bortezomib drug products after any protected retreatment information is carved out as well. An oncologist would consider a dose modification for any relapsed multiple myeloma patient based on factors, such as pre-existing peripheral neuropathy or moderate to severe hepatic impairment, that will continue to be described in the PI for an ANDA or 505(b)(2) application. Additionally, although the Retreatment Study evaluated treatment "for a maximum of 8 cycles," and that is how it is described in the labeling, there is no evidence that the retreatment population would be affected differently from the relapsed population. The Retreatment Study was not designed to measure the safety or efficacy of

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[59] Petition at 13.

[60] Id. at 14. The Petition states, "[i]n contrast, the labeling for the general relapsed patient population states that therapy can be extended for 'more than 8 cycles.'" Id.

[61] Id. at 11-13.

[62] Velcade PI, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021602s043lbl.pdf.

bortezomib when it is used for more than 8 cycles because the study was limited to 8 cycles. Consequently, FDA does not believe that carving out protected information from the Retreatment Study would affect the safety of the dosing and administration of ANDA or 505(b)(2) bortezomib drug products that rely on Velcade.

In addition, FDA disagrees with the Petition's assertion that the Retreatment Study yielded critical safety information that cannot be omitted from bortezomib drug product labeling. According to the Petition, the Retreatment Study provided additional protected information about the safety of bortezomib drug products, including information regarding adverse reactions.[63] The Petition contends that proposed bortezomib drug product labeling that does not contain "all of the known and relevant risk information associated with retreatment" on the bortezomib drug product would be less safe than Velcade.[64] However, the safety profile of patients on the Retreatment Study was consistent with that previously seen in relapsed multiple myeloma patients, with no evidence of any new safety signal or cumulative toxicity. In the phase 2 open label extension study discussed above, there was no evidence of cumulative or new long-term toxicities with prolonged Velcade treatment. [65] The incidence of thrombocytopenia reported in the Retreatment Study was higher overall (52%) compared to the phase 3 relapsed multiple myeloma study (33%). However, there was no major difference in the incidence of ≥ Grade 3 thrombocytopenia (24% versus 28%) and the incidence of serious adverse events between the Retreatment Study and the phase 3 relapsed multiple myeloma study. Therefore, in FDA's view, the omission of protected information would not render ANDAs relying on Velcade to be less safe or effective for the remaining, non-protected conditions of use, nor would the omission of the protected information preclude the approval of a 505(b)(2) application relying on Velcade because the product would be safe and effective under the conditions of use described in the labeling.[66]

B. The Omission of the Protected Mantle Cell Lymphoma Indication Will Not Adversely Affect the Safety or Efficacy of Bortezomib Drug Products.

Velcade was approved as a second-line treatment for mantle cell lymphoma in 2006.[67] The indication was changed in 2014 to include previously untreated patients (i.e., first-line treatment), resulting in a revised indication "for the treatment of mantle cell lymphoma."[68] The Petition states that the "approval of the revised mantle cell lymphoma indication resulted in multiple exclusivity periods, including orphan drug exclusivity."[69] The Petition notes the following:

> VELCADE was awarded orphan exclusivity in 2006 for "Treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy." With regard to the current orphan exclusivity, FDA's orphan database describes the "approved labeled indication" as "Treatment of patients with mantle cell lymphoma who have not received at least 1 prior therapy." That set of patients was incorporated into the labeling through the revised indication statement, which states that "VELCADE is indicated for the treatment of patients with mantle cell lymphoma."[70]

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[63] Petition at 14.
[64] Id.
[65] Safety of Prolonged Therapy with Bortezomib in Relapsed or Refractory Multiple Myeloma. JR, Berenson. 2005, Cancer.
[66] We address the Petition's argument that FDA's response to a citizen petition involving Rapamune (sirolimus) is instructive (Petition at 15) on page 16 of this response.
[67] Petition at 7.
[68] Id.
[69] Id.
[70] Id.

