03 January 2020

Captain Valerie Jensen
Associate Director
Drug Shortage Staff
Food and Drug Administration
WO 22, Room 6204
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

RE: ANDA 071484 Vincristine Sulfate Injection, USP

Letter of Non-Compliance Response

Hospira Inc., a Pfizer Company ("Pfizer") is hereby providing this letter in response to the Food and Drug Administration ("FDA") Letter dated December 5, 2019, sent under Section 506C(f) of the Federal Food, Drug and Cosmetic Act (FD&C Act) concerning notification to FDA of a meaningful supply interruption of Vincristine Sulfate Injection, USP. During this shortage situation that developed very quickly based on a confluence of events, including events outside of Pfizer's control, Pfizer constructively notified the Agency and reacted expeditiously to address clinician and patient needs. Pfizer believes it met the requirements of Section 506C(f) of the FD&C Act. Pfizer now has a sufficient supply of Vincristine in all presentations available to purchases through the standard distribution chain and is working to build sufficient inventory of Vincristine so that supply is on hand to account for un-anticipated interruptions in supply.

Introduction

Pfizer is a leading manufacturer of sterile injectable pharmaceutical products with a large portfolio of medicines that are used in hospital and similar healthcare settings. Pfizer's portfolio of medicines is expansive, with the Sterile Injectable portfolio alone containing approximately 200 molecules and 700 NDCs. Most of these medicines are medically important products and are manufactured at multiple sites around the world. Many of these medicines are high volume, low margin products with complex manufacturing processes and regulatory oversight constructs. Indeed, the Agency's October 2019 report, "*Drug Shortages: Root Causes and Potential Solutions*," captures well the many challenges adversely impacting the viability of the US sterile injectable industry which, among other things, have contributed to the untenable

situation this year where Pfizer became the sole US supplier of generic Vincristine, a product first approved by FDA in 1963 and long available in generic form.[1] Nevertheless, as this response demonstrates, Pfizer is proud of our long-standing commitment to reliably supply critical life-saving therapies of the highest quality like Vincristine to the patients who need them. Indeed, Pfizer's core mission is to deliver breakthroughs that change patients' lives.

Pfizer has processes and systems in place to manage risk associated with potential interruptions in supply of our medicines, including holding inventory levels and prioritizing the manufacture of medically important drug products. Despite our best efforts and given the complexity of the sterile injectable manufacturing process, supply chain, and related market factors, we do experience meaningful interruptions in supply for medicines in our portfolio. In addition to dedicating significant efforts and resources to addressing the root cause for those interruptions in supply to minimize their duration and impact, Pfizer is committed to timely and open communication of those issues to FDA via the Drug Shortages Staff in CDER.

To that end, Pfizer maintains an ongoing program for the identification and reporting of meaningful supply interruptions to FDA. Pfizer colleagues responsible for reporting drug shortages are in close and continuous communication with those in the manufacturing, supply chain and commercial organizations to identify potential interruptions in supply. On a bi-weekly basis, Pfizer submits a product availability report to FDA Drug Shortage noting the supply status of each of Pfizer's sterile injectable medicines. The report is sortable, and notes the product name, configuration, and NDC, manufacturing plant, supply status ("available", "intermittent stock out", "depleted"), the reason for the backorder if applicable ("manufacturing delay"), estimated next date of delivery, and the estimated date of recovery. Pfizer submits this report every two weeks via email directly to FDA Drug Shortage team members.

Pfizer also regularly submits product-specific shortage notifications and follow-up information to FDA via email, holds quarterly drug shortage update meetings (recently increased to bi-weekly), and product specific emails and phone calls, as needed. Pfizer's goal, in addition to meeting the requirements of 21 U.S.C. § 356c and 21 CFR 314.81(b)(3)(iii), is timely and transparent communication of issues as they arise, providing routine updates to FDA Drug Shortage Staff until the supply issue is resolved, and partnering with FDA where possible to alleviate supply interruptions and meet patient needs.

[1] "After reviewing the FDA analysis, published research studies, and stakeholder input, the [FDA] Task Force identified three major root causes: Root Cause1: Lack of Incentives to Produce less Profitable Drugs; Root Cause 2: Market Does Not Recognize and Reward Manufacturers for Mature Quality Management Systems; Root Cause 3: Logistical and Regulatory Challenges Make It Difficult for the Market to Recover After a Disruption." Drug Shortages: Root Causes and Potential Solutions 2019, Executive Summary, Federal Drug Shortage Task Force, chaired by the U.S. Food and Drug Administration (FDA) (October 29, 2019), http://www.fda.gov/medium/131130/download.

