U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Gilead Sciences Inc

Department of Health and Human Services

Public Health Service
Food and Drug Administration
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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

W/L 44-10

September 21, 2010

Mr. Robert J. Hull
General Manager
Gilead Sciences, Inc.
650 Cliffside Drive
San Dimas, CA 91773-2958

Dear Mr. Hull:

During our January 25, 2010 to February 12, 2010 inspection of your pharmaceutical manufacturing facility, Gilead Sciences, Inc., located at 650 Cliffside Drive, San Dimas, CA, 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 March 2, 2010, 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 failed to maintain adequate separate or defined areas or such other control systems for the firm's operation as are necessary to prevent contamination or mixups during the course of aseptic processing [21 CFR § 211.42(c)(10)].

For example,

a. Your aseptic processing room was not adequately constructed to meet design specifications. When the room, in which partially-open sterile drug is transported, failed to meet design criteria for ISO **[b4]** (Class **[b4]**) in August, 2008, you reclassified the room to ISO **[b4]** (Class **[b4]**). Your firm then resumed manufacturing of the parenteral product (AmBisome **[b4]** intravenous injection, lot **[b4]**) on August 21, 2008. The firm's Quality Unit did not approve the revised room qualification until September 17, 2008, nearly one month after you resumed production for distribution in the ISO **[b4]** reclassified room. You continued operating under ISO **[b4]** conditions, and approximately **[b4]** lots of AmBisome partially-stoppered vials were transported through the room by your firm to the lyophilizer loading area prior to re-qualification of the room to ISO **[b4]** on April 3, 2009. Approximately **[b4]** of these lots were released for distribution in the United States.

Your response is not adequate. Your rationale for release of the product is based upon an incomplete assessment of the clean area control parameters, which did not include non-viable particulates and environmental excursions during manufacturing operations. In addition, you did not review the executed batch records to identify discrepancies, deviations, or interventions that may have occurred during the manufacture of these lots that could potentially further impact the quality of the product released. Furthermore, you stated that it is your normal practice to fully investigate such deviations, and implement corrective actions. However, you failed to provide any details regarding the particular corrective actions implemented for the deviations discussed above.

b. Your environmental monitoring program is not adequate in the aseptic filling areas.

1. Procedure SDSOP-0776, *Environmental Monitoring of Product Fill* (Revision 26), requires testing multiple random samples per room for airborne microbial and non-viable particles (NVP) during pre-fill operations. In addition, Procedure SDSOP-0417, *Environmental Monitoring for the Controlled Manufacturing Areas* (Revision 57), requires random sampling locations for airborne microbial, non-viable particles, and equipment surfaces for routine monitoring. These random sampling locations are not documented.

2. You do not have justification that adequate active air sampling locations have been identified to monitor the air quality during aseptic filling operations. You also have not assured an adequate program for post-filling microbial surface monitoring of critical surfaces. Monitoring of these critical areas is an integral part of assuring that the aseptic production area and equipment protect the product from microbial contamination.

Your response is inadequate. You stated in your response that your environmental monitoring program will be enhanced to clearly justify all

monitoring locations and that you will update monitoring procedures accordingly. However, you provided no details regarding the methods by which you will evaluate your program (e.g., environmental trends, product impact, room qualifications, literature search, traffic patterns, etc.). Your response is also inadequate because you failed to address your lack of documentation of the random sampling locations. Random sampling may provide additional valuable information in determining the conditions of the aseptic processing areas. Adequate documentation of the sampling locations is essential for trending and investigational purposes.

c. Your current practice for assessing the unidirectional airflow in the critical product path is inadequate to prevent contamination of the product. Specifically, procedure SDSOP-0325, *Testing and Certification of HEPA Filters* (Revision 30), only requires testing for airflow velocity uniformity testing of HEPA filters housed inside the **[b4]**. CGMP requires, at a minimum, that all unidirectional airflow systems must be tested for uniformity of air velocity. However, your SOP does not include instructions for uniformity of air velocity testing of other HEPA filters within the aseptic processing room, particularly those in the critical path of the product through the room.

Your response is inadequate. You stated in your response that you will update SDSOP-0325 to include the evaluation of all the filters within the ISO **[b4]** dynamic area by March 21, 2010. However, you provided no timeframe for conducting the velocity uniformity test of the untested filters. You also failed to define your term, "ISO **[b4]** dynamic area."

2. Your firm has not 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 procedure, SDSO-0416, *Controlled Area Aseptic Gowning, Qualification, Aseptic Technique, and Monitoring* (Revision 52), defines the requirements of personal behavior in the aseptic filling ISO **[b4]** area. This procedure specifically requires personnel to make slow, deliberate movements during manufacturing operations. However, during aseptic fill of AmBiosome Lot **[b4]** on January 2, 2010, FDA investigators observed a fill operator in aseptic processing room 1079 monitoring the sterile fill and intervening in the **[b4]** without executing slow and deliberate movements. Instead, this operator was observed making excessive body and hand movements and engaging in animated conversations.