The Petition states that FDA may not approve "any bortezomib product for the treatment of patients who have not received at least 1 prior therapy" until the expiration of the orphan drug exclusivity period on April 8, 2022 and further states "[b]ecause VELCADE has only one broad mantle cell lymphoma indication, . . . FDA may not approve any ANDA or 505(b)(2) 'for the treatment of mantle cell lymphoma.'"[71]

The Petition argues that FDA should not allow ANDA applicants to carve out the protected first-line indication and to seek approval for the non-protected aspects of the treatment of mantle cell lymphoma indication.[72] The Petition states that "FDA's carve-out authority and precedent make clear that the agency will permit only omissions and minor attendant changes" to approved labeling.[73] According to the Petition, "[i]t is not possible to omit words from the current mantle cell lymphoma indication and/or to make *de minimis* changes to arrive at an indication that does not disclose the exclusivity-protected use for first-line mantle cell lymphoma."[74] The Petition states that an ANDA applicant "would have to add language to create a new indication for second-line treatment that is not part of VELCADE's current labeling."[75] In other words, because Velcade's current labeling contains a broad indication "for the treatment of mantle cell lymphoma," the Petition contends that applicants may not carve out the protected first-line indication without impermissibly changing the language of the indication or referencing a discontinued version of Velcade's labeling.[76] The Petition asserts, however, that FDA lacks the authority to approve of such a change.[77]

The Petition also argues that omitting the protected first-line indication will render bortezomib drug products less safe and effective for the remaining, non-protected mantle cell lymphoma conditions of use. According to the Petition, Velcade's current PI "represents the current paradigm for safe and effective treatment" of mantle cell lymphoma and that omitting protected information would "raise significant safety and efficacy issues."[78] The Petition states that mantle cell lymphoma "is characterized by a small patient population, an aggressive and rapid disease progression, a high rate of relapse, and a short median survival period."[79] The Petition further states, "[f]irst-line patients will almost certainly become second-line patients, and first- and second-line therapies are not given in isolation but rather as part of an interrelated treatment approach."[80] Thus, the Petition asserts, "first-line information is relevant to the other mantle cell lymphoma conditions of use."[81] In addition, the Petition asserts that "[l]abeling stating that mantle cell lymphoma patients need to have failed on a prior therapy establishes a medically unnecessary condition on use of the drug that would be unsafe and misleading."[82] According to the Petition, "a product that omits the first-line treatment information would instruct mantle cell lymphoma patients to unnecessarily delay initiation of bortezomib therapy."[83]

We address each of these arguments in turn.

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[71] Id.
[72] Id.
[73] Id.
[74] Id. at 7-8.
[75] Id. at 8.
[76] Id. at 7-9
[77] Id.
[78] Id. at 9.
[79] Id.
[80] Id.
[81] Id.
[82] Id. at 9-10.
[83] Id. at 9.

1. Retaining the Indication for Second-Line Treatment of Mantle Cell Lymphoma is Permissible Under FDA's Carve-Out Authority.

FDA disagrees with the Petition's assertion that FDA may not approve ANDAs or 505(b)(2) applications for bortezomib drug products that rely on Velcade and that propose to carve out Velcade's protected first-line information regarding mantle cell lymphoma (i.e., the indication for "treatment of patients with mantle cell lymphoma who have not received at least one prior therapy"). Prior to the approval of supplement 040 to NDA 021602, the labeling for Velcade included the following second-line treatment indication: "VELCADE is indicated for the treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy."[84] The second-line treatment indication for mantle cell lymphoma currently is not protected by exclusivity. Upon approval of supplement 040, the Indications and Usage section was revised to include a new patient population for mantle cell lymphoma, patients who have not received at least one prior therapy. Thus, the revised indication included both patients who have received at least one prior therapy (the second-line treatment indication that is unprotected by exclusivity) and patients who have not received at least one prior therapy (the first-line treatment that is protected by exclusivity). The current approved indication provides that "VELCADE is indicated for the treatment of patients with mantle cell lymphoma." It would be appropriate, in FDA's view, to omit the exclusivity-protected information and retain the non-protected indication for the "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy."