Regulatory Background

NDA and ANDA applicants are required to notify FDA in writing of a permanent discontinuance of manufacture or an interruption in manufacturing of a covered drug product[2] if it is likely to lead to a meaningful interruption in supply of that product.[3] The notification must be submitted to FDA electronically in a format that FDA can process, review and archive at least 6 months prior to the date of a permanent discontinuance or interruption in manufacturing, or if not possible because it was not reasonably anticipated, as soon as practicable, but no later than 5 business days after the discontinuance or interruption occurs.[4] Notification must include the following details:

- The name of the drug subject to the notification, including the NDC;
- The name of the applicant;
- Whether the notification relates to a permanent discontinuance of the drug or an interruption in manufacturing of the drug;
- A description of the reason for the permanent discontinuance or interruption in manufacturing; and
- The estimated duration of the interruption in manufacturing.[5]

In addition, FDA directs companies to "email drugshortages@fda.hhs.gov to report any potential or actual shortage issues."[6]FDA's website also notes that "[s]hortage notifications and updates may be reported to FDA at drugshortages@fda.hhs.gov.[7]

Beyond the information summarized above, FDA has not published regulations or guidance on how or when in the lifecycle of a rapidly evolving supply event it expects to receive drug shortage notifications.

Chronology of Vincristine Supply Interruption and Notifications to FDA

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[2] A product is "covered" if it is "life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and [t]he drug product is not a radiopharmaceutical drug product". 21 CFR 314.81(b)(3)(iii)(a)(1)-(2).

[3] 21 CFR 314.81(b)(3)(iii)(a).

[4] 21 CFR 314.81(b)(3)(iii)(b)(1)-(2).

[5] 21 CFR 314.81(b)(3)(iii)(c)(1)-(5).

[6] U.S. Food and Drug Administration (2019). How to Report a Shortage or Supply Issue. [online] Available at: https://www.fda.gov/drugs/drug-shortages/how-report-shortage-or-supply-issue [Accessed 17 Dec. 2019].

[7] U.S. Food and Drug Administration. (2019). Drug Shortages. [online] Available at: https://www.fda.gov/drugs/drug-safety-and-availability/drug-shortages [Accessed 17 Dec. 2019].

Vincristine Sulfate Injection, USP ("Vincristine") is indicated in acute leukemia. Vincristine sulfate injection has also been shown to be useful in combination with other oncolytic agents in Hodgkin's disease, non–Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor. Vincristine is a critical therapy in the treatment of cancer and is often used in the treatment of childhood cancers. Pfizer is committed to the manufacture of this medicine and to reliably supplying it to patients who need it. Pfizer recognizes the impact on clinicians and patients related to the temporary interruption in supply of Vincristine in the fall of 2019.

The interruption in Pfizer's supply of Vincristine began in September 2019 and Pfizer began providing the market with additional supply in mid-October. While the supply interruption was ongoing, Pfizer reacted quickly to address the supply interruption by expediting manufacturing deliveries and allocating[8] product to ensure practitioners received needed shipments. Our supply continuity team implemented an emergency process with a toll-free call line to help practitioners find and obtain product and instituted express direct shipments to ensure patient access to this critical medicine. While the interruption was addressed by Pfizer very quickly, Pfizer recognizes the impact shortages, particularly for products indicated in the treatment of cancer, have on patients, caregivers, and healthcare practitioners. Pfizer will continue to investigate the causes for the interruption to help improve operations, reduce the risk of a similar interruptions in the future, and further improve reporting of meaningful interruptions in supply.

In summary, the availability of Vincristine to patients in the US was impacted very suddenly in September 2019 following a rapid convergence of several complicated, and in our view, related factors (listed in order of occurrence):

- FDA's posting on July 5, 2019 on the FDA's drug shortage website of another company's decision to discontinue supply of Vincristine;
- FDA's posting on July 23, 2019 of the shortage of Vinblastine Sulfate Injection, USP, a medicine that may be used in patient populations that overlap with Vincristine, on its drug shortage website;
- A near doubling in demand for Vincristine from the historic (b) (4) units shipped per month to more than (b) (4) units shipped in August 2019, which we believe included some hoarding in the market; and,
- A brief delay in release of several oncology medicines, including Vincristine, from our manufacturing facility in Melbourne, Australia in September 2019.

