DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Use this check box to generate the required 483 statement on page 1 for medical device observations. ☐

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
10903 New Hampshire Avenue, Bldg 51, Rm 4225 Silver Spring, MD 20993 Phone: (301)-796-3334 Fax: (301)-847-8738 Industry Information: www.fda.gov/oc/industry	06/15-18/2015
	FEI NUMBER 3003631275

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Zhang Dingfeng, Site Head

FIRM NAME	STREET ADDRESS
Zhejiang Medicine Co. Ltd. Xinchang Pharmaceutical Factory	98 East Xinchang Dadao Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Xinchang, Zhejiang, CHINA 312500	Active Pharmaceutical Ingredient Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

OBSERVATION 1

Laboratory control procedures are not followed.

Specifically, during our review of your firm's Quality Control laboratory electronic chromatography data, we identified significant deviations from your laboratory control procedures. Our review found that samples are pre-tested multiple times prior to performing the official/reported analysis. This trial analysis data was performed and saved within your auxiliary "R&D" project folders. All raw data (e.g. sample weight/dilutions) pertaining to these trial sample analyses are discarded.

Our review of the historical data collected for residual solvent by GC testing of (b) (4) API identified what appear to be potentially significant differences between the trial and official results, including sample results that appear to include unknown peaks, which may cause the batches to be considered out-of-specification. However, due to the lack of supporting raw data (e.g. sample weights/dilutions), an accurate calculation of the residual solvent levels was not possible. Notably, your firm has initiated a total of 1 OOS investigation (including raw materials, in-process and finished products) since 01/2013 deemed to be due to laboratory error.

For example:

A) (b) (4) API batch # (b) (4)

- The initial trial sample analysis was performed on 05/01/13 starting at 11:10am

- The second trial sample analysis was performed on 05/03/13 starting at 10:31am

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		Peter E. Baker, Investigator Dr. Guang Gao, Drug Analyst	06/18/2015

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- The official/reported analysis was performed on 05/03/13 starting at (b) (4)

B) (b) (4) API batch # (b) (4)

- The initial trial sample analysis was performed on 06/18/13 starting at 9:52am

- The second trial sample analysis was performed on 06/18/13 starting at 3:23pm

- The official/reported analysis was performed on 06/18/13 starting at (b) (4)

C) (b) (4) API batch # (b) (4)

- A trial sample analysis was performed on 04/22/13 starting at 9:52am

- The official/reported analysis was performed on 04/23/13 starting at (b) (4)

D) (b) (4) API batch # (b) (4)

- A trial sample analysis was performed on 06/13/13 starting at 10:07am

- The official/reported analysis was performed on 06/13/13 starting at (b) (4)

E) (b) (4) API batch # (b) (4)

- The initial trial sample analysis was performed on 04/22/13 starting at 12:26pm

- The second trial sample analysis was performed on 04/22/13 starting at 4:00pm

- The official/reported analysis was performed on 04/22/13 starting at (b) (4)

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OBSERVATION 2

QC Laboratory records are not documented contemporaneously.

Specifically,

A) During our inspection of your finished API Quality Control Laboratory on June 15, 2015, we observed that a QC analyst pasted balance weighing slips, which were generated on June 11, 2015, onto the "Testing Original Records of (b) (4) DS" worksheet (Lot #: (b) (4) and signed her name and back dated as June 11, 2015.

B) During our inspection of your finished API Quality Control Laboratory on June 15, 2015, we observed an analyst performing a calculation for "SST Record for HPLC Analysis of (b) (4) (USP)-Chromatographic Purity" based on the HPLC test data generated on June 10, 2015. However, the blank "calculation" page was pre-signed and dated June 10, 2015 when the HPLC test was performed.