As described above, sections 505(j)(2)(A)(v) and 505(j)(4)(G) of the FD&C Act allow changes in labeling required because the proposed ANDA and the listed drug are "produced or distributed by different manufacturers." The regulation at 21 CFR 314.127(a)(7) allows for "changes required . . . because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use." Section 314.94(a)(8)(iv) contains similar language and states that the differences between the labeling may include "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity." Consequently, although omissions and minor attendant changes are consistent with FDA's authority, differences in labeling permitted by the regulations are not limited to such changes.[85] We also note that these "same labeling" requirements do not apply to 505(b)(2) applications, and the 505(b)(2) application may revise the wording of the indication to omit the first-line mantle cell lymphoma indication as long as the application can be approved as safe and effective for the conditions of use described in its labeling with that information omitted.

In this situation, FDA may omit the first-line mantle cell lymphoma indication. However, because of the way the indication is currently worded, the only way to omit the protected indication is to add words. FDA could have approached the labeling for Velcade differently. As described above, when the indication for "treatment of patients with mantle cell lymphoma who have not received at least one prior therapy" was granted exclusivity under the Orphan Drug Act, the indications for both first- and second-line treatment of

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[84] See Velcade PI (Dec. 8, 2006), available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021602s010lbl.pdf.

[85] Assuming, *arguendo*, that the Petition is correct that only *de minimis* changes are permitted, FDA would consider the change from "treatment of patients with mantle cell lymphoma" to "treatment of patients with mantle cell lymphoma who have received at least 1 prior therapy" to be appropriate. FDA believes that changes are *de minimis* if they are minimal changes made only to carve out the protected indication. Although labeling language appropriately describing the indication not protected by exclusivity would be the same as the earlier version of Velcade's labeling, it does not "reference discontinued or superseded labeling," as the Petition argues. Petition at 8-9. Instead, that labeling language is what remains when the protected indication is carved-out.

mantle cell lymphoma were written as "treatment of patients with mantle cell lymphoma," which FDA believes to be clear and concise. We note that the mantle cell lymphoma indications could have been written as "treatment of patients with mantle cell lymphoma who have received at least one prior therapy and treatment of patients with mantle cell lymphoma who have not received at least one prior therapy." If the indications had been written as such, then omission of the words describing the protected indication would result in "treatment of patients with mantle cell lymphoma who have received at least one prior therapy" and would presumably be allowable under the Petition's "only omissions" standard. We do not believe it would be appropriate for the scope of exclusivity for Velcade to be broadened due to the writing of labeling in a clear and concise manner. Further, we think this is consistent with our past practice.[86] FDA does not believe there is a need to solicit public comment on this change in labeling.

2. *The Omission of the First-Line Indication for Mantle Cell Lymphoma Would Not Render Bortezomib Drug Products Less Safe or Effective for Second-Line Mantle Cell Lymphoma Treatment.*

FDA disagrees with the Petition's assertion that omitting the first-line indication would render bortezomib ANDAs less safe or effective for the remaining mantle cell lymphoma non-protected conditions of use or that a 505(b)(2) application could not be approved with the omitted information. Omitting protected information about first-line treatment would not require removing the information needed to use bortezomib drug products safely and effectively as a second-line therapy for mantle cell lymphoma. Key information, such as the dosing regimen, schedule, dose modifications, adverse events, and toxicity information for relapsed patients, would remain in product labeling following a carve out of protected first-line information.