Until July of 2019, Vincristine was commercialized in the US market by Pfizer and another manufacturer. Pfizer's market share for Vincristine in the U.S. market averaged approximately (b) (4)% in 2018, and increased to approximately (b) (4)% in June of 2019, before the other manufacturer ceased supply of Vincristine for the US Market. The supply demand for Vincristine then shifted very quickly in August of 2019. Historically, Pfizer shipped

[8] Allocation includes review of each order as compared to corresponding patient need, and is designed to get products to those who need it while limiting the ability of certain buyers to hoard product or buy more than is needed.

approximately (b) (4) units for Vincristine per month. In August of 2019, however, demand for the product spiked and more than (b) (4) units were shipped for the month. This spike could not have been reasonably anticipated by Pfizer.

At roughly the same time that the other manufacturer of Vincristine left the market, a shortage of Vinblastine Sulfate Injection ("Vinblastine")[9] was posted on FDA's drug shortages website on July 23, 2019. It is our understanding that both Vinblastine and Vincristine are frequently used in combination chemotherapy for their respective indications. The common disease state where both are used is in Hodgkin's Lymphoma, and although Vincristine is not a direct therapeutic substitute for Vinblastine, we have received feedback that Vincristine was being used in certain treatment regimens in place of Vinblastine, due to the shortage of Vinblastine.

It is Pfizer's view that the more than doubling of demand for Vincristine that occurred in August may have been the result of the only other manufacturer of Vincristine posting a notice of discontinuation of manufacturing for the product on FDA's Drug Shortages website on July 5, 2019 and the Vinblastine shortage occurring at the same time, shifting some demand to Vincristine. These developments and considering Pfizer had become the sole supplier for Vincristine, caused what Pfizer believes to be hoarding of product by institutions in the US market that became concerned about their ability to obtain product in the future. While Pfizer previously held the majority of market share for Vincristine prior to the other manufacturer's discontinuation, market intelligence suggests that health care providers panicked at this discontinuation notice, prompting an increase in orders for Vincristine in August 2019. This, in addition to the shortage of Vinblastine, we believe accounts for why orders spiked from a monthly average of (b) (4) units in 2019, to more than (b) (4) units in August.

Given the stock we had on hand at the time Pfizer believed that there would have been enough supply in our inventory to meet demand notwithstanding the manufacturing delay (discussed below), had this unforeseen more than doubling of demand not occurred. Moreover, Pfizer was not aware that it had become the sole supplier for the medicine until the notice of discontinuation was posted on FDA's website. Accordingly, it was not reasonably clear at the time, nor could Pfizer have reasonably anticipated these background market factors or the impact they would have when manufacturing delays arose in September. Pfizer was fulfilling orders, but it was not reasonably clear at this point that there would be a meaningful interruption in supply.

[9] Vinblastine is indicated for frequently responsive malignancies: generalized Hodgkin's disease (Stages III and IV, Ann Arbor modification of Rye staging system), lymphocytic lymphoma (nodular and diffuse, poorly and well differentiated), histiocytic lymphoma, mycosis fungoides (advanced stages), advanced carcinoma of the testis, Kaposi's sarcoma, Letterer-Siwe disease histiocytosis X); Less frequently responsive malignancies: choriocarcinoma resistant to other chemotherapeutic agents, carcinoma of the breast, unresponsive to appropriate endocrine surgery and hormonal therapy.

On September 5, 2019, Pfizer's manufacturing facility in Melbourne, Australia[10] opened a quality investigation following a quality test on a different product manufactured at the facility that did not meet specifications. Out of an abundance of caution and to allow a robust quality assessment, the Melbourne site placed all oncology medicines, including Vincristine, within the site's control on hold, pausing release of the medicines to the market, and resulting in a manufacturing delay. The Melbourne site opened a quality investigation into the OOS result on September 5, 2019, and submitted a timely initial Field Alert Report[11] to FDA on September 10, 2019 noting in relevant part, the following:

> "Due to a quality investigation initiated at the Pfizer manufacturing plant, Hospira Australia Pty Ltd, located at 1-5, 7-23, 25-39 Lexia Place, Mulgrave, Victoria, Australia, all oncology products within the manufacturing site's control that are potentially impacted by this investigation have been placed on site release hold. The recommencement of product release is estimated by mid October 2019"[12]

