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DEPARTMENT OF HEALTH AND HUMAN SERVICE

Public Health Service

Food and Drug Administration
Kansas City District
Southwest Region
11630 West 80th Street
Lenexa, Kansas 66214-3340

Telephone: (913) 752-2100

March 3, 2008

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER
Ref. KAN 2008-04

Mr. Paul T. Sudhakar
President/Chief Executive Officer
Midland Pharmaceutical LLC
1201 Douglas Ave.
Kansas City, KS 66103-1405

Dear Mr. Sudhakar:

During an inspection of your drug manufacturing facility located at 1201 Douglas Avenue in Kansas City, Kansas, between July 24, 2007 and September 5, 2007, a Food and Drug Administration (FDA) investigator from this office documented numerous deviations from current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals Title 21, Code of Federal Regulations, Parts 210 and 211. At the conclusion of the inspection a List of Inspectional Observations (Form FDA-483) was issued and presented to you and Jay E. Bergmann. You responded to the FDA-483 by letter dated November 12, 2007. We address this response below, in relation to each of the noted violations. The documented deviations cause drug products being manufactured at your facility to be adulterated within the meaning of Section 501(a)(2)(B) [21 U.S.C. 351(a)(2)(B)] of the Federal Food, Drug, and Cosmetic Act (the Act) in that the manufacture, processing, and holding of drugs do not conform with CGMP to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength and meet the quality and purity characteristics that they purport or are represented to possess.

In addition, as explained in detail below, your firm violates the Act by introducing into commerce certain "new drugs" that do not have FDA approval as required under Sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. These marketed prescription drugs also are misbranded pursuant to Section 502(f)(1) of the Act [21 U.S.C. § 352(f)(1)], because they do not bear adequate directions for use.

(b)(2)Low

The CGMP violations include, but are not limited to, the following:

1. Failure to have written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)]. Specifically, the process validation study for the manufacture of Sulfamethoxazole/Trimethoprim (SMZ/TMP) USP tablets, 800/160 mg and 400/80 mg is deficient for the following reasons:

    a. Although all steps have been identified as critical, not all steps have ranges or settings listed in the process validation protocol or report.

Your November 12, 2007 response acknowledges that validation of critical parameters is required. The response indicates that you have established validation parameters and performed a "retrospective" validation of existing drug product as a corrective action. However, your written procedures and your evaluation of the data submitted in support of the retrospective validation study are inadequate. First, you did not provide the rationale applied to establish the new tablet settings. In addition, it appears that you established the critical parameters by extracting data from a subset of existing batches that you then used to set the retrospective parameters. This is not a scientifically sound means of conducting a retrospective validation. Second, Attachment 6 of the response indicates that there were 26 batches reviewed, but you only used 10 batches to revise the new tablet settings, as shown on Attachment 7, and no rationale was provided demonstrating the selection criteria used to include/exclude batches for the validation study. Third, the retrospective validation study did not include the lower-strength product. Fourth, the new settings shown as Attachment 8 are not consistent with a) the parameters used during the initial validation in 2006, b) the suggested settings as observed in the batch record, or c) the settings used for other manufactured lots (as shown below) despite the fact that the new settings were established from existing batches. Fifth, the new parameters established during the retrospective validation are not set forth in the new validation protocol, which only indicates where the data should be recorded. Sixth, the response does not indicate whether any of the batches subject to the changes in critical parameters were evaluated for stability. All of the above suggest either a manufacturing validation process still under development or one lacking adequate controls.

Press Setting	Initial Process Validation Setting	Lot D0038	Suggested Setting	Retrospective Validation Setting	Lot C0040*
Pre-Compression	(b)(4)	33.8		(b)(4)	28.8 – 29.3
Compression	(b)(4)	37.4		(b)(4)	28.7 – 30.1
Fill Depth	(b)(4)	75.8 – 77.6		(b)(4)	85.1 – 86.1

* This is one of the several lots reviewed and excluded from the retrospective validation study.