The Petition asserts that "[l]abeling stating that mantle cell lymphoma patients need to have failed on a prior therapy establishes a medically unnecessary condition on use of the drug that would be unsafe and misleading."[87] According to the Petition, "a product that the omits first-line treatment information would instruct mantle cell lymphoma patients to unnecessarily delay initiation of bortezomib therapy."[88] FDA disagrees that a product that omits the first-line treatment information instructs mantle cell lymphoma patients to unnecessarily delay initiation of bortezomib therapy. FDA would not expect patients to delay initiation of bortezomib therapy because the labeling for bortezomib ANDA and 505(b)(2) drug products omits information about first-line treatment of mantle cell lymphoma. Instead, the omission of such information would protect Velcade's exclusivity. Velcade will continue to be approved for and labeled with information on first-line treatment of mantle cell lymphoma, and health care practitioners will continue to be able to prescribe it for this use.

The Petition asserts that FDA's response to a citizen petition involving Rapamune (sirolimus) is instructive.[89] Rapamune was approved as an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients receiving renal transplants. However, Rapamune and cyclosporine were found to be associated with increased renal function impairment. Based on the results of an adequate and well-controlled clinical trial, the labeling for Rapamune was revised to add information about cyclosporine

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[86] Although the Petition claims that FDA's precedent makes clear that the agency will permit only omissions and minor attendant changes, it does not cite any specific examples that would require a result contrary from what is described here.
[87] Petition at 9-10.
[88] Id. at 9.
[89] Id. at 10, 15; Letter to Michael S. Labson and Elizabeth M. Walsh, Covington & Burling, from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research (Sept. 20, 2004), Docket No. 2003P-0518/CP1. (Rapamune Response Letter).

withdrawal procedures in patients at low to moderate risk for rejection. Those changes received 3 years of exclusivity protection under section 505(c)(3)(D)(iv) of the FD&C Act.[90]

Rapamune's sponsor submitted a citizen petition in 2003 requesting that FDA refrain from approving an ANDA for sirolimus with labeling that omitted the protected cyclosporine withdrawal information. In granting the Rapamune Petition, we determined that the protected information in the labeling was necessary for safe use, even in the remaining unprotected population (i.e., patients at high risk of immune system reactions) because high-risk patients may be reclassified as low-to-moderate risk and could benefit from information regarding the cyclosporine-sparing regimen.[91] Here, by contrast, the Agency has concluded that the protected first-line information in Velcade's labeling is not necessary for the safe and effective use of bortezomib for second-line treatment of mantle cell lymphoma. Accordingly, the changes in the labeling to remove references to the orphan drug exclusivity-protected first-line treatment indication does not render the drug product with this labeling less safe or effective for the second-line treatment indication of mantle cell lymphoma.[92]

C. Bortezomib is Properly Identified as the Active Ingredient in Velcade.

The Petition requests that FDA identify the active ingredient in Velcade as the mannitol ester of bortezomib.[93] Since Velcade's approval, FDA has identified the drug's active ingredient as bortezomib, a monomeric boric acid. Millennium has identified Velcade's active ingredient as bortezomib in its product labeling. The Petition, however, contends that "the mannitol in VELCADE's formulation forms a bortezomib mannitol ester in Velcade's lyophilized state, which is how the ingredient exists in the finished drug product."[94] The Petition asserts that "VELCADE is a lyophilized product that needs to be reconstituted prior to administration," and bortezomib "exists only after VELCADE is reconstituted into a solution."[95] The Petition also asserts that, under FDA's regulatory framework, "the active ingredient must be identified in the form it exists in the lyophilized powder and not the reconstituted solution."[96] The Petition further asserts that the "mannitol ester is important to" the performance of Velcade.[97]

FDA disagrees with the Petition that the active ingredient in Velcade is the mannitol ester of bortezomib. The Petition's arguments to support its assertions regarding the designation of the mannitol ester of bortezomib as the active ingredient are unpersuasive and unsupported by the data. As stated above, prior to filing the Petition, Millennium itself identified bortezomib as the drug substance in Velcade and mannitol as an inactive ingredient. For example, per Velcade's labeling, bortezomib is listed as the active ingredient, and Velcade's established name and dosing also include bortezomib and not the mannitol ester of bortezomib. Mannitol is listed as an inactive ingredient in Velcade's labeling. Additionally, mannitol is commonly used in lyophilization processes because it often produces a satisfactory solid that is stable and reconstitutes readily. Further, the Petition has not provided evidence that, during in-process, release, and

