U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

PM Resources, Inc. dba Virbac Animal Health, Inc. 12/18/15

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Kansas City District
Southwest Region
8050 Marshall Drive, Suite 205
Lenexa, Kansas 66214
(913) 495-5100

December 18, 2015

WARNING LETTER

VIA UPS

Ref. CMS 450565

Mr. Paul R. Hays, President and CEO
Virbac Corporation, North America
3200 Meacham Blvd.
Ft. Worth, Texas 76137-4611

Dear Mr. Hays:

An inspection of your animal drug manufacturing facility, Virbac Animal Health, Inc., located at 13001 St. Charles Rock Road, in Bridgeton, Missouri, 63044, was conducted October 29 – December 30, 2014, by representatives of the Food and Drug Administration (FDA). During this inspection, our investigators documented significant deviations from the current Good Manufacturing Practice (cGMP) regulations for finished pharmaceuticals, Title 21 CFR Part 211 [21 CFR 211], which caused your drugs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [21 U.S.C. 351(a)(2)(B)]. You can find the FD&C Act and FDA's regulations through links on FDA's web page at **http://www.fda.gov (http://www.fda.gov/)**.

We acknowledge that you initially responded to the FDA 483 in January 8, 2015 and described numerous corrective actions. Since then, you provided a copy of your Quality System Improvement Plan, and have continued to send progress reports approximately every two months including the most recent response dated November 20, 2015. You indicated, among other things, that you hired several additional full time employees to work in Quality Assurance, and that you retained a third party to implement a batch certification process and perform an audit to review your quality improvements. However, we remain concerned about quality practices and quality culture at your facility. We note that many of the observations from your previous inspection are repeat observations from several prior inspections after which you also asserted corrective actions would be implemented.

Significant deviations from the cGMP regulations observed during the inspection at your firm include, but are not limited to, the following:

1. Your firm failed to establish and adequately staff a quality control unit capable of meeting the responsibilities outlined in 21 CFR 211.22. This is a repeat observation from your 2007, 2008, and 2010 FDA inspections. In addition, your firm failed to have written procedures covering significant responsibilities of the Quality Unit, as required

by 211.22(d).

As discussed further throughout this letter, examples of the failure of your firm's Quality Unit include, but are not limited to:

a. Your Quality Unit failed to prevent the release of animal drug products that fail to meet specifications.
b. Your Quality Unit failed to conduct investigations and resolve all discrepancies/failures/deviations, and complaints.
c. Your Quality Unit failed to extend investigations of failures to other products or processes which may also be affected.
d. Your Quality Unit failed to use a change control process to update equipment, processes or written procedures, work instructions, and forms.
e. Your Quality Unit failed to ensure changes made to an approved application were submitted to the appropriate regulatory agency.

Your firm's responses to the FDA 483 indicate your firm has either developed or revised several Quality System Standard Operating Procedures (SOPs). In addition, your firm has hired additional QA staff. In particular, your firm now has an SOP "Responsibilities of the Quality Unit." This SOP reads more like a policy document than an actual procedure as it states responsibilities, but does not provide detailed instructions.

While we acknowledge the steps your firm has taken recently, it appears that your firm has historically lacked quality practices and a quality culture, which has resulted in numerous repeat violations.

2. Your firm failed to reject drug products failing to meet specifications, as required by 21 CFR 211.165(f). This is a repeat observation from your 2010 FDA inspection.

We observed that when you obtained out-of-specification (OOS) results, in some instances you re-tested multiple times without scientific rationale for doing so until passing results were obtained, and then reported either the average of the OOS results and the re-test results, or just the re-test results. We also observed instances in which you re-sampled in order to achieve passing results. Specific examples include, but are not limited to:

a. OOS 14-074 from 2/18/2014 for **(b)(4)** assay – initial result **(b)(4)**%; reported result of **(b)(4)**% was the average of only the re-test results (limits **(b)(4)**%).

b. OOS 14-236 from 6/20/2014 for Iverhart Max® **(b)(4)** assay–initial result **(b)(4)**%; reported result of **(b)(4)**% was the average of **(b)(4)** results (limits **(b)(4)**%).

Your firm's response states you have revised your "Out-of-Specification Results" SOP to ensure that all OOS results are properly recorded, reported, and investigated. This SOP revision states that if the OOS investigation determines the OOS result is valid, then the OOS result is reported. However, the two previous versions of this SOP also required the OOS result to be reported if the OOS investigation found the OOS result to be valid; yet your practice was to re-test. Your firm's practices even included that if the re-test results were still OOS, then the employee would re-sample in order to attain passing results. In addition to revising your SOP, you should take steps to ensure that your employees follow it.

