DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

JUL 11 2014

FDA REQUESTED RECALL

Daniel F. Volney, Chairman and Chief Executive Officer
Unique Pharmaceuticals, Ltd.
5920 S. General Bruce Drive, Suite 100
Temple, TX 76502-5803

Dear Mr. Volney:

The Food and Drug Administration (FDA) is requesting that you immediately initiate a recall of all sterile drug products produced at Unique Pharmaceuticals, Ltd. within expiry.

This request is based on FDA findings during recent inspections of the Unique Pharmaceuticals facility in Temple, Texas from March 17 to April 2, 2014 and from June 9 to 20, 2014. During these inspections, FDA investigators found that you identified non-sterility in several different lots of drug products intended to be sterile that were produced in all (b) (4) of your clean rooms. Product from one of those lots, N-Acetyl Cysteine, is still on the market and within expiry. Furthermore, during environmental monitoring, you identified numerous instances of contamination in your clean rooms. In addition, during the inspections, FDA investigators observed poor aseptic production practices that result in a lack of sterility assurance. Administration of a non-sterile drug product intended to be sterile may result in a local or systemic infection, which in turn may result in hospitalization, significant morbidity (permanent organ damage), or a fatal outcome.

Sterile drug products produced at Unique Pharmaceuticals, Ltd. are adulterated within the meaning of sections 501(a)(2)(A) and 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) [21 U.S.C. §§ 351(a)(2)(A) and 351(a)(2)(B)].

During the recent inspections, FDA investigators found:

1. Your firm obtained failing results on sterility tests on several lots of product, and endotoxin tests on one lot of product, and you failed to adequately investigate these sterility and endotoxin failures. Your firm improperly invalidated failing results, did not conclusively identify a root cause, and did not evaluate the impact on other batches.

   (b) (4) lots produced by your firm between January 27, 2014 to March 26, 2014 failed sterility testing. Your firm retested additional units, found no further positive units, and in three instances distributed the products. These three lots of product that failed sterility testing and that were distributed to patients were: N-Acetyl Cysteine 20% vials lot 86513 produced in clean room (b) on January 27, 2014; Sodium Bicarbonate bags lot 86534 produced in clean room (b) on January 27, 2014; and Oxytocin bags lot 87040 produced in clean room (b) on March 20, 2014. Lot 86513 of N-Acetyl Cysteine that tested positive for *Herbaspirillum huttiense* remains on the market within expiry.

   Other sterility failures include Phenylephrine syringes lot 85051 produced in the narcotic room on August 15, 2013 (distributed); Calcium Gluconate bags lot 86893 produced in clean room (b) on March 5, 2014; and

Neostigmine syringes lot 87100 produced in clean room [redacted] on March 26, 2014. In addition, the Neostigmine lot also failed endotoxin testing.

Of significance, closely related organisms (e.g., spore formers) found in the sterility failures were repeatedly found in the clean room environment. For example, spore forming *Paenibacillus,* spp. were found in two separate products produced in two separate clean rooms. Notably, *Paenibacillus,* spp. and similar bacterial spore formers have been identified frequently throughout your facility's ISO 5, ISO 7, and ISO 8 classified areas over the last year.

2. Your firm has recurring and pervasive contamination problems in your cleanrooms. Areas that were clean prior to disinfection subsequently became contaminated after disinfection. In several instances, your firm found significant contamination (e.g., microbiological sampling plates showed results of microorganisms that were too numerous to count (TNTC)), in different rooms in the facility, after cleaning. Your firm did not adequately remediate these issues, and cleaning issues were typically investigated only when a surface remained contaminated after a second cleaning. Your environmental monitoring data demonstrates a persistent problem with *Paenibacillus*, spp. and closely related organisms. Examples of microorganisms found in your cleanrooms include: *Bacillus cereus* (7/8/13), *Bacillus cereus* (7/12/13), *Bacillus cereus* (8/23/13), *Bacillus* spp (9/6/13), *Bacillus cereus* (9/27/13), *Paenibacillus amylolyticus* and *Bacillus amyloliquefaciens* (11/15/13), *Paenibacillus lautus* and *Bacillus pumilus* (1/10/14), *Bacillus simplex* and *Psychrobacillus psychrodurans* (1/17/14), *Bacillus cereus* (1/20/14), *Bacillus simplex* (2/14/14), *Paenibacillus lautus* (TNTC) (2/21/14), *Bacillus thuringiensis* (4/25/14), *Bacillus benzoevorans* (5/2/14), *Bacillus thuringiensis* (5/9/14). Therefore, it is apparent that your firm's current cleaning procedures are not adequate or consistently executed.

