U.S. Department of Health & Human Services

U.S. Food & Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Hemofarm A.D. 6/20/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-12-019

June 20, 2012

Sonja Pejović
Executive Board Member
Hemofarm A.D.
Beogradski put bb
26300 Vrsac,
Serbia

Dear Ms. Pejović:

During our November 14 to 22, 2011 inspection of your pharmaceutical manufacturing facility, Hemofarm A.D. located at Beogradski put bb, 26300 Vrsac, Serbia, investigator(s) from the 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 product(s) 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 reviewed your firm's response of December 12, 2011, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm has not established scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that **(b)(4)** drug product conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. § 211.160(b)].

For example, your environmental monitoring data is not reliable. This is a serious deviation, as your ability to detect microbial contamination in the manufacturing environment during aseptic processing is fundamentally compromised. This information is critical to monitor the acceptability of the environment that the sterile drug and its container-closure components are exposed to during processing, and assure that these conditions consistently safeguard product sterility.

a) Your firm used dried/desiccated media agar plates for environmental monitoring testing used to support the release of batches. On November 15, 2011, you documented that 155 of a total of 247 media plates evaluated (more than 50%) were dried. The use of dried agar plates, which do not reliably support microbial growth, to recover microbial contamination is inadequate.

b) On November 14, 2011, the FDA investigator observed desiccated environmental monitoring plates in your incubators. However, your analysts only recorded the results as dried media but not the counts from the plates (if any). On this same day, the FDA investigator observed plate "**(b)(4)**," sampled on November 9, 2011, to have growth of 1 Colony Forming Unit (CFU). However, your firm documented the result of this plate's reading as "SAUSEN MEDIUM", dry medium, and failed to report the microbial growth.

c) Your environmental monitoring data for January 2009 through October 2011 contains documentation of only two action limit excursions in the Grade A manufacturing areas. In apparent contradiction, during an FDA visit to your microbiology laboratory on November 14, 2011, nine plates, collected as part of the environmental monitoring program from the Grade A manufacturing area were found inside an incubator in the microbiology laboratory with visible growth of microorganisms.

d) Your environmental sampling and testing program procedure is inadequate because it fails to adequately identify (e.g., with diagrams) the locations from which the surface samples are collected. In addition, you do not collect sufficient active viable air samples and dynamic non-viable particulate air samples from the critical area during manufacturing.

e) The agar level on surface contact plates (used for surface environmental and personnel monitoring sample testing) was below the rim of the plates creating the possibility that the agar would not have contact with the surface intended to be sampled.

f) Your bioburden testing of the **(b)(4)** components is inadequate. Your firm lacks adequate controls to assure that the melted agar is

sufficiently cool to prevent cell death of viable microorganisms. Specifically, your analyst determines by hand touch, without any instruments, the adequacy of the temperature of the melted agar medium used for the bioburden testing of the API, **(b)(4)** and **(b)(4)**, before pouring the agar into the plates and mixing it with the samples. Your response indicated that you completed a study to determine the time required for the agar media to cool to the temperature of the water bath (**(b)(4)**°C) prior to use of that media in pouring microbiological plates. Your response is inadequate because you did not describe the study method, laboratory controls used for temperature monitoring, and time controls during this study. In your response to this letter you should provide a detailed summary of this study and the revised procedures, including appropriate controls, to be used during the pour plate method for the bioburden testing.

2. Your firm has not established or followed appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

For example, your firm utilized inadequate aseptic processing techniques during the water runs (Water Lots C100790 and C100811) conducted during the inspection. For example:

a) The operator of filling line F200 was observed leaning over the top of **(b)(4)** containing filled opened sterile vials during the loading of the **(b)(4)**, thereby blocking the unidirectional airflow over the open vials.

b) The operator was observed compromising the connection's sterility of the filling line by exposing the **(b)(4)** to the Grade B area during this aseptic connection with no further **(b)(4)** of the line after its installation.

c) During the set-up for the filling line, water sprayed from the filling line directly onto an operator, which wet his gown. The operator continued line setup activities without re-gowning until instructed to stop by firm management after an FDA investigator pointed out the concern.

d) Uncovered **(b)(4)** are not maintained under Grade A conditions during their movement from the **(b)(4)** located in Room **(b)(4)** to their Grade A staging area near the F200 filling line in Room **(b)(4)**. The **(b)(4)** are transported through a Grade B area to their staging area. Additionally, during the filling operation, the operator was observed removing the **(b)(4)** and **(b)(4)** from their Grade A staging area through a Grade B area to the Grade A area, where the **(b)(4)** and **(b)(4)** are loaded with vials, and placed on a **(b)(4)**. These **(b)(4)**.

Regarding Items #1 and #2 of this letter, we note that your response includes a commitment to retrain personnel, revise procedures, and use of premade agar plates to address the violations. Your response is inadequate because your firm failed to conduct a comprehensive risk assessment of these poor aseptic process activities, and the inadequate environmental monitoring program, to evaluate their impact on product quality.