In addition, procedure SDSO-0416 requires the placement of a container at all stations where personnel will be working on the aseptic fill line. These containers are used to hold the sterile forceps during operations. However, during aseptic fill of AmBiosome Lot **[b4]** on January 27, 2010, we observed that there was no container for the sterile forceps at the workstation.

You stated in your response that your Quality Unit will perform periodic audits of the filling operator's aseptic technique, but you did not specify how you intend to document and implement such audits. You also stated that you will evaluate where utensils may be placed, but you provided no timeline for completing this evaluation. In addition, you did not discuss measures to ensure that your SOPs are adequate or what steps you are taking to reduce human error in your facility.

3. 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/or purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].

For example, your contract manufacturer, **[b4]**, performed a process re-validation study for a change in the **[b4]** supplier and for using a new tablet press for your **[b4]** drug product manufacturing process. These process re-validation batches were sent to Gilead in **[b4]** and Gilead in San Dimas, California [b4] and [b4] for packaging. Lots manufactured during the process validation study (**[b4]**) exhibited excessive amounts of defective tablets (**[b4]**, and **[b4]**) above the pre-determined acceptance criteria.

You stated in your response that the investigation into the re-validation study concluded that neither the new tablet press nor the **[b4]** from the secondary supplier had an adverse effect on the **[b4]** manufacturing process. We disagree with your assessment and we do not consider your process validated. Your investigation report conclusion was based on finished product test results alone, and did not consider in-process testing and analyses.

4. 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, you conducted an inadequate investigation into the acceptable quality limits (AQL) failures of **[b4]** tablets process re-validation lots **[b4]**, and **[b4]**. These lots repeatedly failed visual inspection for AQL of**[b4]** and **[b4],** and **[b4]** tablets. Instead of conducting an adequate investigation into this event, you culled out defective tablets and packaged the remainder of the lots.

Your investigation report of May 2009 concluded that this event impacted the process validation. However, in your report of September 2009 you concluded that the process validation was successful based on tablet **[b4]**, and **[b4]** testing results.

You stated in your response that these "cosmetic defects" are not related to the changes in the process (change in the **[b4]** supplier and use of a new tablet press). Your response is inadequate because you did not provide the scientific rationale you used to make this determination including your rationale for naming these types of defects "cosmetic defects." In addition, your response did not include any assessment of the lot (**[b4]**) sent to your site in **[b4]** although this lot also exhibited these defects.

5. Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product [21 C.F.R. § 211.67(a)].

For example, during the filling of AmBisome **[b4]** intravenous injection lots **[b4]** and **[b4]** isolates were recovered from settling plates in the aseptic area. Your investigation determined that the source of the **[b4]** was the lack of sanitation of the conveyor belt. You revised your procedure SDSOP-0433, *Controlled Environment Area Cleaning Building 502* (revision 64), to include **[b4]** cleaning of non-product contact conveyer belts and filler parts in the ISO **[b4]** and**[b4]** areas. However, you had no rationale for selecting the cleaning frequency of this equipment in the aseptic area.

You stated in your response that you will establish a rationale for the cleaning frequency of non-product contact belts and non-product contact filling in the ISO **[b4]** area by April 30, 2010. In addition, you committed to review other cleaning procedures to determine if deficiencies exist. However, your response is inadequate because you did not describe how you will evaluate the suitability, efficacy, and limitation of the disinfecting agents and procedures used.

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. It is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

Please note that repeat observations and discussions with our office indicate that your quality unit is not adequately exercising its responsibilities, and may not have appropriate authority to carry out its responsibilities. As an example, it appears that as part of your batch release criteria you rely on a practice of sorting and rejecting tablets with quality defects as a quality control measure. It is our expectation that firm's senior management ensure a systematic approach to designing their products, processes, and quality systems, and require that deviations and flaws are promptly identified and corrected to assure the identity, strength, quality, and purity of their drug products.

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.

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 of distribute any of the drug products manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address:

Blake Bevill
Director, Compliance Branch
U.S. Food and Drug Administration
19701 Fairchild
Irvine, CA 92612-2506

If you have questions regarding this letter, please contact Ms. Mariza Jafary, Compliance Officer at 949-608-2977.

Sincerely,
/S/
Alonza E. Cruse
District Director

Cc: Ingeborg Small, Branch Chief
California Department of Public Health
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1500 Capitol Avenue, MS-7602
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