Inspections, Compliance, Enforcement, and Criminal Investigations

Jubilant HollisterStier, LLC 11/27/13

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Seattle District
Pacific Region
22215 26th Avenue SE, Suite 210
Bothell, WA 98021
Telephone: 425-302-0340
FAX: 425-302-0402

November 27, 2013

OVERNIGHT DELIVERY
SIGNATURE REQUIRED

In reply refer to Warning Letter SEA 14-01

Marcelo A. Morales, CEO
Jubilant HollisterStier, LLC
3525 North Regal Street
Spokane, Washington 99207-5788

WARNING LETTER

Dear Mr. Morales:

During our April 15, 2013 to May 10, 2013, inspection of your pharmaceutical manufacturing facility, Jubilant HollisterStier, LLC, located at 3525 North Regal Street, Spokane, Washington, investigators from the U.S. Food and Drug Administration (FDA) identified significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 351(a)(2)(B), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm’s response dated May 30, 2013, and noted that it lacks sufficient corrective actions. We also acknowledge receipt of your firm's additional correspondence dated July 12, 2013, and August 15, 2013.

Our investigators observed specific violations during the inspection, including, but not limited to, the following:

1. Your firm failed to establish appropriate written procedures, that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes (21 CFR 211.113(b)).

a) For example, your firm's SOP 1608.9, "Quality Control of HollisterStier Facility During and After Shutdown" lacks provisions for adequate impact evaluation of significant maintenance shutdowns and assurance that acceptable conditions are restored to ISO classified areas before restart of operations. In April 2013, your firm shut down filling lines SVP Line 1 and SVP Line 2 used to manufacture aseptically filled injectable drug products. The April 2013 shutdown activities on SVP **(b)(4)** included removal of the existing **(b)(4)**, rebuilding of the**(b)(4)** upgrade, and replacement of **(b)(4)**. On SVP**(b)(4)** the **(b)(4)** was upgraded on the **(b)(4)**, which included replacement of the **(b)(4)**. Major facility repairs in the April 2013 shutdown included window replacement, floor resurfacing, dead bolt installation, and ceiling painting.

In your response, your firm acknowledges the lack of an adequate, documented evaluation of the effect of major equipment and facility modifications. You also provide a retrospective impact assessment that you performed. Furthermore, you state that SOP 1608.9, "Quality Control of HollisterStier Facility During and After Shutdown" has been revised to include an improved impact assessment process. Your response is inadequate because you do not commit to conducting media fill process simulations to assure the aseptic processing operations are acceptable after major shutdown activities. In addition, your July 12, 2013, response states that SOP 1608.9, "Quality Control of HollisterStier Facility During and After Shutdown" revisions are complete. However, you failed to provide an official procedure.

b) Your firm also failed to adequately document all work orders associated with the April 2013 shutdown and include appropriate Quality Unit oversight. Your firm's SOP 1608.9, "Quality Control of HollisterStier Facility During and After Shutdown," requires Quality Assurance review of work orders "which affect ISO classified areas and/or utilities during shutdown" in the "Shutdown Maintenance Work Order Requests List," in Attachment 1. In the April 2013 shutdown, 11 of **(b)(4)** work orders were not documented in Attachment 1. Examples of work orders not documented in Attachment 1 include facility repairs and equipment maintenance at SVP Line 1 and SVP Line 2. Release of the classified production areas after shutdown includes review of Attachment 1.

In your response, you state that SOP 1608.9, "Quality Control of HollisterStier Facility During and After Shutdown" has been revised to include appropriate documentation and Quality Unit approval prior to performing shutdown work. However, your response is inadequate because you have not provided an official procedure.

2. Your firm failed to assure an adequate system for cleaning and disinfecting aseptic processing areas and equipment (21 CFR 211.42(c)(10)(v)).

a) For example, your firm's SOP 101.74, "General Cleaning, Sanitization and Disinfection of Aseptic and Controlled Areas," lacks provisions to ensure adequate use of sporicidal agents. According to SOP 101.74, sporicidal agents are not required on aseptic filling line stainless steel, non-removable components, and the ISO 5 rigid barriers. According to SOP 101.74, **(b)(4)** will be used to sanitize/clean stainless steel components in the aseptic or controlled areas.

In your response you state that SOP 402.12, "Controlled and Classified Area Out-of-Service Process" has been revised to include **(b)(4)** disinfection of aseptic fill-lines and non-removable ISO5 equipment and platforms when out-of-service activities require scrubs or street clothes. However, your response is inadequate because you failed to address the routine use of sporicidal agents.

b) Your firm's SOP 101.74, "General Cleaning, Sanitization and Disinfection of Aseptic and Controlled Areas," also lacks adequate details on how many times mops and wipes can be used.

Your response is inadequate because you did not provide scientific data that the corrective actions implemented in SOP 101.74, "General Cleaning, Sanitization and Disinfection of Aseptic and Controlled Area" are adequate. While this SOP instructs staff to replace mops, wipes, and other supplies when visually soiled, it is unclear whether this revision will provide for acceptable

standards of sanitization and disinfection in the controlled area.

We are also aware of the unexplained increased levels of Unknown **(b)(4)** Impurities **(b)(4)** in **(b)(4)**. We understand that you withdrew **(b)(4)** lots of **(b)(4)** from the market and expiry was reduced from **(b)(4)** to **(b)(4)** months in response to the possibility that **(b)(4)** levels might exceed specifications. Although your initial actions are appropriate, it is essential that your firm also implement corrective actions to ensure the quality of the finished drug product throughout the product lifecycle. Your firm does not appear to have adequate control of the **(b)(4)** in **(b)(4)**. Your firm cannot assure product quality by reducing the expiry without understanding the root cause of the increased **(b)(4)**.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

The items listed above, as well as other deficiencies our investigators found, lead us to question the effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of drugs manufactured by Jubilant HollisterSteir, LLC. FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Other federal agencies may take this warning letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates, or approval of pending drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

If, as a result of receiving this Warning Letter or for other reasons, you are considering a decision that could reduce the distribution or production of finished drug products or active pharmaceutical ingredients at your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products. In appropriate cases, you may be able to take corrective action without interrupting supply, or to shorten any interruption, thereby avoiding or limiting drug shortages.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of violations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, if you no longer manufacture or distribute the drug product(s) at issue, provide the date(s) and reason(s) you ceased production.

Please send your written response to Lisa M. Althar, Compliance Officer, Seattle District Office, Food and Drug Administration, 22215 26th Avenue SE, Suite 210, Bothell, Washington 98021. If you have any questions about the contents of this letter, please contact Ms. Althar at (425) 302-0427.

Sincerely,
/S/
Gerald D. Bromley, Jr.

Acting District Director

cc: Washington State Department of Health
Pharmacy Quality Assurance Commission
Office of Investigations and Inspections
P.O. Box 47874
Olympia, Washington 98504-7874

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