Inspections, Compliance, Enforcement, and Criminal Investigations

Jiangsu Province Jianerkang Medical Dressing Co. 7/30/12

Department of Health and Human Services

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

Warning Letter

VIA UPS MAIL

WL: 320-12-021

July 30, 2012

Mr. Chen Guoping
President
Jiangsu Province Jianerkang Medical Dressing Co., Ltd.
Zhixi Town
Jintan City, Jiangsu 213251
P.R. China

Dear Mr. Guoping:

During our September 13 to 19, 2011 inspection of your pharmaceutical manufacturing facility, Jiangsu Province Jianerkang Medical Dressing Co., Ltd., located at Zhixi Town, Jintan City, Jiangsu 213251, China, investigators 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 dated October 5, 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 failed to establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile [21 C.F.R. § 211.113 (a)].

The FDA collected samples of multiple lots of Zee Antiseptic Wipes and tested them. Several antiseptic wipes tested from two lots contained *Burkholderia cepecia.* The following is a summary of the results:

a. Lot JT1511-1 (manufactured in August, 2011): *B. cepacia,Staphylococcus intermedius,* and *Staphylococcus sciuri.*

b. Lot JT23210 (manufactured in August, 2010): *B. cepacia and Burkholderia pseudomallei.*

We note that the label for Zee Antiseptic Wipes indicates that their intended use is to "help prevent infection in minor cuts, scrapes and burns." The user is instructed to "dab the wound with the wipe" and "cover with a *sterile* bandage" [emphasis added]. We also note that your firm is not producing this product as sterile, but instead tests it for microbial contamination. It is essential that your firm's topical antiseptic drugs be produced in a manner that is appropriate in view of their intended use. The presence of organisms such as *Burkholderia cepacia* in a product intended to be used for wounds is unacceptable.

Please include in your response the source of the contamination, as well as a list of all products that are potentially impacted by the contamination. In addition, please include the in-process and finished product test results for all potentially impacted lots, distributed or undistributed. Include an explanation of the validated test methods that have been used to test your in-date marketed products for microbiological quality. Provide details on how your firm determined the identity of microbes in your non-sterile topical products, including whether only limited indicator organism testing, or routine speciation of bioburden, was performed when testing each batch for absence of objectionable microorganisms.

We are concerned about your firm's failure to assure appropriate microbial quality of batches shipped to the US, and the insufficient basis for your actions thus far to address the potential patient hazard posed by your manufacturing practices. Provide a risk assessment of all products that have been released to the market and an action plan with a strong scientific rationale that supports your plans regarding all potentially impacted lots, both distributed and undistributed.

2. Your firm failed to include validation of all sterilization processes in its written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. § 211.113(b)].

The following are examples of this violation:

a) Your "**(b)(4)** sterilization process" (**(b)(4)** for **(b)(4)** hours) for Povidone-Iodine Gel Swab Sticks appears to be inadequately designed to achieve robust sterilization of your firm's drug products.

b) Your firm's validation report of the sterilization process for the Povidone-Iodine Gel Swab Sticks did not include **(b)(4)** studies for the **(b)(4)** identified as **(b)(4)**.

There is no data in the **(b)(4)** validation report to support a determination that the biological indicator used by your firm is appropriate for your chosen sterilization method and conditions or is representative of microorganisms that are particularly resistant to the sterilization conditions. In response to this letter, provide an evaluation of whether this **(b)(4)** process is an appropriate sterilization method. Include a revised protocol for validating the sterilization cycle method that you will be using for Povidone-Iodine Gel Swab Sticks and a timeline for executing the protocol. Describe how the executed protocol will demonstrate that a robust and reproducible sterilization method is used for your products.

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, in response to FDA 483 observation 6E regarding the failure to document the non-conformance of not meeting specified temperature range during the **(b)(4)** sterilization cycle, you stated that your firm had recently initiated an investigation into the non-conformance. Your investigation focused on the instances when your firm exceeded the range, and the impact on product quality but did not identify that the same sterilization runs also dropped below the specified range of **(b)(4)**°C ± **(b)(4)**°C as follows:

- During processing of Sterilization Lot **(b)(4)**, sterilization thermometer T1 dropped below the specified range with a temperature reading of **(b)(4)** at 17:08:26 and did not reach the minimum specification of **(b)(4)**°C until 17:58:28.

• During processing of Sterilization Lot **(b)(4)**, T1 dropped below the specified range with a temperature reading of **(b)(4)** at 9:11:53 and did not reach the minimum specification of **(b)(4)**°C until 9:41:52. Probe T2 also dropped below the minimum allowed temperature during this run.

• During processing of Sterilization Lot **(b)(4)**, T1 dropped below the specified range with a temperature reading of **(b)(4)** at 9:11:49 and did not reach the minimum specification of **(b)(4)**°C until 9:41:48. Probe T2 also dropped below the minimum allowed temperature during this run.

Sterilization lots **(b)(4)** were used to manufacture Povidone- Iodine Gel Swab Sticks finished product lot **(b)(4)**, which was distributed to the US.

Include in your response to this letter, an evaluation of the impact of the failure to operate within the specified range of the sterilization process on the finished product lot **(b)(4)**, including the sterility testing results of retain samples. Your evaluation should extend to other batches of the same drug product that may have been associated with the failure. Additionally, your response should include your corrective and preventive action plan to ensure a thorough investigation of future out-of-specification cycle parameters, test results, or other non-conformances.