3. Your firm failed to establish control procedures which validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product, as required by 21 CFR 211.110(a). This is a repeat observation from your 2013 FDA inspection.

Specifically, your firm failed to validate your **(b)(4)** and manufacturing processes for several products, including but not limited to, Iverhart Max®/Quadriguard Chewable Tablets , Iverhart Plus® Flavored Chewable Tablets, Clinsol®/Clindacure Liquid, and Soloxine®**(b)(4)** Tablets.

In your response dated May 28, 2015, you indicated you validated your **(b)(4)** on April 9, 2015. You provided a copy of your performance qualification (PQ) report, however your PQ failed total organic carbon testing. You did not investigate this failure. You have concluded that your system is considered qualified under these conditions. However, the failure to investigate and identify the root cause of the failure draws into

question your validation.

4. Your firm failed to establish and follow written procedures for the storage of drugs products under appropriate conditions of temperature and humidity so that their identity, strength, and purity are not affected, as required by 211.142(b). This is a repeat observation from 2007 and 2008 FDA inspections.

Specifically, all veterinary drugs products manufactured and distributed at this facility have temperature requirements listed on their labels such as 59º F – 86 º F, 68 º F – 77 º F, and do not store above 77 º F. You did not, however, have and follow written procedures to control and/or monitor the temperature in your warehouse areas, which are used to both receive and store product until it is distributed, to assure temperatures are controlled in accordance with your products' label requirements.

In your May 28, 2015 response, you indicated you implemented SOP "Warehouse Area Temperature Monitoring" and performed a winter performance qualification (March 2015) for your receiving warehouse, but your temperature mapping had failures. Your conclusion was that your qualification protocol for the Virbac Receiving Warehouse temperature profile met cGMP and Virbac requirements for resourced material, component, and drug storage, and therefore is acceptable for continued use. You indicated that an assessment of the areas that did not meet the temperature requirements and all storage areas in relation to temperature-sensitive materials and products will be performed; relocation of any materials and products will be determined and performed; and an evaluation will also be made to determine what changes or improvements to air circulation and heating or cooling can be made to improve those areas that do not meet proper storage temperature requirements. While we acknowledge these planned corrective actions, your performance qualification failed to meet your acceptance criteria, and your qualification should be performed again.

5. Your firm failed to thoroughly investigate any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed, as required by 21 CFR 211.192. This is a repeat observation from your 2013 FDA inspection.

For example:

a. Your firm failed to complete investigations into deviations and failures. Corrective and Preventive Action (CAPA) CAPA 11-010 was opened on 7/11/11 due to the failure of the ivermectin and praziquantel assays in the final blend of Iverhart Max® Process Validation lot #110065. At the time of the inspection, this CAPA was still not complete as it lacked identification of an official root cause, there was incomplete documentation of the work completed to date, and there was no plan for assessing the effectiveness of corrective actions taken.

Your firm's responses indicate the final blend study for Iverhart Max® failed final blend uniformity testing, but passed heightened tablet uniformity testing. **(b)(4)** does not guarantee that the final blend or the finished product is uniform. There are limitations to sampling, and your test results may not ensure that your product is uniform. This may not reflect a well-controlled manufacturing process. The manufacturing of the final blend should be adequately validated. In addition, it appears that your firm has attempted to conduct medical assessments of your products to justify releasing products with potential quality issues. This is not an adequate method to determine the quality of your drug products after having questionable testing results.

Additionally, your responses state that your firm has revised the "Out-of-Specification Results" SOP to ensure that all OOS results are properly recorded, reported, and investigated. However, based on your past history, your firm's problems may not only be rooted in deficiencies in a given SOP, but instead in a lack of quality practices. While we acknowledge that you have attempted to evaluate and closeout overdue investigations since your last FDA inspection, we note that you had an OOS procedure prior to the inspection, yet you still reported approximately 2000 overdue investigations of test results. In addition to revising your SOP, it is necessary to establish quality oversight and provide adequate training of your employees.

6. Your firm failed to extend investigations of an unexplained discrepancy and failure of a batch or any of its components to meet any of its specifications to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy, as required by 21 CFR 211.192.