On September 18, 2019, Pfizer notified FDA's Drug Shortage Staff via email[13] of an open investigation at the Melbourne, Australia site that would impact release of oncology products. On September 25, 2019, Pfizer submitted to FDA Drug Shortage Staff personnel its bi-weekly Sterile Injectable Portfolio Availability Report[14], which reflected the supply status for Vincristine as of September 23, 2019. As discussed above in the section titled "*Introduction*", Pfizer provides this report to the Drug Shortage Staff to maintain open and transparent communication on Pfizer's large portfolio of critical products. In relevant part, the September 23 report noted the following:

- Vincristine Sulfate Injection, USP 1 mg/mL Vial (NDC 61703-0309-06) was listed as "Depleted" with "Next Delivery" and "Estimated Recovery" of September 2019, and attributed the issue to a manufacturing delay.
- Vincristine Sulfate Injection, USP 2 mg/2 mL (1 mg/mL) Vial (NDC 61703-0309-16) was listed in "Limited Supply" with "Next Delivery" and "Estimated Recovery" in September 2019 and attributed the issue to a manufacturing delay.
- Vincristine Sulfate Injection, USP 1mg/mL Single Dose Onco-Tain Glass Fliptop Novaplus® (NDC)51703-0309-26 was listed in "limited supply-short dated product" with the Next Delivery and Estimated Recovery in October 2019 and attributed the issue to a manufacturing delay.
- Vincristine Sulfate Injection, USP (Preservative-Free) 2mg/2mL Single Dose Onco-Tain Fliptop Vial Novaplus® (NDC61703-0309-25) was listed as "available".

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[10] Pfizer manufactures Vincristine and three other sterile injectable oncology medicines at its Melbourne, Australia facility.

[11] Field Alert Reports are required by 21 CFR 314.81(b)(1) for certain potential quality matters.

[12] See Attachment 1

[13] See Attachment 2

[14] See Attachment 3

On October 3, 2019, FDA Drug Shortage notified Pfizer that they received an inquiry on supply availability of Vincristine. Pfizer communicated that the inventory had since stocked out.

On October 7, 2019, Pfizer submitted its next routine Sterile Injectable Portfolio Availability Report to FDA Drug Shortage via email[15]. The October 7 report included the following entries for Vincristine:

- Vincristine Sulfate Injection, USP 1 mg/mL Vial (NDC 61703-0309-06) was listed as "Depleted" with Next Delivery and Estimated Recovery in December 2019.
- Vincristine Sulfate Injection, USP 2 mg/2 mL (1 mg/mL) Vial (NDC 61703-0309-16) was listed as "Depleted" with "Next Delivery" and "Estimated Recovery" in October 2019.
- Vincristine Sulfate Injection, USP (Preservativ-Free) 2mg/2mL (1mg/mL) Single Dose ONCO-TAIN™ Glass Fliptop Vial Novaplus® (NDC 61703-0309-25) was listed as "Intermittent Stock Out" with "Next Delivery" and "Estimated Recovery" in December 2019.
- Vincristine Sulfate Injection, USP 1 mg/mL Single Dose ONCO-TAIN™ Glass Fliptop Vial Novaplus® (NDC 61703-0309-26) was listed as "Supply Available".

In the time between the September 5 pause in product release at the manufacturing site, the email sent to FDA on September 18 notifying the Drug Shortage Staff of a product release pause at the Melbourne site for oncology products, and the supply reports sent to FDA on September 25 and October 7 noting supply status for Vincristine, Pfizer was working diligently to both address the underlying manufacturing issue and to understand the potential impact of this dynamic and quickly evolving supply situation. While the multi-faceted and converging factors in the marketplace and within Pfizer are better understood now, they were not clear in September when they first emerged. In that uncertainty, Pfizer made reasonable efforts to understand the impact on supply and to comply with the spirit of the shortage notification statute and regulation by providing information to FDA as it became available, though it may not have yet been complete or its impact reasonably clear.

Additionally, on October 15, 2019, Pfizer provided posting information for the FDA Drug Shortages website for Vincristine Sulfate Injection, which was posted on the website by FDA on October 16, 2019. By the time Vincristine was posted by FDA as an active drug shortage, release of product had resumed; deliveries were being expedited to the US. Product was shipped to clinicians and available for patients on October 21, 2019.

To address the interruption in supply and mitigate product "hoarding", Pfizer began allocating Vincristine and directed its Supply Continuity Team to begin following our escalation, approval and fulfillment process in place for customers who request emergency and expedited orders, worked closely with hospitals to fulfill, help place, and track orders. Customers with questions or a need were instructed to contact our Supply Continuity Team at 1-844-646-4398.