4. Your firm failed to establish scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity [21 C.F.R. §211.160(b)].

The following are examples of this violation:

a. Your firm failed to prove that the methods used to perform the bacteriostasis and fungistasis tests on Povidone-Iodine Gel Swab Sticks are equivalent to or better than the USP methods. The test methods used to evaluate the inhibitory effects of the Povidone-Iodine on the ability of the **(b)(4)** and **(b)(4)** to support microbial growth lacked the requirement to use **(b)(4)** as part of the validation test as well as adequate incubation times and temperatures.

In your response to the FDA 483, you stated that you will perform a method validation on the bacteriostasis and fungistasis testing according to USP; however you failed to provide the protocol you will use to perform the validation.

b. Your "Protocol of sterility test" states **(b)(4)** and **(b)(4)** will be incubated for **(b)(4)** days at **(b)(4)**°C and **(b)(4)**°C, respectively. However, according to your "Report of sterility test," the sterility testing was conducted using only **(b)(4)** incubated at **(b)(4)**°C for **(b)(4)** days. Your protocol entitled "Protocol of sterility test" for the Povidone-Iodine Gel Swab Sticks is not supported by the "Report of sterility test."

You did not address this in your FDA483 response.

In your response, include the test method validation and studies that you have conducted to ensure reliable testing for sterility. Identify the method used to neutralize the antimicrobial effects of the Povidone-Iodine. Identify the microbial cultures, incubation times, temperatures, and media used during sterility testing. Also provide sample size justification if it is different from the USP-recommended sample size. In addition, provide your risk assessment of the impact of this deficiency on products distributed to the US that are still within expiry, and any actions planned for these lots.

5. Your firm has not conducted at least one specific identity test and has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals [21 C.F.R. § 211.84(d)(2)].

For example, your firm failed to conduct identity testing on incoming lots of the active

pharmaceutical ingredient (API) Povidone Iodine, but rather relied on the Certificate of Analysis from the API supplier. Your firm used this API in the manufacture of the finished product, Povidone-Iodine Gel Swab Sticks, lots **(b)(4)**, and **(b)(4)**. Your firm also was not consistently collecting retain samples of incoming API for Povidone Iodine.

In your response to the 483 observation, you stated that you conducted identity testing on the retain samples of Povidone Iodine API used to manufacture finished product lots **(b)(4)**, and **(b)(4)** of the Povidone-Iodine Gel Swab Sticks; however, you did not provide the results of the identity tests. Furthermore, you did not address the inconsistent sampling and testing of the incoming lots of Povidone Iodine API.

In your response to this letter, include your review of all Povidone Iodine API lots used to manufacture finished products, within expiry, distributed to the US. State which of these API lots lacked testing and provide results of tests on API retain samples and the corresponding finished product lots. Your response should also include your vendor qualification procedures and processes for ensuring collection of retain samples of incoming batches of Povidone Iodine API.

6. Your firm does not have a written testing program designed to assess the stability characteristics of drug products in order to determine appropriate storage conditions and expiration dates [21 C.F.R. § 211.166(a)].

For example, your firm failed to conduct supportive stability studies prior to the release of Povidone-Iodine Gel Swab Sticks with shelf life of **(b)(4)** years and sterile Alcohol Prep Pads with a shelf life of **(b)(4)** years.

In your response to the FDA 483 observation, you stated that you conducted stability studies on samples of the Povidone-Iodine Gel Swab Stick lot **(b)(4)** that was manufactured in 2009 and Alcohol Prep Pad lot **(b)(4)** that was manufactured in 2010. However, the methods used to conduct the package integrity testing for the Povidone-Iodine Gel Swab Sticks *in lieu* of sterility testing lack scientific evidence to justify the use of the methods selected.

In your response to this letter, include a detailed stability program that will ensure all stability characteristics of each of your products throughout their intended shelf-life, as well as a commitment to ensure that all products are tested according to an approved stability program. List the test methods, testing frequencies, and acceptance criteria, and provide summary validation information for any methods that are not USP methods.

The items listed above, as well as other deficiencies found at your site, 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. Examples are the presence of objectionable microorganisms in non-sterile products and inadequate validations to ensure sterility of products purporting to be sterile. Be advised that corporate management has the responsibility to ensure the quality, safety, and integrity of its drug products. FDA expects that your executive management will immediately undertake a comprehensive and global assessment of your manufacturing operations, including facility design, procedures, personnel, processes, and systems, including your aseptic processing and sterilization capabilities, to ensure that drug products conform to FDA requirements.

Due to continuing CGMP issues at your firm, we recommend you engage a third party consultant with appropriate CGMP expertise to assess your firm's facility, procedures, processes, and systems to ensure that the drugs you manufacture have their appropriate identity, strength, quality, and purity.

The Agency is concerned about the response of Jiangsu Province Jianerkang Medical Dressing Co. Ltd. to this matter. It appears that your firm continues to lack an appropriate resolution to significant microbial quality issues relating to your firm's antiseptic drug products. Senior management has the responsibility to ensure the quality, safety, and integrity of its products. A fundamental part of this responsibility is assuring timely investigation and resolution of the

issues and preventing distribution of defective products.

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 US standards for CGMP and all applicable US 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 on FDA Import Alert and FDA will continue to refuse admission of all articles manufactured at Jiangsu Province Jianerkang Medical Dressing Co. Ltd., Jintan City, Jiangsu, China, into the United States. Because your firm is currently on 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)].

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, in your response, you should state if you no longer manufacture or distribute any specific drug products and for each, provide the product name, date, and reason(s) you stopped producing it. Please identify your response with FEI # 3006403682.

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

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Sincerely,
/Steven Lynn/
Steven Lynn
Director
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Page Last Updated: 08/07/2012
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