Ei LLC 4/16/18

U.S. FOOD & DRUG ADMINISTRATION

Office of Pharmaceutical Quality Operations,
Division 2
4040 N. Central Expressway, Suite 300
Dallas, Texas 75204

April 16, 2018

CMS Case # 543233

WARNING LETTER

UPS OVERNIGHT MAIL

William Smith, President and CEO
Product Quest MFG, LLC
330 Carswell Avenue
Daytona Beach, Florida 32117

Mr. Smith:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Ei LLC at 2865 N. Cannon Blvd., Kannapolis, North Carolina 28083-9124, from October 2 to 6, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your firm's October 30, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

1. Your firm failed to maintain adequate separate defined areas necessary to prevent contamination or mix-up (21 CFR 211.42(c)).

Your firm manufactured topical human drugs and several pesticides in the same building, using shared equipment. It is unacceptable as a matter of CGMP to continue manufacturing drugs using the same equipment that you use to manufacture pesticides or other non-pharmaceutical products due to the risk of cross-contamination.

Records we reviewed during our inspection and information you submitted in your response confirmed that two of the human drugs you manufactured contained the pesticide **(b)(4)**. You manufactured the pesticide and the human drugs using shared equipment.

In your response, you committed to improving your contamination controls and to test for the presence of other cross-contaminating pesticides in other human drugs that you manufacture. You also described plans for a multi-phase shutdown during which you would make certain corrections, including discontinuing the use of shared equipment for human drug and non-pharmaceutical products, using self-contained suites for non-pharmaceutical manufacturing, and enhancing controls of in-process bulk material transport throughout your facility. These corrections will be verified on the next inspection.

If you intend to continue to manufacture both pharmaceutical and non-pharmaceutical products at your facility, provide a plan to show how you will maintain adequately separated and dedicated manufacturing equipment for your pharmaceutical and pesticide manufacturing operations. In addition, provide an analysis of your results for testing additional human drugs for pesticides and include a risk assessment for all drugs you have previously produced on equipment also used for pesticide production. For each product, assess the risk of potential contamination due to the shared equipment, and provide your plans for addressing the product quality and patient safety risks for any product still in distribution within expiry, including potential recalls or market withdrawals.

2. Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment (21 CFR 211.67(b)).

Your firm did not adequately validate your cleaning procedures to ensure that your human drug products are not contaminated by other human drugs that you manufacture on the same equipment or in your facility.

In your response, you identified shared equipment used to manufacture various pesticides and committed to conducting cleaning validation for a pesticide which you manufactured in the same area as human drugs.

Your response is inadequate because it only addressed the potential for contamination of your drugs by the pesticides you were manufacturing in the same facility. You did not evaluate the potential cross-contamination of your human drugs with other human drugs you manufacture, and have not demonstrated that your cleaning procedures ensure that your drugs are not cross-contaminated with other human drugs.

In response to this letter provide:
• A comprehensive risk evaluation that addresses the potential for each of your human drugs to be cross-contaminated with any other products, including human drugs and any other drugs, cosmetics, pesticides, or other products you manufacture in your facility.
• Your detailed plan for performing adequate cleaning validation of production equipment for all drugs you manufacture. Include summary reports of cleaning validations with corresponding acceptable limits of any residual drugs or other impurities; effectiveness of your cleaning procedures and agents; and analytical methods to prevent cross-contamination of your drugs.

3. Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

Your investigations regarding equipment cleaning and product contamination were not thorough and scientifically sound. You also did not complete investigations of potential instances of contamination in a timely manner.

For example, you investigated an out-of-specification result showing an unknown impurity in your topical drug product erythromycin pledgets 2%. Your equipment logs confirm that you manufactured this drug on the same equipment used to manufacture pesticides. Your July 2016 investigation report (IR160166) for this product documented improper cleaning and residual product as the likely root causes of the impurity. Your investigation was open for at least 14 months when we examined it during our inspection. You also failed to implement adequate corrective and preventive actions.

Our investigator also found evidence of contamination from unknown impurities in six engineering batches of clobetasol propionate 0.05% topical spray. You produced these drug products using the same equipment and facilities that you use for commercial manufacturing. You also used data describing these engineering batches in a report to FDA in support of your application requesting FDA review and approval of a generic drug. Your firm did not identify a root cause of the unknown impurities, and you did not conduct any follow-up investigation to determine whether the commercial equipment was a source of the impurities. You continued to use the same equipment for commercial manufacturing after you detected the impurities, potentially cross-contaminating other products.

All drugs are required to comply with CGMP under section 501(a)(2)(B) of the FD&C Act (21 U.S.C. section 351(a)(2)(B)). The CGMP regulations in 21 CFR parts 210 and 211 apply to the engineering batches reported to FDA in the generic drug application because the process you used to manufacture them is characterized by large-scale, repetitive production that simulates commercial batch manufacture.

We acknowledge that you have taken some corrective actions and preventive actions (CAPA), including revising your investigation procedure, reviewing previous investigations for similar issues, testing retains to further assess cross-contamination, and intend to take appropriate remedial actions as necessary.

However, your response did not fully assess the effect of your failure to adequately investigate contamination on the quality and safety of your drugs on the market within expiry. For example, you committed to reviewing previous investigations of impurity or related substance failures from October 2016 to November 2017. You did not demonstrate that the timeframe you selected is adequate to ensure review of all potentially affected drug products on the market within expiry for cross-contamination.

You also did not explain your failure to implement an effective CAPA following your investigation into an out-of-specification (OOS) result for an impurity test (IR160166). You documented improper cleaning and residual product from a previous fill as the most probable root cause for the OOS result under investigation in that report, but you did not explain why any resulting CAPA were ineffective to prevent recurrence.

In response to this letter provide:
• An assessment of the quality and safety of your products still in distribution and within expiry based on the outcome of your retrospective review of investigations. Explain your inclusion and exclusion parameters for the retrospective review of investigations.
• Your plan to assure the adequacy of investigations in conjunction with your global approach to preventing cross-contamination and assuring product quality.

CGMP consultant recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant, qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm’s obligation to comply with CGMP. Your firm’s executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at **drugshortages@fda.hhs.gov (mailto:drugshortages@fda.hhs.gov)**, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

Correct the violations cited in this letter promptly. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction. Unresolved violations in this warning letter may also prevent other Federal agencies from awarding contracts.

Until these violations are corrected, we may withhold approval of pending drug applications listing your facility. We may re-inspect to verify that you have completed your corrective actions. We may also refuse your requests for export certificates.

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your written response to Mr. Mark W. Rivero, Compliance Officer, at **ORAPHARM2_RESPONSES@fda.hhs.gov (mailto:ORAPHARM2_RESPONSES@fda.hhs.gov)**. Please identify your response with FEI 3005832998 and CMS Case # 543233.

If you have questions regarding any issues in this letter, please contact Mr. Rivero, Compliance Officer, at (504) 846-6103.

Sincerely,
/S/

Ms. Monica R. Maxwell
Program Division Director
Office of Pharmaceutical Quality Operations,
Division II

CC:
Ms. Kathryn Weingart, Vice-President Quality Control
Product Quest LLC and Ei LLC
2865 N. Cannon Blvd
Kannapolis, North Carolina 28083-9124

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