[15] See Attachment 4

Given the importance of this product to our patients, we also prioritized Vincristine manufacturing and increased our production to meet increasing demand. In addition, Pfizer has addressed requests from FDA's Drug Shortage Staff to contact healthcare providers directly to ensure direct shipment of needed product to practitioners.

Current Supply Status

Pfizer remains committed to the manufacture of this important therapy. Pfizer continues to increase production and expedite all deliveries of Vincristine to the US market. Product is also available to purchasers through the standard wholesale distribution chain. During the four month period from August – November 2019, Pfizer shipped vincristine at a rate of (b) (4)% versus the prior 12 month average. In addition to that elevated shipment level, as of December 23rd Pfizer has on-hand released inventory at our US distribution centers equivalent to approximately six months' historic average demand (as observed during the Aug 2018 – Jul 2019 period).

While the shortage has been addressed, Pfizer continues to manage customer orders in response to ongoing elevated ordering volumes. During Q1 Pfizer will further increase its vincristine inventory coverage so that sufficient supply remains on hand to account for unanticipated interruptions in supply or further market demand increases.

Corrective and Preventive Actions

Pfizer remains committed to addressing drug shortages and to communication with FDA's Drug Shortage Staff. Pfizer is in frequent communication with the Drug Shortage Staff, holds quarterly calls with FDA, including FDA CDER's Drug Shortage Staff and Office of Compliance Manufacturing Quality, submits bi-weekly Sterile Injectable Portfolio Availability Reports with the sortable status of its entire sterile injectable portfolio, and sends ad hoc product specific shortage notifications. In addition to the routine communication that already occurs, on December 1, 2019, Pfizer also began to voluntarily enter new product specific shortage notifications into the CDER NextGen Portal. Pfizer also recently initiated bi-weekly calls with the FDA Drug Shortage Staff, in addition to the quarterly meetings mentioned above to provide new shortage information and follow-ups to the Drug Shortage Staff.

Notwithstanding the communications to FDA on the on September 18, 23 and October 3, 7, Pfizer recognizes that there are opportunities to further enhance our notification process with respect to product specific notifications to enable FDA to evaluate and respond to significant new shortages rapidly and is conducting an assessment to identify enhancements. While the current program provides very frequent communications with FDA, Pfizer will continue to maintain and improve close communication between manufacturing sites, supply chain, commercial and those responsible for shortage reporting, and to increase the speed and detail of reporting of meaningful interruptions in supply to FDA.

Anticipated Guidance and Additional Opportunities to Engage

FDA noted in its recent report titled "Drug Shortages: Root Causes and Potential Solutions" that it intends to publish new draft guidance by the end of 2019 related to notification requirements

outlined in 21 U.S.C. § 356c and 21 CFR 314.81(b)(3)(iii). Pfizer welcomes this initiative and looks forward to additional guidance from FDA on how to meet the regulatory requirements in dynamic supply situations, which will help us to further improve our drug shortage reporting program. Pfizer would welcome an opportunity to discuss the challenges manufacturers face in understanding and addressing supply interruptions as they arise, providing meaningful communications to FDA, and to sharing our learnings and in-market experience with policymakers at FDA.

Conclusion

Pfizer understands the importance of Vincristine to patients and is committed to supplying this vital therapy to patients in the US. Pfizer remains dedicated to open and timely communication with the Drug Shortages Staff on emerging supply interruptions and to compliance with 21 U.S.C. § 356c and 21 CFR 314.81(b)(3)(iii). To that end, Pfizer has managed a shortage notification program that works closely with the Drug Shortages Staff to provide open and frequent communications, including regular teleconferences, bi-weekly updates on the status of our sterile injectable portfolio, and ad hoc product specific supply notifications. The interruption in supply of Vincristine that occurred in September 2019 was in our view the result of several background market forces that created a situation where, when a temporary delay in release of product from the manufacturing site occurred, Pfizer was not reasonably able to anticipate that the delay in release of product would impact supply. While Pfizer worked to address the manufacturing issue and understand the potential impact on supply, it shared with FDA the information that was readily available and reasonably understood. Pfizer reacted expeditiously to address clinician and patient needs, and now has supply of Vincristine in all presentations. Pfizer believes it met the requirements of Section 506C(f) of the FD&C Act. We recognize there are opportunities to improve our reporting program, including, among other things, submission of product-specific shortage notifications. We look forward to additional guidance from FDA and to continued partnership with FDA's Drug Shortage Staff.

Should you have any questions regarding this response, please contact me via phone at (224) 212-4874; or via e-mail at lisa.skeens@pfizer.com.

Sincerely,

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