The response also acknowledges that the dials used for tablet compression purposes are excessively worn and need to be adjusted when required in order to meet the critical parameters, but there is no written protocol addressing these adjustments. Nor does the response describe any actions taken to prevent similar occurrences, including written protocols requiring the maintenance of equipment for its intended use and adequate training.

As a general matter, your response to this charge does not address the additional fact that you have made significant changes to the critical process parameters without initiating a change request through your change control program to evaluate the impact of the changes in your product. The response also fails to address whether the changes were approved by the appropriate organizational units and the quality control unit.

b. Sampling details including specific sampling locations, sampling utensils, and instructions for mixing the samples, all of which are necessary to assure uniformity and homogeneity, are not listed in the validation protocol or recorded in the validation report or batch record. In addition, the sampling information obtained during the validation study is inconsistent with current practice.

Your November 12, 2007 response is inadequate in that it fails to address from where the samples are taken and instructions for compositing samples, if that is your practice, as supported by the validation study. Your explanation that "the test on the composite was performed for some parameters because that was the purported process during the finished product testing" is inadequate. Compositing portions of a sample during the validation study has an "averaging effect" and does not provide adequate information to demonstrate the homogeneity of the product. There is also a lack of scientific rationale to support your assessment that individual blend sampling locations do not impact moisture testing results. Please provide evidence to demonstrate that compositing samples from the beginning, middle, and end of the (b)(4) equipment assures a homogenous blend product. In addition, please provide supporting information to demonstrate that collecting samples from the (b)(4) equipment during process validation is equivalent to the current practice of collecting samples from a built-in sample (b)(4) in the (b)(4) equipment.

2. Failure to follow written production and process control procedures in the execution of the various production and process control functions and failure to justify any deviations from the written procedures [21 C.F.R. § 211.100(b)]. For example,

a. The manufacturing process is not conducted within the critical parameters established during the process validation. For instance, tablet press settings such as Pre-Compression, Compression, Fill Depth, and Turret Speed recorded during the manufacture of the SMZ/TMP USP tablets 800/160 mg are outside

the ranges used during process validation and outside the suggested settings on the batch record, as illustrated by the example included under item #1a.

b. Tablet press settings deviations from operational parameters used during the process validation such as Pre-Compression, Compression, Fill Depth, and Turret Speed are not recorded and justified. In addition, the scientific rationale was not provided to explain the need for the deviations.

As explained under item #1a, your November 12, 2007 response is inadequate.

3. Failure to thoroughly investigate unexplained discrepancies or a batch or any of its components not meeting any of its specifications, failure to extend investigations to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy, and failure to ensure that written records of the investigation include conclusions and follow-up [21 C.F.R. § 211.192]. For example,

   a. Investigations into out-of specification (OOS) results for Content Uniformity testing concluded that laboratory error had occurred and required test method changes and validation. However, drug products tested using the same method that caused the OOS results have not been evaluated to determine the lot quality using the newly-modified, valid method.

Your November 12, 2007 response states that the investigation concerning Content Uniformity results included a review of similar problems previously observed and resulted in significant changes including sample preparation revision and revalidation of the analytical method. The response failed to address the impact of the method changes on all batches of SMZ/TMP drug product tested by the suspect method, including batches with passing test results. There is no assurance that any of the test results are accurate and reliable. In addition, the corrective action to the test method resulting from the OOS investigations was not implemented in a timely manner. For instance, our investigator noted that the change control to modify the test method had not been finalized and that the sample test method used at the time of the inspection was the method in use in 2006.

