Inspections, Compliance, Enforcement, and Criminal Investigations

SANUM-Kehlbeck GmbH & Co. KG 4/11/14

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

Warning Letter

WL: 320-14-07
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

April 11, 2014

Mr. Reiner G.D. Kehlbeck
Chief Executive Officer Kehlbeck Holding GmbH and SANUM Verwaltungs GmbH
SANUM-Kehlbeck GmbH & Co. KG
Hasseler Steinweg, 9
D-27318 Hoya
Germany

Dear Mr. Kehlbeck:

During our March 18, 2013 through March 26, 2013 inspection of your pharmaceutical manufacturing facilities, SANUM-Kehlbeck GmbH & Co. KG (SANUM) located at Bahnhofstrasse 2 (Werk I) and Hasseler Steinweg 9 (Werk II), Hoya, Germany, 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 and deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These violations and deviations cause your drug products and APIs 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.

Our inspection also revealed that your homeopathic manufacturing facilities failed to fulfill their registration obligations under Section 510(i)(1) of the Act and its listing obligations under Sections 510(i)(2) and 510(j), which is prohibited under Section 301(p). 21 U.S.C. 360(i)(1) and (2), 360(j), and 331(p).

We acknowledge receipt of your firm's correspondences dated April 15, November 5, and December 17, 2013.

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

API CGMP VIOLATION

1. Drug substance production of highly sensitizing materials, such as penicillin, were not performed in dedicated production areas, which include facilities, air handling equipment and/or process equipment.

Specifically, your firm performs **(b)(4)** of *Penicillium* species, including *Penicillium chrysogenum*, in the Werk 1 facility. The sensitizing antibiotic penicillin is a metabolic by-product from the growth of *Penicillium chrysogenum*.

In your response to our observation concerning inadequate cleaning validation on shared equipment, you indicate that you would revalidate your process by the middle of 2014 for equipment in Werk I. Your response is inadequate because you manufacture non-penicillin APIs on shared equipment used for penicillin production. You provided no commitment to fully and comprehensively segregate penicillin production facilities. Your response also fails to provide a detailed description of your decontamination plans for your facility if you plan on continuing non-penicillin production in the future. In your response to this letter, describe all of the actions you will implement to prevent potential contamination of non-penicillin APIs with penicillin. Please note that a test for the presence of penicillin cannot substitute for segregated facilities (and would provide only a small degree of assurance in any case). We acknowledge your March 18, 2014 voluntary recall of products derived from Penicillium (56 lots of Pleo-FORT, Pleo-QUENT, Pleo-STOLO, Pleo-NOTA-QUENT, and Pleo-EX) that may have undeclared penicillin. Additionally, provide your plan for addressing products made in the shared API facility that were released into U.S. distribution.

CGMP DRUG PRODUCT VIOLATIONS

1. Your firm failed to perform operations related to the manufacture, processing, and packing of penicillin in facilities separate from those used for other drug products for human use (21 CFR 211.42(d)).

Specifically, your firm produces non-penicillin and penicillin containing finished products in Werk II using shared equipment. As such, all non-penicillin products produced in your facility are potentially adulterated with penicillin, and constitute a potential serious allergenic hazard to patients who are sensitive to beta-lactams.

In your response to the inspectional observation related to inadequate cleaning validation on shared equipment in Werk II, you indicate that you will revalidate your processes by the end of 2013. As stated above for your API production, you failed to provide a commitment that the manufacture of penicillin containing products would be fully and comprehensively segregated and that proper decontamination of this facility would occur if it is to be used for non-penicillin production in the future. Additionally, you failed to provide assurance that products currently marketed in the U.S. are not contaminated with penicillin. The current practices at your facility present an unacceptable risk of penicillin contamination. We acknowledge your March 18, 2014 voluntary recall of products derived from Penicillium (56 lots of Pleo-FORT, Pleo-QUENT, Pleo-STOLO, Pleo-NOTA-QUENT, and Pleo-EX) that may have undeclared penicillin. In your response to this letter, describe all of the actions you will implement to prevent potential contamination of non-penicillin products with penicillin. Additionally, provide your plan for addressing products made in the shared finished product facility that were released into U.S. distribution.

2. Your firm failed to establish and follow 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)).

For example,

a) Your firm has not performed smoke studies under dynamic conditions to ensure that unidirectional airflow protects the product during aseptic filling operations.

In your response, you indicate that you are making arrangements to perform dynamic smoke studies. However, your response fails to provide any justification that the aseptic processing

line has proper airflow and that product made within your facility to date was adequately protected from contamination.

b) Your firm has failed to validate the **(b)(4)** used to produce sterile drug products since 2011. The inspection documented that you relied solely on the vendor's qualification.

In your response, you indicate that you have commissioned the vendor to perform process and product-specific **(b)(4)** validation. We remind you that it is your responsibility to review the validation data on the efficacy of the **(b)(4)** in producing a sterile effluent. Your response is inadequate in that it fails to address the impact on product produced since 2011.

c) Our investigators observed poor aseptic practices that increase the risk to product sterility assurance. For example, operators with exposed skin were observed making interventions over open product using a non-sterile **(b)(4)**.