We note that inadequate aseptic technique is a repeat observation from the May 2007 inspection. Also, the discrepancies observed in your documentation of environmental monitoring data raises concerns regarding the reliability and validity of the data generated in your microbiology laboratory, and therefore the quality of the sterile finished drug products manufactured at your facility. In your response to this letter please include the specific steps you are taking to ensure that accurate and reliable microbial data, essential to support the aseptic processing operations used during the manufacturing of sterile finished drug product, is generated. In addition, please provide a copy of your revised procedures containing detailed instructions regarding the location of your samples, as well as specific provisions relating to the proper custody, handling, and reading of plates.

3. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].

For example,

a) Your firm failed to conduct adequate investigations of three media fill failures in the aseptic filling line used to produce sterile products. Your firm uses **(b)(4)** vials to fill **(b)(4)**, which is shipped to the US market. Your firm performed the last successful media fill using the **(b)(4)** vials on November 28, 2010, Lot **(b)(4)**, and the last successful media fill lot for **(b)(4)** vials on February 26, 2011.

Significantly, the three media fill failures on filling line F200 occurred from May to September 2011. While the last successful **(b)(4)** media fill on this line (F200) was conducted on November 28, 2010, your firm released batches manufactured on this same filling line between November 28, 2010 and February 26, 2011. Your firm failed to adequately evaluate the impact of the contamination hazards revealed by these media fill failures on commercial batches (e.g., **(b)(4)**).

b) Your investigation concluded that the probable root cause for the media failure was the contamination of Media Fill Lot **(b)(4)** by an earlier media fill Lot **(b)(4)** that had failed. In your response, you attribute these two media fill failures to the testing of your **(b)(4)** Vessel **(b)(4)** procedure, and proposed changing the **(b)(4)** and revising your procedures. Your firm's investigation found that both of these media fills were contaminated with *Burkholderia cepacia*. Your investigation was not extended to other areas of the aseptic operation. For example, deficient design or control of rooms, equipment, or the Water for Injection (WFI) system, may also have caused the introduction of these water-borne microbes to the aseptically processed vials.

In your response to this letter you should include a detailed action plan describing the changes and improvements made in your investigations procedures, personnel qualifications and aseptic filling area operations that will prevent recurrence of similar or new violations. Your response should include an updated investigation including well-supported, substantive conclusions as to the cause of the media fill failures, appropriate corrective actions, and your assessment of batches that may be affected and distributed in the US.

4. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, your firm failed to have a procedure or process in place to evaluate the changes at your facility that might impact the quality of your product. The FDA investigators documented that Quality Assurance did not evaluate the change to the **(b)(4)**, later implicated in the media fill failure of Media Fill Lot **(b)(4)**. Your response indicated that your firm is revising the Critical Material Management procedure to require Quality Assurance approval for all changes. However, your response failed to adequately describe the new procedures for review and approval of any changes to your production and process controls by Quality Assurance.

In your response to this letter please provide a retrospective review of all the changes that occurred to your processes implemented without Quality Assurance approval since the initial validation, and the impact of these changes on the batches that remain within expiry and released for distribution to the U.S. market.

We are concerned that your response lacks a commitment to assess the impact of these violations on your distributed drug products. We recommend you engage in a comprehensive evaluation of your sterile drug operations, including but not limited to a thorough review of material flow, personnel practices, production supervision, operational procedures, QA oversight, training program, room design, equipment suitability, environmental monitoring program, adequacy of systems used to investigate contamination events (e.g., media fills, sterility test failures), and clean area classification. In your response to this letter, please include a detailed description of the actions you will take to correct these issues and prevent recurrence. Finally, we note that the CGMP violations listed in this letter include similar violations to those cited in the May 2007 FDA inspection. It is apparent that Hemofarm A.D. is not implementing sustainable corrective actions. We remind you that you are responsible for

ensuring that your firm's drug manufacturing operations comply with all applicable requirements, including the CGMP regulations. FDA expects Hemofarm A.D. to undertake a comprehensive and global assessment of your manufacturing operations to ensure that the drug products you manufacture conform to FDA requirements. Repeat citations from prior inspections indicate that your quality unit is either not exercising its responsibilities, or may not have the appropriate authority to carry out its responsibilities. Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant having appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that your drug products consistently have their appropriate identity, strength, quality, and purity.

The violations cited in this letter are not intended to be an all-inclusive statement 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 you wish to continue to ship your products to the United States, it is the responsibility of your firm to ensure compliance with all U.S. standards for CGMP and all applicable U.S. laws and regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations 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, until such time as your manufacturing practices are verified to comply with CGMPs, your firm will remain under FDA Import Alert, and FDA will continue to refuse admission of all articles manufactured at Hemofarm A.D. located at Beogradski put bb, 26300 Vrsac, Serbia into the United States. Because your firm is currently under Import Alert, the articles are 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 Current Good Manufacturing Practice within the meaning of section 501(a)(2)(B) of the Act [21 U.S.C. § 351(a)(2)(B)].

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical ingredients being 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 in order to ensure that your action(s) does not adversely affect the public health

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 violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture or distribute the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production. Please identify your response with FEI # 3006082102.

If you have questions or concerns regarding this letter, contact Maan Abduldayem, Compliance Officer, at the below address and telephone number.

U.S. Food and Drug Administration
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White Oak, Building 51
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Sincerely,
/Steven Lynn/
Steven Lynn
Director
Office of Manufacturing and Product Quality
Office of Compliance
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