Med-Pharmex, Inc. 5/17/17

U.S. FOOD & DRUG ADMINISTRATION

U.S. Food and Drug
Administration
Los Angeles District
19701 Fairchild Road
Los Angeles, CA 92612

WARNING LETTER

VIA UNITED PARCEL SERVICE
SIGNATURE REQUIRED
May 17, 2017

WL 31-17

Gerald P. Macedo, Owner
Med-Pharmex, Inc.
2727 Thompson Creek Road
Pomona, California 91767
Dear Mr. Macedo:

The U.S. Food and Drug Administration (FDA) conducted an inspection on January 17, 2017 to February 1, 2017 at Med-Pharmex, Inc., located at 2727 Thompson Creek Road, Pomona, California and determined your firm is a manufacturer of animal drug products such as sterile injectables, oral suspensions, ointments, creams, non-sterile injectable and non-sterile topical ointments. Our investigators from the FDA identified significant violations of the current good manufacturing practice (CGMP) regulations for finished pharmaceuticals, Title 21 Code of Federal Regulations (C.F.R.), Part 211. These violations caused your animal drug products 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 received your response dated February 22, 2017, concerning the Form FDA 483 (FDA 483), List of Inspectional Observation that was issued to your firm. We have conducted a detailed review of your firm's response and note that it lacks sufficient corrective actions for the concerns noted in this letter.

These violations include, but are not limited to, the following:

1. Your firm does not follow procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 C.F.R. 211.113(b)]. For example, on January 17, 2017, during the aseptic filling of **(b)(4)**, our investigators observed the following aseptic technique deviations:

A. The technique used by an Aseptic Fill Operator to remove the tray lid containing **(b)(4)** vials allowed for the operator's left hand and forearm to pass directly above empty, exposed vials.

B. Upon exiting the cleanroom at approximately 11:20 AM, one Aseptic Fill Operator was observed changing gloves immediately before personnel monitoring samples were taken. At approximately 2:51 PM, another Aseptic Fill Operator exiting the cleanroom was observed spraying gloves with **(b)(4)** before personnel monitoring samples were taken.

These instances of poor aseptic technique are critical and similar issues were observed during the previous FDA inspection of your firm, conducted February 8-17, 2016. In your response, you indicate that retraining of personnel occurred, however you did not evaluate individual aseptic processing operator trends for each operator. An evaluation was not conducted to determine if aseptic processing operators would require re-certification. Your response states these observations are not standard practice, but you did not provide a written Standard Operating Procedure to support this claim. Nor did you outline the training reportedly given to the cleanroom personnel.

2. Your firm does not exercise appropriate controls over computer related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel [21 C.F.R. 211.68(b)]. For example:

A. Your "Processed By" dates and times listed on printed chromatograms do not always show the same "Processed By" dates and times listed on the system chromatograms.

B. Your data in the audit trails does not always show the same data listed on your printed chromatograms.

Your response states you have not observed any test result data discrepancies between your printed versions of the test results. However, this does not address adequate electronic data controls to prevent inconsistencies between the printed and electronic data. Your responses for 2A and 2B above are not adequate in that your firm did not provide any corrective action addressing the assessment of all relevant data in the audit trails.

C. Your firm enters data into **(b)(4)** files to complete plate assay calculations but they are not locked from editing once the file has been reviewed.

Your response fails to include any corrective action to ensure that there is no further access or ability to save over test results in **(b)(4)** spreadsheets once reviewed and approved.

D. Your firm did not give unique sample set names to different sequences of samples run on different instruments on the same day.

Your response is not adequate. Your firm did not address the concern of the possibility of sample sets with the same name overwriting each other during the data backup process.

3. Your firm's aseptic processing areas are deficient regarding air supply that is filtered through high-efficiency particulate air filters under positive pressure [21 C.F.R. 211.42(c)(10)(iii)]. Specifically, your Standard Operating Procedure ENP-0002-07-07, Certification of Classified Cleanrooms, Effective 10/20/15, indicates airflow velocities of HEPA filters are recertified by an outside vendor at a minimum of **(b)(4)** regular intervals. Regarding recertification activities conducted in April 2016 and October 2016:

A. Your firm did not evaluate work height velocities in ISO 5 East Fill Room (Room **(b)(4)**). Your outside vendor's airflow velocity measurements only evaluate the velocities at the filter face, no more than **(b)(4)** from the source of the laminar flow air supply.

Your response states neither the current ISO guidance nor USP requires the evaluation of work height velocities in ISO 5 areas. Your response is not adequate. USP General Chapters: <1116> MICROBIOLOGICAL CONTROL AND MONITORING OF ASEPTIC PROCESSING ENVIRONMENTS indicates that while absolute measures of airflow velocity and exchange rates are not defined, they are still a useful indicator of airflow movement.

Furthermore, FDA recommends HEPA-filtered air should be supplied in critical areas at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within the critical area. The work height airflow velocity measurements are essential to obtain since differences in velocities at this height can directly affect product sterility. FDA recommends velocities of unidirectional air should be measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area.

B. During the recertification of the ISO 5 East Fill Room (Room **(b)(4)**) in October 2016, HEPA filter airflow velocity measurements from **(b)(4)** of **(b)(4)** HEPA filters performed on October 3, 2016 were found to be **(b)(4)** the your specification of greater than or equal to **(b)(4)**. Your firm replaced the pre-filters and retested the filter velocities the following day without conducting an investigation into the **(b)(4)** velocity readings.

C. Your firm lacks uniformity assessment specifications for airflow velocities within the same filter and between adjacent filters in the ISO 5 East Fill Room (Room **(b)(4)**).

