

# Failure to Launch: Why Some Generics Don't Take



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Prescription drug affordability is a growing health policy concern. In 2019, pharmaceutical spending accounted for an estimated 12.6% of overall health spending in the United States.<sup>1</sup> The annual rise in US pharmaceutical costs consistently outpaces the consumer price index. In this context, much attention has been devoted to various strategies to mitigate or reign in pharmaceutical expenditures.<sup>2</sup> Newer prescription drugs are inherently immune to free market competition on price owing to lengthy patent protections, which pose a considerable barrier to the entry of competitors.<sup>3</sup> Although this legislative monopoly protection fosters innovation, when unduly prolonged it has a detrimental effect, leading to high unchecked prices. One strategy to bring prescription drugs in alignment with conventional free market principles is to encourage the entry of generics and biosimilars. These often compete with the original innovator compound on price.

The proteasome inhibitor Velcade (bortezomib) is a frequently used therapy in the treatment of several hematologic malignancies including multiple myeloma (MM) and mantle cell lymphoma (MCL). In 2019, annual spending by Medicare Part B for bortezomib was in excess of \$407 million with an average spending per beneficiary of \$20,800.<sup>4</sup> In 2018, a comparator form of bortezomib by Fresenius Kabi was approved by the Food and Drug Administration (FDA), with the current average sales price (ASP) approximately one-third lower than the reference product.<sup>4,5</sup> A second comparator of bortezomib manufactured by Dr. Reddy's Laboratories was introduced in 2019.<sup>6</sup> Despite the presence of more affordable alternatives, most patients continue to receive Velcade. Using Velcade as a test case, here

we highlight the challenges in regulatory considerations, limitations of recent legislation, and potential opportunities for tackling rising drug prices.

## BRIEF BACKGROUND

Velcade (bortezomib) was first approved as an intravenous (IV) injection by the FDA in 2003 for the treatment of MM in the relapsed or refractory setting.<sup>7</sup> In 2008, it won approval as treatment in the frontline setting for newly diagnosed MM. A subcutaneous (SQ) form of Velcade subsequently received approval in 2012 and has since increasingly become the standard default in many treatment regimens owing to patient convenience and lower rates of peripheral neuropathy in comparison with the IV formulation.<sup>7,8</sup>

In addition to use in MM and MCL, the National Comprehensive Cancer Network guidelines support bortezomib therapy for a wide variety of indications (with a category 1 or 2A recommendation) and many large insurers, such as Aetna, support its compendial use for acute lymphoblastic leukemia (ALL), adult T-cell leukemia/lymphoma, Kaposi sarcoma, multicentric Castlemans disease, pediatric ALL, pediatric Hodgkin lymphoma, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome, systemic light chain amyloidosis, and Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma.<sup>7,9-19</sup>

Velcade, in combination with lenalidomide (Revlimid) and dexamethasone, is a common induction treatment regimen for patients with newly diagnosed MM, with patients traditionally receiving 4 to 8 cycles of therapy before either proceeding to high-dose chemotherapy with autologous stem



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cell rescue/transplantation or transitioning to maintenance therapy.<sup>20</sup> For individuals with higher risk MM, Velcade can be used as maintenance therapy, either alone or in conjunction with lenalidomide, after transplantation with planned treatment until disease progression or unacceptable toxicity.<sup>20</sup> Many patients receiving Velcade, Revlimid, and dexamethasone will receive Velcade either once or twice weekly. With a 2021 average wholesale price of \$1923.60 per 3.5 mg vial, treatment costs can be substantial.

In November 2017, the first comparator form of bortezomib (made by the manufacturer Fresenius Kabi) received FDA approval.<sup>5</sup> In October 2019, Dr. Reddy's Laboratories also received regulatory approval for their bortezomib product.<sup>6</sup> Because these bortezomib alternatives were approved via a 505(b)(2) new drug application (NDA), they are not considered a "classic" generic product. As a result, there are some subtle and not so subtle differences in the products and how/when they can be used. For example, Velcade is approved as a first-line agent in MCL but bortezomib is approved only in the second-line setting. Velcade can be administered by either IV or SQ routes, but bortezomib can only be administered IV. The significance of these differences in route of administration will be expanded on in a later section. Lastly, there are some changes in product formulation and inactive ingredients, with Velcade containing mannitol, bortezomib Fresenius Kabi containing glycine, and bortezomib Dr. Reddy's containing citric acid and tromethamine.<sup>5,6</sup>

