Inspections, Compliance, Enforcement, and Criminal Investigations

Jilin Shulan Synthetic Pharmaceutical Co. Ltd. 5/13/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring MD 20993

Warning Letter

VIA UPS MAIL

WL: 320-10-005

May 13, 2010

Mr. Li DaQian
President
Jilin Shulan Synthetic Pharmaceutical Co., Ltd.
No. 2066 Peoples Main Road
Shulan City, Jilin Province
People's Republic of China (PRC) 132600

Dear Mr. Li:

During our August 24-28, 2009 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Jilin Shulan Synthetic Pharmaceutical Co., Ltd. located at No. 2066 Peoples Main Road, Shulan City, Jilin Province, People's Republic of China (PRC) 132600, an investigator from the Food and Drug Administration (FDA) identified significant deviations from Current Good Manufacturing Practice (CGMP) for the manufacture of APIs. These deviations cause your 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.

We have reviewed your firm's response of October 12, 2009, and note that it lacks sufficient corrective actions.

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

1. Production personnel fail to ensure that all production deviations are reported and evaluated, and that critical deviations are investigated and the conclusions are recorded.

For example, during the **(b)(4)** of **(b)(4)** sub-batch **(b)(4)**, our investigator observed that the pressure and temperature of the **(b)(4)** equipment fell out of range (below **(b)(4)** mPa and **(b)(4)**°C). The investigator observed no initiation of an investigation into this deviation and received no assurance that an investigation would take place. Any deviations from processing parameters should be documented and explained, whereas critical deviations should be thoroughly investigated.

In addition, the investigator observed a shift change while sub-batch **(b)(4)** was undergoing **(b)(4)**, in which operators from the new shift had not reported to their duty stations for more than 30 minutes after their shift began. You should have adequate systems in place to ensure that critical operations are witnessed, or are subjected to another appropriate control.

2. Master production records do not include complete production instructions.

Your master production records do not include all steps in the production of **(b)(4)** and your batch production records are not accurate reproductions of your master production records. The master production record does not include the **(b)(4)** stage of the **(b)(4)** production.

Your October 12, 2009 response states you will revise your DMF for **(b)(4)** USP to include the information regarding **(b)(4)** treatment and the manufacturing of **(b)(4)**. However, you provide no evidence to show that these steps have been included in your master batch records. We are also concerned that you did not comprehensively evaluate the manufacturing process, for this and other drugs, in its entirety to ensure that all steps are included in your master batch records and your DMF. Adequate batch records are a critical part of a manufacturing operation because they provide confidence that the established procedures were followed, processes were controlled, and quality API was manufactured.

In addition, there is no assurance that the **(b)(4)** obtained from the **(b)(4)** recovering steps included in your current process is of adequate quality. Please provide information on studies performed to characterize the **(b)(4)** obtained from this part of the process.

3. The buildings and facilities used in the manufacture of **(b)(4)** USP are not designed and constructed to facilitate cleaning, maintenance, and operations as appropriate to the stage of manufacture. Facilities are not designed to minimize potential contamination.

Your facility consists of surfaces that are not easy to clean and can potentially lead to product contamination. In **(b)(4)** your " Clean Room" our investigator observed peeling foil-faced tape, which was used to seal wall and ceiling joints. Our investigator observed accumulated debris within wall and floor joints throughout your **(b)(4)** USP production facility. You used adhesive tape around hoses in the **(b)(4)** and **(b)(4)** rooms that became covered in production material. The **(b)(4)** routinely spills onto the floor of the **(b)(4)** rooms, causing the undersurfaces of your **(b)(4)** to become rusty and caked with production materials. The investigator also observed **(b)(4)** accumulation on the rusty stairs in the **(b)(4)** room. When your personnel cleaned the **(b)(4)** area in response to our investigator's comments regarding caked material on the underside of the **(b)(4)** your personnel used mops soaked in dirty water. Your October 12, 2009 response includes some corrective actions concerning the noted deficiencies that make your facility difficult to clean, but we are concerned that you have only addressed items specifically pointed out by our investigator during the inspection. We request that you fully evaluate your current cleaning procedures. You should also thoroughly assess the adequacy of your facility design to facilitate cleaning and minimize potential contamination, as well as the training provided to your employees on appropriate cleaning procedures and to ensure CGMP.

You continued to use the **(b)(4)** in the **(b)(4)** area, although approximately 5% of the **(b)(4)** cover was peeling due to rust. You state in your October 12, 2009 response that you repaired the deteriorated cover of this **(b)(4)** and that your corrective action plan includes a recheck of all production equipment, and the strengthening of the check and maintenance for equipment in the future. However, you provide no information regarding what other equipment was identified as needing repair, the repairs conducted, or supporting documentation to show that your preventive maintenance program was improved.