C) During our inspection of your finished API Quality Control Laboratory on June 17, 2015, we found that an analyst had set up microbiology testing for finished dosage (b) (4) (b) (4) Injection (for domestic market) and (b) (4) Water. Culture plates will be monitored for bacteria growth (b) (4) starting June 18 for (b) (4). The testing report, however, was signed on June 17; before completing this testing.

OBSERVATION 3

Deviations from critical control points are not investigated.

Specifically, from 01/2013 to 08/2013, your firm initiated a total of 7 deviation investigations regarding (b) (4) (b) (4) excursions during (b) (4) of (b) (4) API. This (b) (4) limit is considered a critical control point. Our review of the 7th deviation found that your firm had concluded no further

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deviation investigations were necessary regarding [redacted] (b) (4) excursions during [redacted] (b) (4) due to a historical data review demonstrating that 27 previously manufactured batches (01/2012 to 06/2013) had met the final release specifications. SOP-PMP310010-2 "Disposing Procedure for Abnormal Events" was revised on 08/27/13 to reflect this change.

However, this [redacted] (b) (4) limit is still considered a critical control point within your written procedures, and no further studies (e.g. stability) or other scientific justification are available to support a lack of investigation.

OBSERVATION 4

There is no assurance that software used to control critical processing equipment is capable of meeting user requirements for data security.

Specifically, during our review of the validation package for the [redacted] (b) (4) software used to control your [redacted] (b) (4) #D3001, we found the following deficiencies:

A) There is no written document describing the User Requirement Specifications (URS)

B) There are a total of three common login IDs (Admin, Manager, Operator) with various access levels. There are no unique usernames/passwords established. There is no written procedure to define the access level (e.g. ability to alter recipe) for each of the three login IDs.

C) The validation package was written, performed, and reviewed by a third party contractor. There is no evidence that the validation was reviewed by your Quality Unit and deemed acceptable.

OBSERVATION 5

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Electronic records are not adequately maintained, archived and retrieved.

Specifically,

A) The electronic raw data for your (b) (4) D3001 and D3002, controlled using the (b) (4) and (b) (4) (b) (4) software, respectively, is transferred onto a USB drive and then to another desktop for archival After transferring to this second desktop, the original electronic data on the first desktop and USB drive are deleted. There are no written procedures for electronic data retention, transferring, and archiving in order to ensure data security.

B) For the electronic raw data transfer process described above, there is and has been no verification step to ensure the accuracy and completeness of the transfer. Furthermore, for review, the data must be re-copied and transferred (using the USB drive) back to the original desktop with the appropriate software, and is not readily retrievable for evaluation.

OBSERVATION 6

Critical control parameters are not adequately monitored and controlled.

Specifically,

A) Our review of restored (b) (4) data for (b) (4) Batch No. (b) (4) found that the run parameters including (b) (4) and (b) (4) were not recorded for the time period from 13:28:37 to 15:08:37, May 29, 2015. No deviation was documented; not root cause was identified, and no investigation was conducted.

B) During this (b) (4) process, there were 20 alarms generated including two FV29 chamber inlet valve 1 failures. There are no written procedures in place to define the significance of alarms. When questioned, the responsible operator was unable to define the significance of alarms generated during manufacturing operations.

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OBSERVATION 7

Laboratory electronic raw data is not controlled and protected.

Specifically, during our review of the electronic potency raw data for [redacted] (b) (4) collected using the ZY-300IV Multifunction Microbiology Analyzer, we noted the following deficiencies regarding data security:

A) There is no provision in place to create raw data records for each analysis performed. Test results are required to be saved manually.

B) There are no individual user names/passwords configured. All analysts use a common login ID/password.

C) There are no controls in place to prevent data from being deleted between the [redacted] (b) (4) server back-ups.

OBSERVATION 8

Adequate washing and toilet facilities are not provided.

Specifically, during our inspection of the [redacted] (b) (4) area within unit # [redacted] (b) (4) we found there was no soap available at the entrance hand-washing station. Soap is required to be used per your posted entrance instructions.

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