### REGULATORY CONSIDERATIONS

There are 3 approval pathways for NDAs and abbreviated NDAs (ANDAs): 505(b)(1) NDA, 505(j) ANDA, and 505(b)(2) NDA. These refer to the parts of Section 505 of the Federal Food, Drug, and Cosmetic Act, which respectively covers the approval of innovator drugs, generic drugs, and drugs that share key similarities with approved drugs but differ in other potentially crucial ways.<sup>21</sup>

The 505(b)(2) NDA is a streamlined process in which the manufacturer applicant

relies on investigations or clinical studies conducted by someone other than the 505(b)(2) NDA applicant (typically the innovator drug manufacturer) and for which the applicant has not previously obtained right of reference. This pathway allows manufacturers to apply for approval without repeating all the drug development work done for the innovator agent. The 505(b)(2) pathway allows applicants to avoid unnecessary duplication of research for the approval of a clinically significant improvement to a drug previously vetted and approved drug by allowing the use of clinical data not developed by the 505(b)(2) NDA applicant. This approval pathway for noninnovator drugs is abbreviated by design and is meant to enable a quicker time to market.<sup>22</sup>

There are multiple reasons why it may be advantageous for a manufacturer to seek an approval via the 505(b)(2) route. Applications are allowed to use the safety and efficacy data presented in previous applications for medications approved by the FDA. Hence, the research and development costs behind these agents are considerably lower and they can be developed in a timelier manner than the originator product. These drugs also have the advantage of longitudinal self-reported safety data, with prescribers being familiar with their adverse effect profile. The length of market exclusivity also markedly favors the 505(b)(2) pathway. An ANDA, the pathway for traditional generic drug approval, allows the first generic manufacturer a 180-day market exclusivity period, after which additional generic manufacturers are allowed to come online. In contrast, the market exclusivity for a 505(b)(2) application may be as long as 7 years, with the duration dependent on whether additional clinical trials are required (3 years), whether the product constitutes a new chemical entity (5 years), or receives orphan drug status (7 years). According to the contract development company Alkami, "Drugs that are targeted for the 505(b)(2) pathway are often variations of well-understood commercial products. Since 2004, the top three reasons for 505(b)(2)

applications are new formulation or manufacturer, new dosage form, and a new combination of active ingredients.”<sup>21-23</sup>

### DELAYED ADOPTION

According to the Medicare Part B Spend and Utilization dashboard, for the calendar year 2019 there were 19,586 beneficiaries receiving Velcade, with an average spending per beneficiary of \$20,830.28 and a total spending of \$407,981,778.<sup>4</sup> In contrast, there were 831 beneficiaries receiving the alternative bortezomib products, with an average spending per beneficiary of \$8,547.39 and a total spending of \$7,102,883. These differences in spending per beneficiary are not wholly explained by differences in ASP as Velcade recipients had an average of 13.4 claims vs 8.7 claims for alternative bortezomib products. The differences in spending per claim favored the alternative bortezomib products with reported savings of \$570.10 per treatment. It is worth noting that the Medicare Part B Spend and Utilization data do not reliably capture Medicare Advantage Plan data, which encompass approximately 35% of Medicare beneficiaries.<sup>4</sup>

Despite the potential savings, why has adoption been muted? Several issues are at play. First, Medicare uses J codes to identify unique products on the market. When a generic is approved, it receives the same J code as the reference product. When products are all stacked under the same J code, reimbursement typically drive payers to the less costly generic products. The reimbursement to institutions when a generic is available is based on the average ASP across all products, both reference and generic, + 6%. This creates an incentive for the institutions to use the generic, because the ASP is calculated with all the drugs combined rather than just off the generic ASP. Because the bortezomib alternatives were approved by the 505(b)(2) NDA, they are not considered true generics. Instead, they have been assigned a unique J code and reimbursement to institutions will be based on ASP + 6% rather than the weighted average we would expect with a “classic” generic.<sup>4</sup>