Specifically:

a. Your firm's process validation of Iverhart Max®/QuadriGuard (ivermectin/pyrantel pamoate/praziquantel) Chewable Tablets failed in February 2011 due to out-of-specification ivermectin and praziquantel assays in the final blend. There is still no assignable cause, and your investigation of the failure did not extend to Iverhart Plus®/Wormshield/Heart Shield Plus (ivermectin/pyrantel pamoate) Chewable Tablets which also contain ivermectin. Subsequently, in 2013, 26 lots of Iverhart Plus®/Wormshield/Heart Shield Plus products were recalled and production was ceased while an investigation into stability failures with ivermectin potency was conducted.

b. In the QA Disposition section of OOS report OOS 14-307, dated 9/12/2014, a Manufacturing Investigation MI 140082 was to be initiated for further investigation of a confirmed Total Aerobic Microbial Count and Yeast/Mold out-of-specification result on lot # 140818 of Iverhart Plus® Medium Chewable Tablets. However, at the time of our inspection, no investigation had been initiated for lot # 140818 and there was no investigation to determine if the products manufactured just prior to and after the contaminated batch were affected. While lot # 140818 was rejected, production and distribution of Iverhart Plus® and other similar products were continued despite the lack of an identified root cause for this contamination.

We acknowledge your firm's response which states your SOP "Deviation & Corrective and Preventative Action Procedure" now explicitly requires extension of investigations to all other potentially impacted products. However, we have some concern that you may fail to fully understand your responsibilities under 21 CFR 211.192 because you also state in your response that the Iverhart Max® OOS failure for OOS ivermectin and praziquantel assays in the final blend was not extended to other products because the lot was considered uniform based upon the results of the final tablet assay. There are limitations to sampling, and your test results may not ensure that your product is uniform. This may not reflect a well-controlled manufacturing process. The manufacturing of the final blend should be adequately validated.

With respect to the OOS report OOS 14-307, dated 9/12/2014, your response states that the root cause for your microbial count failure was sample related. You have attributed it to improper glove changing by your operators, but you have also addressed moving mops and buckets in your 1st floor production wash room, and changing your towel procedure in 1st floor production wash room used by your mechanics to clean equipment. Your conclusion fails to fully identify the actual cause and also draws into question if other products produced were affected and how long this has been occurring. We expect a microbial assessment to determine the root cause of this issue.

7. Your firm failed to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product, including provisions for review by the quality control unit of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such products, a determination as to the need for an investigation in accordance with 211.192, as required by 21 CFR 211.198(a).

Specifically, your "Product Complaints" SOP in effect prior to the most recent inspection (SOP 0300-004 effective May 29, 2012) stated: "Oral and written complaints on finished products are directed to Quality Assurance by Contract Costumers via Virbac Ft. Worth Veterinary Technical Support Services." However from January 2014 through November 2014, your Pharmacovigilance Department received approximately 1900 complaints regarding approved products. Only approximately 21 of those complaints were forwarded to Quality Assurance. Out of those approximately 21 complaints received by Quality Assurance, only approximately 8 were investigated. Of the approximately 30 death complaints our investigators reviewed, your Pharmacovigilance Department failed to forward approximately 28 of them to the Quality Assurance for their review and investigation.

In your response, you indicated you have implemented several revised pharmacovigilance SOPs for product complaints and a decision tree for complaint investigations. You also indicated you have completed an audit of all product defect complaints and adverse events received during 2013 and 2014, and completed investigations resulting from your audit of product defect complaints.

Although you have several procedures related to complaints, your revised "Customer Complaints" SOP, Document No. QA SOP-00102 (SOP 0300-004 effective November 14, 2014) does not identify or reference all of your other complaint related procedures, including your SOP related to your 3-day Field Alert Procedure, which contains the criteria for when a complaint must be reported to FDA. In addition, SOP 0300-004 lacks information about when complaints are to be investigated.

In Section 7.3.6, your Complaint SOP states that QA shall maintain the customer complaint report files. Your firm's QA unit maintains a separate Excel spreadsheet for those complaints that come directly into the Bridgeton QA unit. You have no centralized system for tracking all your complaints. The use of Excel requires many management controls to prevent data alteration, and Excel does not have an audit trail to identify data changes.

The issues and violations noted above are not intended to be an all-inclusive list of violations that exist with respect to the manufacture of veterinary drugs at your facility. You are responsible for investigating and for preventing recurrence of these, or other violations, to ensure that you comply with all requirements of the federal law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations of the FD&C Act may result in enforcement action being initiated by the Food and Drug Administration without further notice, such as injunction and/or seizure.

Please notify this office in writing, within fifteen (15) working days of the receipt of this letter, as to the specific steps you have taken to correct the violations identified in this letter and any other violations of the FD&C Act, and to ensure similar violations do not occur. Your response should include an explanation of each step that has been taken or will be taken to achieve and maintain compliance with the regulations. Please include copies of any available documentation demonstrating that corrections have been made. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time frame within which the corrections will be completed.

Please direct your response to Amy E. Devine, Compliance Officer, Food and Drug Administration, at the above letterhead address. Please refer to CMS 450565 in your response.

Sincerely,
/S/
Cheryl A. Bigham
District Director
Kansas City District

Cc: Steven Buchholz, Ph.D.
Vice President, Quality and Compliance
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