Our investigator observed **(b)(4)** uncovered carts containing approximately **(b)(4)** in the corridor adjoining production areas. You state in your October 12, 2009 response that all in-process **(b)(4)** contained in the carts should be covered and stored in their dedicated room during their temporary storage period. However, you have not provided updated procedures implementing this new requirement, or training documentation to ensure all pertinent personnel were trained in this procedure.

In addition, you provided no information regarding the disposition of the **(b)(4)**, observed uncovered in the corridor adjoining production areas during the inspection.

The investigator also observed that doors leading to corridors and adjoining rooms throughout the "**(b)(4)** Clean Room" building (including the **(b)(4)** room) failed to close properly during production. You indicate in your October 12, 2009 response that all doors would be checked and repaired if necessary. However, we are concerned that you have not addressed the failure of your personnel to identify this and other deficiencies, nor have you identified a mechanism through which future problems will be reported and addressed.

4. Your Quality Unit failed to reject APIs contaminated with foreign material.

For example, **(b)(4)** lot numbers **(b)(4)** were reprocessed after the breakage of an overhead light. These lots were retested and renumbered as **(b)(4)**, respectively.

We are concerned that you did not reject the two lots once they became contaminated with glass and other material associated with the broken overhead light. Please provide your rationale for reprocessing these batches and explain what steps you took to ensure these final API lots, and other lots produced in the same equipment, were not contaminated with foreign material from the broken light. In addition, we request that you provide a detailed description of the corrective actions you implemented to prevent future recurrence of this type of incident.

We note that your firm performs maintenance operations at the same time that production activities are occurring. Please be advised that this is an inappropriate practice.

You also identified black spots in the **(b)(4)** API lot number **(b)(4)**. Your deviation states, "Operators shake off the floating material on the **(b)(4)** into the materials." Please provide an explanation for what is meant by this statement. It is unclear if you have identified the source of these "black spots," but you reprocessed this lot and identified it as **(b)(4)**. Please provide your investigation regarding the identity of this contamination and your rationale for reprocessing this batch.

Also, please provide us with your procedures for placing reprocessed batches on stability and inform us if your firm placed these and other batches on stability.

5. You lack scientifically sound and appropriate test procedures to ensure APIs conform to established standards of quality and/or purity.

For example, you routinely failed to utilize a suitable standard for the spectral comparison during the FTIR testing of **(b)(4)** Instead, you compared sample spectra with the spectrum of **(b)(4)** in the Chinese Pharmacopeia. The USP requires that you compare the spectrum of your test sample with that of your reference standard. Your October 12, 2009 response states that you have strengthened laboratory management and made it a requirement to compare the spectrum from every batch to the spectrum obtained from the reference substance in routine testing. However, you provide no details as to how you strengthened laboratory management, and you include no updated procedures requiring the comparison of the sample spectrum to that of the reference standard. You also provide no documentation to show adequate training of your personnel in the new testing procedures.

You failed to include testing for method precision and ruggedness in your HPLC Assay Method Validation SHY1110-004-00-2 for **(b)(4)** USP. We are concerned that you have not established the degree of reproducibility or repeatability of the analytical procedure under normal operating conditions. In addition, you failed to establish adequate system suitability parameters to ensure that the complete testing system (including instrument, reagents, columns, and analysts) continues to operate suitably for the intended application. You currently only use one standard injection for system suitability, which is unacceptable.

In addition, you evaluate the HPLC signal to noise ratio and analyze the baseline for drift annually. Your October 12, 2009 response indicates that you revised the Standard Operating Procedure (SOP) for calibration of the HPLC to increase the frequency of these determinations to every **(b)(4)** months. Our concern is that you may not be evaluating the signal to noise ratio during system suitability. Evaluation of the signal to noise ratio during system suitability is a normal laboratory practice when testing low level impurities or degradant content by HPLC. Furthermore, you only compare the working standards to the **(b)(4)** USP reference standard annually. Please provide your scientific rationale and stability assessment of the working standard solution to justify performing the verification of the suitability of the working standard annually.

6. Personnel fail to wear clothing suitable for the manufacturing activity with which they are involved to protect **(b)(4)** USP from contamination.