Your response indicates that you will make changes to minimize the need for interventions. However, your response does not address the training of operators that is essential to ensure that all employees working on the filling line have been properly instructed on aseptic technique and cleanroom behaviors that minimize risk to product sterility assurance. Furthermore, your firm should ensure proper daily supervision and evaluate training effectiveness.

d) Your firm has failed to establish a program to qualify the operators' ability to gown in an aseptic manner. At the time of the inspection, our investigators observed aseptic filling operations performed by operators who had failed to undergo gowning qualification. Gowning qualification ensures that operators possess proper aseptic technique and are able to maintain the quality of the gowning that will protect exposed product from contamination.

Your response indicates that you plan to develop a gowning qualification program. Please note that only personnel who have been properly qualified and appropriately gowned should be permitted access to the aseptic manufacturing area.

3. Your firm failed to ensure that manufacturing personnel wear clothing appropriate to protect drug product from contamination (21 CFR 211.28(a)).

Our investigators observed inadequate gowning of operators in the aseptic filling operations. Specifically, operators routinely reused gowning throughout the day to enter the sterile core for set-up and filling. Additionally, not all components (masks, hair and beard covers) of the gowning are required to be sterile. Our investigators also observed gowned personnel in the aseptic filling areas with exposed skin. These questionable practices raise concerns regarding your firm's understanding of basic aseptic process controls that are needed to prevent the introduction of microbial contamination into an aseptically filled product.

In your response, you indicate that that you are exploring options for goggles, will replace non-sterile masks with sterile masks, and will not allow the reuse of gowning until you are able to scientifically justify the practice. Your response is inadequate in that does not address the exposed skin of operators.

4. Your firm failed to ensure that each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform his or her assigned functions (21 CFR 211.25(a)).

Your firm performs microbiological testing activities related to your aseptic processing operations without including any qualified staff with microbiology background. Specifically, production personnel with no microbiology background perform environmental monitoring and evaluate the samples collected for microbial growth. Production personnel also perform in-process testing for bioburden. In addition, the media from media fills are evaluated by packaging employees.

In your response, you indicate that a consultant educated in microbiology will train your operators every **(b)(4)** to perform and evaluate viable environmental monitoring samples and bioburden test samples of in-process materials. In addition, you commit to **(b)(4)** have a consultant train packaging personnel to evaluate media fills. Your proposal is inadequate in that training exercises alone cannot replace the appropriate combination of education, training, and experience necessary to perform these critical microbiological activities that monitor the aseptic operation.

5. Your firm failed to establish and follow adequate written procedures that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch, to assure batch uniformity and integrity of drug products (21 CFR 211.110(a)).

The in-process bioburden testing conducted on your **(b)(4)** has not been validated. For example, you have failed to demonstrate that a single **(b)(4)** mL rinse is effective in removal of the product preservative and allows for accurate recovery.

In your response, you indicate that you have commissioned a contract testing laboratory to perform the validation. We remind you that you are responsible for review of the method validation to ensure it is appropriate.

REGISTRATION AND LISTING VIOLATIONS

Your firm failed to fulfill its registration obligations under Section 510(i)(1) of the Act and its listing obligations under Sections 510(i)(2) and 510(j), which is prohibited under Section 301 (p). 21 U.S.C. 360(i)(1) and (2), 360(j), and 331(p). As a result, your drugs appear to be misbranded under section 502(o) of the Act. 21 U.S.C. 352(o).For example, in 2013 your firm offered for import into the United States drugs that you manufactured or otherwise processed at the above-referenced establishment located at Bahnhofstrasse 2. During that same time period, however, your firm did not maintain a current establishment registration, and complete and accurate drug product listing with the FDA.Please note that a drug offered for import into the United States is subject to refusal of admission under section 801(a)(3) of the Act (21 U.S.C. 381(a)(3)), if the drug appears to be adulterated or misbranded. Under section 502(o) of the Act (21 U.S.C. 352(o)), the failure to register an establishment as required by section 510 or to list a drug as required under section 510(j) renders a drug misbranded.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.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by 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.

Until all corrections have been completed and FDA has confirmed corrections of the violations and deviations and your firm’s compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug product manufacturer. In addition, your failure to correct these violations and deviations may result in FDA continuing to refuse admission of articles manufactured at SANUM in Hoya Germany into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may be subject to refusal of admission pursuant to Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3), in that the methods and controls used in their manufacture do not appear to conform to CGMP within the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

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 products at issue, provide the date(s) and reasons you ceased production. Please identify your response with FEI #3002128313.

Please send your reply to:

Tamara Ely
Consumer Safety Officer
U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Manufacturing and Product Quality
Division of International Drug Quality
White Oak, Building 51 Room 4234,
10903 New Hampshire Ave
Silver Spring, MD 20993

Sincerely,
/S/
Steven J. Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

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