Second, financial incentivization by the original drug manufacturer by discounted contract pricing may prevent adoption of alternatives. It is possible that Takeda may be discounting their contracted prices with payers or institutions to financially incentivize them to stay with Velcade. A facility will ultimately be financially better off by purchasing the product that has the highest margin (reimbursement from Part B minus the acquisition cost). Because contracted drug prices are confidential and unique to each payer, a patchwork of negotiated prices that affect uptake are plausible but details remain unclear. Third, large health centers and systems may have a more complex decision-making process involved in making changes to the formulary, which may slow down the responsiveness to take up new products. Fourth, the overall patient composition may be different between community and academic centers or between urban and rural facilities, which may influence the payer mix and the variety of coverage restrictions regarding alternative agents.

Lastly, there may be delayed adoption by prescribers despite access to alternative bortezomib products owing to perceived differences in the adverse effect profile between the SQ and IV administration routes. A phase 3 randomized controlled trial of twice weekly SQ vs IV Velcade reported no difference in outcomes; however, rates of grade 3 peripheral neuropathy were double in the IV arm.<sup>24</sup> Although twice weekly bortezomib has become less common in clinical practice, there are retrospective data suggesting similar rates of neuropathy from weekly SQ and weekly IV Velcade.<sup>8</sup>

### RECENT LEGISLATION: INFRASTRUCTURE INVESTMENT AND JOBS ACT

The rising cost of pharmaceuticals has not escaped the notice of legislators nor their constituents. The recently passed Infrastructure Investment and Jobs Act specifically targets spending related to drug waste.<sup>25</sup> Although most of the focus has been on reducing the cost of newer drugs, reducing wastage of anticancer drugs remains a

significant method to reduce the overall expenditure and health care costs.

In 2019, Medicare Part B reimbursed \$752,901,610 for discarded medications.<sup>26</sup> This represents approximately 1.9% of overall Part B spending. Velcade was a notable standout with \$114,039,382.63 in reimbursement for discarded units, which represents 26.8% of Velcade spending. This is likely a by-product of the dosing of Velcade and its 3.5 mg single-use vial. The standard dosing of twice weekly bortezomib is 1.3 mg/m<sup>2</sup>.<sup>7,26</sup> The average American male weighs 197 lb and has a height of 5'9", which translates to a body surface area (BSA) of 2.05 m<sup>2</sup>. Based on standard dosing, this would translate into approximately 24% of each vial being discarded, which approximates the Medicare Part B findings. That same adult male would need to weigh 375 lb to justify using the entire vial.

Starting in 2023, the Infrastructure Investment and Jobs Act mandates drug manufacturers to refund Medicare any waste in excess of 10%.<sup>25</sup> The justification for this 10% cutoff is unclear. Using the 10% cutoff for 2019 Medicare spending data on oncology drugs with annual reimbursement for discarded drug in excess of \$100,000, the spending on wasted drugs would still near \$168 million.<sup>26</sup> Whether this drives drug manufacturers to change the dose sizes available, adopt fixed dosing, or raise the drug price to compensate for refunds to Medicare remains to be seen. Of note, the recently signed Inflation Reduction Act caps increases in drug cost to Medicare by requiring manufacturers to start paying a rebate in 2023 if price increases exceed the inflation rate. This may result in especially dynamic price changes for the remainder of 2022 or disparate price lists for government and commercial payers.<sup>27</sup>

It is unknown whether the 26.8% in discarded Velcade translates to value of product lost. It is likely that the incremental cost of the approximately 1 mg of discarded Velcade with each administration is smaller than 26.8% quoted. The assumption that pharmaceuticals are priced as commodities, for example, 2 oz of gold is worth double the

value of 1 oz of gold, may not be valid. The fact that European countries use 1 mg vials of bortezomib does raise the question why only large-dose vials are available to US patients.<sup>28</sup> Furthermore, unused reconstituted bortezomib is stable for up to 15 days stored at 4 °C in the original manufacturer vial.<sup>29</sup>