3. Poor aseptic practices were observed during production, including:

    - During the April inspection technicians were observed reaching over open and previously sterilized vials, which is a fundamental breach of aseptic technique, and with exposed skin in the aseptic processing areas;
    - During the April inspection a technician was observed stoppering vials without use of a sterile implement (i.e., a gloved hand);
    - During the June inspection investigators observed stored weight ticket printers in the ISO 5 area on the stainless steel tables approximately 20 inches away from drug products being filtered sterilized and filled. Paper is torn at the end of each production batch. This is a problem because particulates are generated when paper is torn from the printer and when the printer is used;
    - During the June inspection investigators observed technicians transferring de-pyrogenated items into the ISO 5 areas without removing the second wrap or sanitizing the item prior to entering the ISO 5 area.

4. The environmental monitoring conducted by your firm is inadequate. For example, fingertip monitoring was only performed (b) (4) and work surfaces were only sampled (b) (4) despite the manually intensive processes that increase the likelihood of contamination by your technicians, and the large batch sizes produced at your facility. In addition, you ignored the findings of your limited environmental monitoring program that indicated problematic trends and failed to adequately remediate the problems identified. Environmental monitoring is critical to provide assurance that the aseptic processing area is adequate for use.

5. In addition, investigators observed that the design of the facility is inadequate and your media fill simulations are also inadequate, and as of June 20, 2014, you had failed to implement adequate corrective actions to address these observations.

We acknowledge receipt of your responses dated April 25, May 2, 12, 15, 20, and 21, and June 30, 2014, which describe your proposed corrective actions. Your responses do not address the impact of objectionable practices and conditions on the production of sterile drugs produced and distributed prior to implementation of these corrective actions. In addition, the corrective actions you have implemented are insufficient to address all of the objectionable practices found at your firm and to assure sterility.

The FDA has determined that due to the lack of sterility assurance of Unique Pharmaceuticals' purportedly sterile drug products, these products present a risk of illness or injury to consumers. To date, Unique Pharmaceuticals has not initiated a recall of all of its sterile products that are within expiry. FDA action is necessary to protect the public health and welfare. FDA will classify this FDA requested action as a Class I recall for the contaminated N-Acetyl Cysteine 20%, lot 86513, and a Class II recall for the remainder of the products for which there is a lack of sterility assurance. A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote. FDA recommends level A (100%) effectiveness checks be performed to the user level.

FDA's recall policy and guidance is found in Title 21 Code of Federal Regulations (CFR), Part 7. FDA's Dallas District Office will provide guidance in implementing and assuring the effectiveness of your recall of these products, including reviewing the proposed recall communication to your consignees. We are requesting that you work closely with the district office and that you provide any necessary information regarding the recall in a timely manner. Title 21 CFR, Part 7 provides for, among other things, publishing your recall in an upcoming issue of the weekly FDA Enforcement Report.

Please respond to this letter within two business days of receipt. Your response to this letter should be directed to:

Reynaldo R. Rodriguez, Jr., District Director
Dallas District Office
4040 North Central Expressway, Suite 300
Dallas, TX 75204
Phone 214-253-5201, Fax 214-253-5318

Due to the seriousness of this situation, FDA is issuing a press release today, advising consumers of the FDA Requested Recall letter and warning health care providers and healthcare professionals to discontinue use or sale of these products and of the health risk associated with the use of these products.

Failure to comply with this request can result in further regulatory action being taken against you, your firm, and the adulterated products distributed by your firm.

Sincerely,

Ellen F. Morrison for
Melinda K. Plaisier
Associate Commissioner for Regulatory Affairs