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[90] Rapamune Response Letter. at 1-2. Subsequent to the grant of exclusivity to Rapamune, subparagraph (D) of section 505(c)(3) of the FD&C Act was redesignated as subparagraph (E) by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Thus, the relevant exclusivity provision is now located at section 505(c)(3)(E)(iv) of the FD&C Act.

[91] Id.

[92] We also note that, as described above, the Agency has concluded that the protected multiple myeloma indication information in Velcade's labeling is not necessary for the safe and effective use of bortezomib for the remaining multiple myeloma conditions of use. Thus, the Rapamune Response Letter is similarly not instructive with respect to the omission of protected information about retreatment of multiple myeloma patients.

[93] Petition at 16.

[94] Id.

[95] Id. at 16-17.

[96] Id. at 17.

[97] Id. at 19.

stability testing of the drug product, Millennium controls for and specifies the amount of the mannitol ester of bortezomib, as would be necessary if the mannitol ester of bortezomib were the active ingredient in Velcade. We note that postapproval changes must be made in accordance with section 506A of the FD&C Act and 21 CFR 314.70. Accordingly, if Millennium wishes to identify the active ingredient as the mannitol ester of bortezomib, then Millennium would need to seek approval of a supplement to its NDA. This supplement would need to provide chemistry, manufacturing, and controls data and information to show that Millennium controls for the amount, content uniformity, purity, and stability during in-process, release, and stability testing, among other things (e.g., labeling updated to reflect active ingredient change in name and in dosing).

D. FDA Disagrees With the Petition's Arguments Regarding the Use of Boric Acid and Glycine in Fresenius's Bortezomib Drug Product.

According to the Petition, Fresenius has submitted a 505(b)(2) application for a bortezomib drug product that, unlike Velcade, contains boric acid and glycine.[98] The Petition states that the use of boric acid and glycine raises a number of concerns regarding the safety and efficacy of Fresenius's proposed product.[99] The Petition further states that Fresenius may not "rely solely – and perhaps not even substantially – on FDA's 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."[100] Instead, the Petition asserts that Fresenius must conduct preclinical testing, human bioequivalence testing, and possibly additional human clinical studies to demonstrate the safety and efficacy of its proposed product.[101] Further, the Petition asserts that Fresenius's proposed product would expose patients to levels of boron that exceed the permitted daily exposure (PDE).[102]

1. In Determining the Safety of a Bortezomib Drug Product That Contains Boric Acid and Whether Additional Testing Would Be Necessary, the Agency Considers Many Factors, Including Previous Experience With Other Products Containing Boric Acid.

In determining whether the Fresenius proposed product presented safety concerns related to the inclusion of boric acid and whether additional testing would be necessary, FDA considered many factors, including the toxicological evidence in the published literature, the PDE for boron (described more fully in section D.2), and prior experience with boric acid in approved drug products, including those with intravenous administration. After a thorough examination of all these factors, FDA has concluded that additional studies of the toxic effects of boric acid are not deemed necessary given the levels of boric acid in the Fresenius product and likely boric acid exposures to patients.

In particular, FDA considered a number of publications. For example, the Agency for Toxic Substances and Disease Registry (ATSDR), published by the Public Health Service of the U.S. Department of Health and Human Services in November 2010, describes the toxicological profile of boron. The ATSDR "succinctly characterizes the toxicologic and adverse health effects information," which "identifies and

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[98] Id.

[99] Id. at 20. Fresenius's bortezomib for injection is approved for intravenous use only. Consequently, this response does not address the Petition's arguments related to the subcutaneous route of administration of Fresenius's product.

[100] Id. at 21.

[101] Id. at 24.