Moreover, the changes to the Content Uniformity test method may not be sufficient and/or adequate to assure accurate and reliable test results because the first dilution step in the preparation of the sample test solution for the Content Uniformity and Blend Uniformity testing may result in a super-saturated solution and incomplete extraction of the active ingredient. Please address this concern. We note that you must implement meaningful corrective actions, including full validation under actual conditions of use.

   b. Investigation conclusions including laboratory sampling error are not specific enough to implement adequate corrections. In addition, they are not always substantiated by sound scientific evidence. For example, for an OOS result for high drug residue, the investigation concluded "no effect on any product[,]

contact surface area is very insignificant[,] and level of TMP found was only slightly over recommended residue." This conclusion is unclear and no rationale was provided to explain or support it. For an OOS result for Appearance (i.e., illegible tablets with black spots) the investigation concluded "one batch problem, no additional investigation recommended, no risk to other batches, force feeder could have malfunctioned at start." Again, no rationale was provided to support the conclusion. In addition, the latter OOS investigation provided several examples of equipment problems during tablet compression with no actions taken or recommended to prevent recurrence of the same problems in subsequent batches. Further, for OOS stability results for Content Uniformity determination at time zero, the investigation revealed that the test solutions which caused the OOS results were retested. However, once the root cause of the OOS results was identified, the OOS results were replaced by release testing results for Content Uniformity, without first implementing corrective actions and performing the analysis of ten additional tablets to confirm the quality of the batches.

Your November 12, 2007 response states that the drug residue cleaning process has been completed and all required tests met appropriate specifications. Please provide information to support the foregoing statement, including test results in subsequent manufactured batches. In addition, please provide documentation demonstrating that you have determined the root cause of the OOS results for the high drug residue and Appearance determinations and have implemented adequate corrections. Further, we acknowledge your response stating in part that in regards to the Content Uniformity test for stability purposes, the test did not have to be performed as it was not part of your stability program. However, we disagree with your approach to the related investigation in that once the OOS results at time zero were obtained, you did not perform an adequate and complete investigation in a timely manner. Rather, we note that your firm decided to disregard the OOS results at time zero and accept the release test results for Content Uniformity on the basis that the time zero test was "a stability analysis." As a consequence, your firm did not make the crucial determination of whether the three OOS Content Uniformity results obtained represented the character and quality of the batch.

c. Investigations are inadequate in that the test solutions that resulted in the OOS results are not always evaluated and no justification was provided for such inaction. For example, in a Blend Uniformity determination, the investigation revealed that samples 3, 4, and 7 produced low OOS results. Rather than examining these samples, however, you examined samples 5 and 6, and no rationale was provided to explain why you selected those samples to the exclusion of the samples that produced low OOS results. In addition, for a high OOS result in an Assay determination for a twelve-month stability sample, the test solution that generated the OOS result was discarded without explanation, even though the solutions were within expiry as recorded in the investigation. Further, for a high OOS result in an Assay determination for a six-month

stability sample, the vials containing the test solution that generated the OOS result were discarded without explanation.

We reiterate the FDA Inspector's reference to FDA's "Guidance for Industry: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" published in October 2006 to assist in further revising your standard operating procedures. This Guidance can be found at http://www.fda.gov/cder/guidance/3634fnl.pdf.

4. Failure to follow the procedures applicable to the quality control unit (QCU) [21 C.F.R. § 211.22(d)]. Specifically, the QCU failed to ensure that your procedure on the evaluation and investigation of OOS and out-of-trend (OOT) results is followed. For example,

    a. The procedure does not apply to analytical results "in which USP or other compendial monographs or chapter give guidance for re-testing" before considering the results to be OOS, yet the QCU allowed the use of the procedure to investigate and prematurely invalidate original test results for SMZ/TMP USP tablets.

    b. The procedure specifies that if investigations are not completed within twenty working days a justification will be provided and approved by the QCU. The QCU did not ensure that the rationale was provided and approved to justify at least twenty-seven instances when the investigations extended beyond twenty working days.

    c. The procedure requires tracking and periodic review of failure investigations, yet the QCU failed to ensure that these functions were performed by the firm's responsible personnel.

    d. The procedure stipulates that if the investigation is inconclusive, the original results and the retested results must be individually reported in the final report of analysis or reported as an average, yet the QCU allowed the reporting of only the passing results, thus disregarding the original failing results that could not be invalidated by the investigation.

Please refer to "Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulations," published in September 2006 to assist you in revising your QCU processes, available at http://www.fda.gov/cder/guidance/7260fnl.pdf.