During this inspection, the investigator observed individuals in the " **(b)(4)** Clean Area" (including **(b)(4)** areas) with open toe or open foot sandals, torn plastic booties, wearing no masks, and wearing no gloves. We are concerned that you have not assessed the adequacy of these practices during drug manufacturing operations, particularly during the latter steps of **(b)(4)** USP manufacturing. Your October 12, 2009 response states that the Standard Operating Procedure (SOP) for "Clean area management Procedures for Personnel Passing In and Out" was updated to stipulate that all visitors and personnel operating in the clean area should wear gloves, masks, and white shoes, instead of slippers. However, you have not provided this SOP in your response, nor have you provided any documentation indicating that the appropriate personnel have been trained on this updated SOP.

7. Your Quality Unit fails to ensure that new and modified equipment used in the manufacture of **(b)(4)** USP are qualified and suitable for their intended use.

During the inspection, our investigator observed **(b)(4)**, used in the production of **(b)(4)** USP, operated by low, high, stop, and reset buttons. Your practice of listening to the **(b)(4)** in order to detect problems while in operation is not adequate. Also, you failed to perform equipment calibration for this equipment. Your October 12, 2009 response states that you installed calibrated display devices for the rotational speed of the **(b)(4)** but you failed to demonstrate that the **(b)(4)** and the designated rotational speeds are suitable for their intended use. Please provide the qualification documentation for your **(b)(4)** in your response.

You have not qualified the **(b)(4)** used in your **(b)(4)** process. There is no description of the detectable **(b)(4)** sizes, or feed speed in your procedures. Furthermore, your **(b)(4)** procedures in SOP 1308-062 " **(b)(4)** Finished Product Finished Position SOP" state: "When **(b)(4)** rings, operator should stop feeding material and check the material once again. If no abnormal situation is found, the material can pass, but if the **(b)(4)** rings again, the questioned material will be kept alone and treat as unqualified product." This practice is unacceptable. Material that causes your **(b)(4)** to sound should not be deemed acceptable material once it is passed through the **(b)(4)** a second time. Please indicate how you intend to address this issue.

During the inspection, the investigator observed a rusted balance and counterweight in the **(b)(4)** area that appeared to be unusable. These pieces of equipment are used to weigh reagents, including **(b)(4)**. During the inspection, you painted over the rust on both the balance and the counterweight, but there continues to be no assurance that either is suitable for use in its current condition. In addition, the operational range of the scale is **(b)(4)**, whereas your production records indicate that the balance is used to weigh **(b)(4)** of **(b)(4)**. Production equipment should only be used within its qualified operating range.

8. Your Quality Unit does not maintain revision histories and, therefore, fails to control the issuance, revision, and withdrawal of all documents.

For example, standard operating procedures (SOPs) and batch records do not include version numbers or effective dates. Your lack of document control can lead to the use of outdated procedures or work instructions. Your October 12, 2009 response states that you have revised all your SOPs to provide version control numbers, but we are concerned with the APIs that were previously manufactured under uncontrolled procedures. You provide no information regarding which SOPs and batch records were not previously identified with version control numbers, nor did you provide an example of your master batch records for **(b)(4)** USP, including the version control number. In addition, you fail to address your general approach to document control. Please provide the procedures and associated training you have in place to ensure that revision histories will be maintained, and that only the most current documents will be available for use.

During this inspection, you indicated to our investigator that your firm has only shipped **(b)(4)** to the United States for use in **(b)(4)**, and that you have not shipped product to the United States for use in pharmaceutical products. However, our records indicate that you have distributed **(b)(4)** USP, as well as **(b)(4)** USP and **(b)(4)** USP, to the United States for use in pharmaceutical products. In future correspondence please include clarification on this issue.

The deviations detailed in this letter are not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviations identified above and for preventing their recurrence and the occurrence of other deviations. If you wish to ship APIs 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 deviations and your firm's compliance with CGMP, this office will recommend withholding approval of any new applications or supplements listing your firm as an API manufacturer. In addition, failure to correct these deviations may result in FDA denying entry of articles manufactured at Jilin Shulan Synthetic Pharmaceutical Co., Ltd. located at No. 2066 Peoples Main Road, Shulan City, Jilin Province, People's Republic of China (PRC) 132600, into the United States. The articles could 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 Current Good Manufacturing Practice 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 deviations. Include an explanation of each step being taken to prevent the recurrence of deviations 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 **(b)(4)** USP, and provide the date and reasons you ceased production. Please identify your response with FEI #3003091092.

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

U.S. Food and Drug Administration
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Division of Manufacturing and Product Quality
International Compliance Branch
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Silver Spring, MD 20993
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Sincerely,

/S/

/Richard L. Friedman/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research

[1] **(b)(4)** API is a USP article.

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