[102] Id. at 22.

reviews the key literature that describes a substance's toxicologic properties."[103] Also, the U.S. Environmental Protection Agency published an integrated risk information system chemical assessment summary for boron and compounds titled the "Toxicological Review of Boron and Compounds" in June of 2004.[104] The purpose of the review was "to provide scientific support and rationale for the hazard and dose-response assessment . . . [pertaining to] chronic exposure to boron and compounds."[105] In addition, the European Medicines Agency published a background review for the excipient boric acid in September 2017.

FDA also considered experience with other approved drug products that contain boric acid as an excipient. As we have stated in the guidance for industry on *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*:

> The Centers recognize that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined in this guidance. For example, the Centers will continue to consider factors such as use in previously approved products or GRAS status as a direct food additive. Under some circumstances (e.g., similar route of administration, level of exposure, patient population, and duration of exposure) experience associated with the prior use may adequately qualify an excipient.[106]

With respect to the human exposure to boric acid, there are a number of FDA-approved drug products administered through various routes, including intravenous administration, that are relevant to determining the safety of the Fresenius bortezomib drug product. In this case, FDA determined that toxicities associated with systemic boric acid exposures resulting from routes of administration other than the intravenous route can be informative of toxicities occurring with exposures via the intravenous route.[107] As reflected in the Inactive Ingredient Database,[108] FDA has had experience with numerous other drug

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[103] Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service, U.S. Department of Health and Human Services. Toxicological Profile for Boron. (November 2010) (https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=453&tid=80).

[104] U.S. Environmental Protection Agency, Toxicological Review of Boron and Compounds (June 2004), available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0410tr.pdf.

[105] Id.

[106] Guidance for Industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (May 2005), at 2. FDA's guidances for industry are available on the FDA Drugs guidance web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page.

[107] See Guidance for Industry and Review Staff: *Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route* (Oct. 2015), at 3 ("All routes of administration can result in systemic exposure."); Guideline for Industry: *Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies* (Mar. 1995), at 4 ("The quantification of systemic exposure provides an assessment of the burden on the test species and assists in the interpretation of similarities and differences in toxicity across species, dose groups and sexes. The exposure might be represented by plasma (serum or blood) concentrations or the AUC's of parent compound and/or metabolite(s)."). The intravenous route of administration is directly into the circulation and results in systemic exposure. Other routes of administration of (and exposure to) boric acid, such as topical, ophthalmic, and oral, may also result in systemic exposure. Consequently, toxicities associated with systemic boric acid exposures resulting from routes of administration other than intravenous can be informative of toxicities occurring with exposure through the intravenous route.

[108] See Inactive Ingredient Search for Approved Drug Products, available at https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. The Petition (at 28) states that "it would be inappropriate for FDA to rely on any 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." Applicants submitting all

products containing boric acid, including those administered by otic, ophthalmic, oral, and topical routes. In addition, as the Petition notes, boric acid is used in approved drug products administered intravenously, including in NDA 203923 (sodium thiosulfate injection solution) and in NDA 20166 (sodium thiosulfate injection solution).[109] FDA may consider its experience with boric acid in these formulations, alongside any additional information to support the use of boric acid as an inactive ingredient, in its review of marketing applications for bortezomib drug products intended for intravenous administration.

According to the Petition, Fresenius must conduct additional studies because the boric acid used in its formulation "is not qualified by existing safety data with respect to the proposed routes of administration."[110] The Petition also states that "Fresenius must conduct . . . toxicity studies to establish the safety of boric acid for long-term use by injection because bortezomib is dosed in lengthy treatment cycles . . . ."[111] Further, the Petition states that "FDA must require Fresenius to conduct additional human clinical testing to establish the safety of its product if there are any unresolved risks" following the testing the Petition has proposed.