From a global health equity standpoint, the fact that roughly a quarter of US Velcade is discarded is concerning when patients in lower resource countries lack access to effective therapies. Notably, bortezomib is included in the 2021 WHO Model List of Essential Medicines for the treatment of multiple myeloma.<sup>28</sup> It is well known that the outcomes between lower- and middle-income countries and high-income countries are disparate, with lack of access being a major issue.<sup>30,31</sup>

#### POTENTIAL OPPORTUNITIES

The subdued uptake of generics and biosimilars is well documented and not unique to cancer therapeutics.<sup>32</sup> An abbreviated version of a report commissioned by the Office of the Inspector General at the US Department of Health and Human Services notes: "In 2019, Medicare Part D spent approximately \$2.5 billion for hepatitis C drugs to treat 50,000 beneficiaries. Harvoni, Epclusa, and Mavyret accounted for 93 percent of expenditures, with annual Medicare costs ranging from \$28,000 to \$77,000 per beneficiary.<sup>4</sup> In early 2019, Gilead launched authorized generic versions of Harvoni and Epclusa with the expressed goal of reducing patients' out-of-pocket costs. The retail price of authorized generic versions was \$24,000, significantly less than the prices of Harvoni and Epclusa. However, a preliminary analysis indicates that Medicare utilization has not shifted from brand name versions of Harvoni and Epclusa to their significantly cheaper, authorized generic versions or to Mavyret."<sup>4,33</sup>

Previous publications have highlighted a myriad of culprits on the end of payers, including tier switching and delays in generic substitution. On the manufacturing end, generic parking, evergreening, product

hopping, and patent thickets may culminate in delayed adoption of less expensive alternatives. Efforts to improve adoption of alternative bortezomib products and ultimately reduce health care spending require a multi-pronged approach.

From a payer perspective, Medicare could require the adoption of more affordable therapeutic equivalents on formularies upon FDA approval. Where appropriate, Medicare could consider assigning the same J code to approvals through the 505(b)(2) pathway similar to what is done with generics and eliminate the distinction of product to avoid complexities. To incentivize biosimilar uptake in health systems, Medicare Part B reimburses the biosimilar at its own ASP but pays 6% of the ASP of the originator biologic and a similar strategy could be developed to encourage the adoption products approved through the 505(b)(2) pathway.<sup>34,35</sup>

From a prescriber standpoint, physicians may be initially reluctant to use a more affordable alternative given the ease of administration and reduced adverse effects. However, there is a growing body of literature to suggest that bortezomib-induced peripheral neuropathy is not dose dependent and usually presents early in treatment. A pilot study presented at the American Society of Hematology 2019 annual meeting reported that 11 patients were able to successfully transition from SQ to IV Velcade if they had no greater than grade 1 neuropathy after 4 cycles of therapy. This resulted in no new cases of neuropathy, and the authors concluded that global adoption of their protocol had the potential to substantially reduce drug costs related to the treatment of MM.<sup>36</sup> Where practical, this approach may allow clinicians to curtail drug costs while not placing patients at higher risk of treatment toxicity. Alternatively, the FDA approving SQ administration of the alternative bortezomib products would further alleviate the additional concerns of toxicity. It merits attention that both the Fresenius Kabi and Dr. Reddy's formulations of bortezomib are approved for SQ administration in Canada and Western Europe.<sup>37,38</sup>

## CONCLUSION

Despite these options being less costly, we highlight potential barriers to commercial uptake when generics and therapeutic alternatives come to market. This case study highlights a unique FDA approval pathway and its potential downstream consequences on prescribing patterns. Identifying and eliminating barriers to the utilization of less expensive alternatives transcend pharmaceutical spending in cancer care alone. Strong legislative attempts, redesigning of designations and reimbursement models, and clinician education may help curb the problem of unsustainable and rising health care expenditure. Ultimately, vigilance, advocacy, and a little creativity on the part of clinicians are necessary to ensure affordable and sustainable access to effective therapies.

## POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

**Abbreviations and Acronyms:** ANDA, abbreviated new drug application; ASP, average sales price; FDA, Food and Drug Administration; IV, intravenous; MCL, mantle cell lymphoma; MM, multiple myeloma; NDA, new drug application; SQ, subcutaneous

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