5. Failure to maintain adequate records for returned drug products and to follow written procedures related to returned drug products [21 C.F.R. § 211.204]. For example,

    a. Records do not include the reason for the return, date of disposition, and ultimate disposition of returned drug products.

b. As per written procedure, returned drug products require a Return Goods Form be affixed to the product for further processing. Out of [redacted] entries, with [redacted] corresponding to SMZ/TMP USP tablets, only two entries documented that the required form had been issued, and those forms could not be found. Although multiple products were returned, no such forms were issued from November 2006 to June 2007.

Your November 12, 2007 response indicates that the Returned Goods procedure has been revised and training has been provided. The response acknowledges that the procedure was inadequate and that the required forms could not be located. However, your response does not explain the status and disposition of all the returned drug products currently in your inventory. In addition, your revised procedure does not conform to all of the elements in 21 C.F.R. § 211.204. For example, there is no space on the new forms for the date and details of the ultimate disposition of returned product.

Moreover, your firm violates the Act by introducing into commerce "new drugs" that do not have FDA approval, as required under Sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)]. Your firm's [redacted] (b)(4) [redacted] (b)(4)

[redacted] of Section 201(g) of the Act [21 U.S.C. § 321(g)], because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases. Further, they are new drugs within the meaning of Section 201(p) of the Act [21 U.S.C. § 321(p)], because they are not generally recognized as safe and effective for their labeled uses. Under Sections 301(d) and 505(a) of the Act [21 U.S.C. §§ 331(d) and 355(a)], a new drug may not be introduced into or delivered for introduction into interstate commerce unless an FDA-approved application is in effect for the drug.[1] Based on our information, you do not have any FDA-approved applications on file for these drug products, and your sale of these products without such approved applications violates the Act.

[1] FDA is aware that some firms market products that they claim are "grandfathered" under the 1938 Act or the 1962 Amendments to the Act, as defined by section 201(p)(1) of the Act [21 U.S.C. § 321(p)(1)] and Section 107(c)(4) of the 1962 Amendments. The grandfather clauses in the Act have been construed very narrowly by the courts (see the appendix of our marketed unapproved drugs CPG, http://www.fda.gov/cder/guidance/6911fnl.htm, lines 323-329). Companies claiming that their products are grandfathered are responsible for fully documenting their products' grandfathered status. Any company marketing a product on this basis must provide documentation, including but not limited to pre-1938 or pre-1962 labeling, to demonstrate that the product meets all the criteria for grandfather status, including that the product as marketed today has the same formulation, strength, dosage form, route of administration, indications, intended patient population, and other conditions of use as the pre-1938 or pre-1962 product. For additional information please refer to 21 C.F.R. § 314.200(e).

In addition, the above-mentioned drugs are misbranded. Adequate directions cannot be written for these prescription drugs to allow an ordinary individual to use them safely for their intended uses. Consequently, their labeling fails to bear adequate directions for use as required under Section 502(f)(1) of the Act, 21 U.S.C. § 352(f)(1), and they lack required approved applications, for which they are not exempt under 21 C.F.R. § 201.115. The interstate distribution of these products without approved new drug applications violates Sections 505(a) and 301(a) and (d) [21 U.S.C. § 355(a) and 21 U.S.C. §§ 331(a) and (d)].

The issues and violations cited in this letter are not intended to be an all-inclusive list 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 or the occurrence of other violations. It is your responsibility to ensure 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 violations may result in legal action without further notice, including without limitation, seizure and/or injunction. Other federal agencies may take this Warning Letter into account when considering the award of contracts. Additionally, FDA may withhold approval of requests for export certificates or approval of pending new drug applications listing your facility as a manufacturer until the above violations are corrected. A reinspection may be necessary to confirm any corrections.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the time within which you will complete the corrections. If you no longer manufacture or market SMZ/TMP USP tablets (800/160 mg and 400/80 mg), your response should so indicate, including the reasons for, and the date on which you ceased production.

Please direct your response to Amy E. Devine, Compliance Officer, at the above address.

Sincerely,

John W. Thorsky
District Director
Kansas City District