Your firm's response references Standard Operating Procedure ENP-0002-07-07 which only addresses the average airflow velocity of the HEPA filters in the ISO 5 area and does not address establishing specifications for individual HEPA filters. Also, your response is not adequate in that you do not specify how airflow velocities will be evaluated to determine if airflow visualization is necessary. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity can cause turbulence that increases the possibility of contamination and should be investigated.

4. Your firm's aseptic processing areas are deficient regarding the system for monitoring environmental conditions [21 C.F.R. 211.42(c)(10)(iv)]. Specifically, your firm's SOP-0024-05-17, Environmental Monitoring Program, Effective March 7, 2016, indicates a "**(b)(4)**" and set a **(b)(4)** contamination recovery rate limit for the following categories in the ISO 5 East Fill Room (Room **(b)(4)**): active air samples, settling plates, contact plates/swabs, and gloves/garments.

A. Your firm does not perform any investigations if the **(b)(4)** limit is exceeded during a single sampling period, such as one batch, or at one sampling location over the twelve month span. For example, your firm's November 2016 trending data showed a **(b)(4)** recovery rate at equipment surface sample Area **(b)(4)** (filling nozzle) and a **(b)(4)** recovery rate at floor surface sample Area **(b)(4)** (south side of the fill room) but no investigations were conducted for these sites.

B. Your firm's May 2016 trending data did not accurately report an aseptic operator's personnel bioburden for personnel monitoring samples taken during Media Fill, batch 051616. The trending data indicated zero counts for the operator with an entry time of 8:50 AM on 05/18/16, while the batch record indicated counts of **(b)(4)** CFU each on the operator's **(b)(4)** and **(b)(4)**.

Your firm's response does not address evaluating trends and investigating individual environmental monitoring excursion on a batch when you exceed the [b4] limit per SOP 0024-05-17 Environmental Monitoring Program, effective date March 7, 2016.

5. Your firm does not have an adequate system for cleaning and disinfection of the aseptic processing area [21 C.F.R. 211.42(c)(10)(v)]. Specifically, on January 17, 2017, during the aseptic filling of **(b)(4)**, our investigators observed the following conditions in East Fill Room (Room **(b)(4)**).

A. Vinyl tape surrounding wheels of **(b)(4)** carts used to transport vials and environmental monitoring equipment did not appear to be completely affixed to the wheels with overlapping material protruding on the sides of the wheels. The overlapping material appeared worn and dirty.

B. An area of the ceiling spanning across at least two HEPA filters **(b)(4)** the **(b)(4)** had dark stains on the ceiling frame and the HEPA filters. Your routine cleaning of the cleanroom does not cover cleaning of the ceiling and HEPA filters which are only replaced when there is damage.

Your firm states that clean room **(b)(4)** surrounding wheels of the **(b)(4)** carts used to transport vials and environmental monitoring equipment is replaced on a minimum of **(b)(4)** basis. Your response is inadequate to address our concerns. Your firm did not investigate the cause or identify the apparent splattered dark stain on the ceiling frame and the HEPA filters in the cleanroom. Your firm has not established a frequency sufficient to evaluate the cleanliness of all parts of the cleanroom prior to processing.

6. Your firm does not have laboratory records that include complete data derived from all tests necessary to assure compliance with established specifications and standards, including examinations and assays. [21 C.F.R. 211.194(a)]. Specifically, on January 26, 2017, our investigator observed your microbiologist read **(b)(4)**, **(b)(4)** for Tri-Otic Ointment, lots H6510 and H6514, using the antibiotic zone reader (instrument Asset **(b)(4)**). Our investigator verified your microbiologist recording the correct value as read from the plate reader; with a range of **(b)(4)** to **(b)(4)**. Then our investigator copied the handwritten zone diameter test results taken at the time of testing for the **(b)(4)** and **(b)(4)** zones of the standard series from the microbiologist's issued worksheet.

Your procedure is to then enter the raw data into document number MIC-0066-13-01 titled "**(b)(4)**", Attachment 1. On the completed form, the **(b)(4)** test results for the **(b)(4)** zones were not the same as observed by our Investigator; the range was 11.4 to 15.1. Your firm used an Excel spreadsheet to calculate the potencies of Tri-Otic Ointment lots H610 and H6514 as **(b)(4)** and **(b)(4)**, respectively.

Your response does not provide documentation of the January 26, 2017 handwritten zone diameter results for Tri-Otic Ointment (Lots H6510 and H6514), which you allege differ from our investigators' direct observation. We note your response acknowledges that you should have provided our Investigator a copy of the handwritten zone diameter results. You have not subsequently verified complete raw data was maintained.

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 that your firm complies with all requirements of federal law and FDA regulations. You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions may include, but are not limited to, seizure of your products and/or injunction. Federal agencies are advised of the issuance of all Warning Letters relating to drug products so that they may take this information into account when considering the award of contracts.

Finally, we note that your website at www.medpharmex.com contains the FDA logo with a direct link to www.fda.gov. The FDA logo is for the official use of the FDA and not for use on private sector materials. Unauthorized use of the FDA logo may violate federal law and subject those responsible to civil and/or criminal liability.

Within fifteen (15) working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete the corrective actions within fifteen days, state the reason for the delay and the date by which you will have completed the corrections.

Your firm's response should be sent to:

CDR Steven E. Porter, Jr.
Los Angeles District Director
United States Food and Drug Administration
19701 Fairchild
Irvine, California 92612

If you have any questions regarding any issues in this letter, please contact Ms. Mariza Jafary, Compliance Officer via email at Mariza.Jafary@fda.hhs.gov or by phone at (949) 608-2977.

Sincerely,
/s/
CDR Steven E. Porter, Jr.
Los Angeles District Director

Cc: David M. Mazzera, Ph. D.
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