FDA, however, disagrees with the Petition regarding the need for additional testing. As described above, toxicities associated with boric acid have been examined in published literature, and reviewed extensively by United States government agencies, as well as scientific and regulatory bodies outside the United States.[112] And as discussed in greater detail below, the relatively low amount of boric acid included in Fresenius's bortezomib drug product does not present safety concerns.[113] Consequently, additional studies to examine the toxic effects of boric acid are not deemed necessary.

2. FDA Disagrees with the Petition's Argument that Fresenius's Bortezomib Drug Product Includes an Unsafe Amount of Boric Acid.

The Petition raises concerns that the amount of boric acid in Fresenius's proposed bortezomib drug product exceeds the PDE. The Petition states that the PDE "is the maximum acceptable intake per day of residual solvent in a pharmaceutical product, and it is commonly used to evaluate toxicity."[114] The Petition further states, "[t]he U.S. Environmental Protection Agency (EPA) considers boric acid to be moderately acutely toxic due to acute effects, including dermal toxicity and skin irritation."[115] According to the Petition,

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types of applications (505(b)(1) NDAs, 505(b)(2) NDAs, and ANDAs) have long pointed to information made publicly available by FDA through the Inactive Ingredient Database (IID) without reference to a particular drug product or application number. In fact, the publicly available IID does not provide drug product names or application numbers associated with any particular inactive ingredient listing. A single line listing may represent the level of the excipient in multiple products. This is reflected by the fact that the IID refers to the maximum potency as a "dynamic value" that changes when FDA approves products with new, higher levels of the excipients. Thus, with respect to the IID, an applicant is not expected to nor could it cite reliance on any one specific drug included in the IID.

[109] Petition at 21.

[110] Id. at 25.

[111] Id.

[112] See, e.g., European Medicines Agency, *Background review for the excipient boric acid* (July 2015), available at http://www.ema.europa.eu/docs/en_GB/document_library/Report/2015/08/WC500191476.pdf; Agency for Toxic Substances & Disease Registry, *Toxicological Profile for Boron* (Nov. 2010), available at https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=453&tid=80; U.S. Environmental Protection Agency, *Toxicological Review of Boron and Compounds* (June 2004), available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0410tr.pdf.

[113] See, e.g., European Medicines Agency. Boric acid and borate used as excipients. (September 10, 2017) (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001674.jsp&mid=); World Health Organization. Boron in drinking-water. (2009).

[114] Petition at 27.

[115] Id. at 22.

"Fresenius has stated that its formulation contains boric acid in excess of 15:1 relative to bortezomib."[116] The Petition asserts that Fresenius's proposed bortezomib drug product would seem to exceed the PDE, using calculations based on information from EPA and guidance from the International Conference on Harmonisation.[117]

However, we disagree with the Petition's calculations regarding the boric acid in Fresenius's proposed bortezomib drug product. The Petition has incorrectly presumed that the 15:1 ratio described by Fresenius is in mass units. Instead, the ratio of 15:1 refers to a molar ratio. The Fresenius product contains 3.5 mg/vial of bortezomib and 10.5 mg/vial of boric acid. The ratio of boric acid-to-bortezomib in Fresenius's bortezomib for injection is 3:1 weight to weight. Therefore, the Petition's calculations regarding boron exposure are in error by a factor of five. Using the correct value for boric acid in Fresenius's proposed product and using Millennium's approach to calculating PDE, the boric acid level in Fresenius's proposed bortezomib drug product falls below the PDE for boron cited by Millennium. Thus, based on Millennium's assertion that PDE "is the maximum acceptable intake per day of residual solvent in a pharmaceutical product, and it is commonly used to evaluate toxicity,"[118] the amount of boron in Fresenius's proposed drug product does not pose a significant and unnecessary safety risk.

3. Fresenius is Not Required to Conduct In Vivo Bioequivalence Testing at Multiple Doses to Support its 505(b)(2) Application.

The Petition states that Fresenius must conduct in vivo human bioequivalence testing to support its reliance on the Agency's finding of safety and effectiveness of Velcade (i.e., to establish a bridge between Fresenius's product and Velcade).[119] According to the Petition, "[*i*]*n 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."[120] It also states that such testing "will provide important information regarding the safety of Fresenius's formulation."[121] The Petition further contends that Fresenius must conduct in vivo bioequivalence testing at multiple doses in light of bortezomib's "time-dependent kinetics" and complex dosing cycles.[122] The Petition asserts that FDA should not grant a waiver of in vivo bioequivalence testing under 21 CFR 320.22 because Fresenius's product "does not contain the same ingredients as Velcade" and "there is very little FDA and patient experience to support a bioequivalence waiver."[123]

FDA, however, disagrees with the Petition's assertion that in vivo human bioequivalence data from multiple dose testing are required to demonstrate a bridge between Fresenius's product and Velcade. Bridging studies may take a variety of forms depending on the particular facts of each 505(b)(2) application, and are not necessarily limited to in vivo bioavailability/bioequivalence studies.[124] Fresenius submitted evidence to demonstrate that the physiological disposition of the proposed drug product does not differ from that of Velcade. In addition, Fresenius submitted comparative osmolarity data for its proposed product and Velcade. The Agency requested additional evidence to demonstrate that the removal of mannitol and the inclusion of glycine did not have an effect on the physiological disposition of the proposed product. In response, Fresenius conducted an in vitro study to compare the proteasome inhibition activity of its product and Velcade because of the clinical relevance of proteasome inhibition of bortezomib. The study suggested

[116] Id. at 20.
[117] Id.
[118] Id. at 20.
[119] Id. at 25-26.
[120] Id. at 26.
[121] Id.
[122] Id. at 26-27.
[123] Id. at 27; see also 21 CFR 320.22(b)(1)(i), (e).
[124] See 21 CFR 314.54(a); 320.22; 320.24(b)(6).

that the in vitro proteasome inhibitory activity of Fresenius's product and Velcade are comparable. In other words, the study indicated that the excipients used in Fresenius's bortezomib for injection and in Velcade did not contribute to the pharmacological activity of the drugs. Based on the evidence submitted, FDA determined, consistent with 21 CFR 320.24(b)(6), that Fresenius established comparable bioavailability between its product and Velcade. Therefore, Fresenius established an appropriate bridge between its proposed bortezomib drug product and Velcade.

4. The Use of Glycine as an Excipient in Fresenius's Bortezomib Drug Product Does Not Present Concerns Regarding Safety or Efficacy.

The Petition also suggests that the use of glycine in Fresenius's bortezomib for injection "raises safety and efficacy issues."[125] The Petition, however, offers little explanation of the issues that may arise due to the inclusion of glycine. It merely states:

> Fresenius's own patent indicates that boric acid may react with bortezomib to form anhydride structures. The glycine in Fresenius's formulation also may interact with these structures.[126]

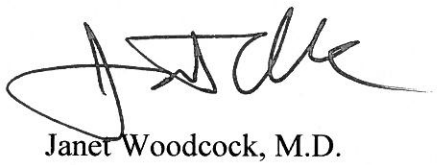
The Petition does not clarify the nature of glycine's alleged effect on safety or efficacy or further elaborate on its assertion.

We have examined the use of glycine in Fresenius's bortezomib drug product and determined that its inclusion does not present concerns. Glycine is an amino acid made by the human body (i.e., biosynthesized). It is considered a conditionally essential amino acid, meaning that, under some circumstances, it must be obtained from the diet even though the human body is capable of synthesizing it. The amount of glycine that Fresenius's bortezomib drug product contains is negligible compared to the approximately 3 grams of glycine that is biosynthesized in humans per day. The Petition has not identified, nor have we found, issues regarding the safety and efficacy of Fresenius's bortezomib drug product caused by the relatively small amount of glycine included in the formulation.

III. CONCLUSION

For the reasons discussed above, your Petition is denied.

Sincerely,



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

[125] Petition at 19.
[126] Id. at 19-20 (internal citations omitted).