



Department of Health and Human Services

Public Health Service
Food and Drug Administration
New York District
158-15 Liberty Ave.
Jamaica, NY 11433

August 31, 2011

WARNING LETTER NYK-2011-33

VIA UNITED PARCEL SERVICE

Mary Jane Helenek
President and CEO
Luitpold Pharmaceuticals, Inc.
One Luitpold Drive
Shirley, New York 11967

Dear Ms. Helenek:

During our February 9, 2011 to March 15, 2011 inspection of your pharmaceutical manufacturing facility, Luitpold Pharmaceuticals, Inc., located at One Luitpold Drive, Shirley, New York, investigator(s) from the Food and Drug Administration (FDA) identified significant violations of Current Good Manufacturing Practice (CGMP) regulations for Finished Pharmaceuticals, Title 21, Code of Federal Regulations, Parts 210 and 211. These violations cause your drug product(s) 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 have reviewed your firm's response of April 5, 2011, and note that it lacks sufficient corrective actions.

Specific violations observed during the inspection include, but are not limited, to the following:

1. Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and/or purity they purport or are represented to possess [21 C.F.R. § 211.100(a)]. For example:
 - a. The **(b)(4)** threshold used by your firm to trigger an investigation, as per your Standard Operating Procedure (SOP) 103.14, "Master Production and Control Records," is not appropriately defined or scientifically justified. SOP 103.14 requires the initiation of an

investigation if (b)(4). This (b)(4) reject limit is uniformly applied to all products you manufacture. Furthermore, the investigation instructions in SOP 103.14 contradict the need for an investigation if the number of vials rejected during inspection exceeds the reject limit. Notably, if the rejection limit is exceeded, (b)(4).

In your response, your firm states that you will conduct a thorough review of every product and apply statistical criteria to establish scientifically justifiable reject limits. Your response, however, is inadequate because you do not commit to assess the different types of observed particulate matter or develop appropriate criteria for each type of particulate matter. In addition, adequate interim controls had not been implemented at the time of your response to improve risk mitigation of this recurring problem during ongoing production.

b. You have not adequately justified the sample sizes used by the QC Microbiology Laboratory to determine sub-visible particulates via (b)(4) method in your small volume parenteral products. Your firm based your lot or batch acceptance/rejection criteria on a (b)(4). According to your SOP 302.11, (b)(4). Your response is inadequate because the inspection plans referenced in the SOP (302.110) and protocol PR-90-195 do not adequately address detection of the atypical variability present in your current manufacturing operation. It is important that each lot is appropriately sampled and tested for particulate matter prior to its release. While your response indicates that adjustments are being made, the SOP is unclear as to what inspection level you are using, and the corresponding (b)(4) and (b)(4) values are incorrect as demonstrated in the following:

- Your response states that your future statistical sampling plan is based on using the valid (b)(4) value from (b)(4) at a batch size between (b)(4) and (b)(4) at an (b)(4) sampling plan letter (b)(4). In your response your firm committed that all Particulate Matter testing will be based on (b)(4) inspection with an (b)(4) of (b)(4). However, (b)(4), equates to an (b)(4), which is inconsistent with your commitment of an (b)(4). For (b)(4), to achieve an (b)(4), you will have to use (b)(4). For (b)(4) to achieve an (b)(4) at (b)(4) with lot sizes of (b)(4) to (b)(4), you will have to use (b)(4) with accept on (b)(4).
- For fill sizes less than 25 ml, you are collecting (b)(4) samples (b)(4), this equates to a lot disposition action on (b)(4) with corresponding (b)(4) and (b)(4) respectively. This is not equivalent to an (b)(4) plan as claimed in your SOP.
- There is no scientific rationale for selecting (b)(4) for lot release and (b)(4) for retain sample inspections. According to (b)(4)

c. SOP 103.05, “(b)(4),” does not provide adequate instructions to assure correction of significant deviations and CAPA implementation. For example, the root cause analysis provisions do not include extending the investigation to other lots, examining trends for a product or deviation category, or evaluating adequacy of limits (e.g., for incoming raw materials, drug product).

This contributed to your failure to resolve the particulate contamination, which is a persistent and serious issue at your firm for many years. For example in 2009, there were (b)(4) lots with observed particulate matter and since 2010, there have been over (b)(4) lots observed with

particulate matter. Your failure to follow written procedures, complete investigations, adequately scrutinize different defect types, determine root cause, and implement appropriate corrective action resulted in exposure of patients to adulterated drugs.

Your response provides an outline of a new investigation process and the commitment to reexamine prior investigations. Your response is deficient since you have not included or implemented a revised procedure as part of your response.

2. Your firm has not thoroughly investigated the failure of a batch or any of its components to meet its specifications whether or not the batch has already been distributed, or extend those investigations to other batches of drug product that may have been associated with the specific failure or discrepancy [21 C.F.R. § 211.192].

For example, your firm failed to conduct a thorough investigation or extend such investigations to other unexpired lots when a 12 month reserve sample of Potassium Phosphate (lot 0048) revealed translucent visible particles. Without adequate justification, your firm's Deviation Report (DR) 2457 stated the root cause was glass delamination resulting from a manufacturing variation in the 5ml **(b)(4)** glass (lot 1001055). Your firm failed to extend the investigation to other unexpired lots of Potassium Phosphate made with the same **(b)(4)** glass. Between February 2nd and 10th, 2011, two additional lots of Potassium Phosphate (lots 0625 and 9065) were found with translucent visible particles.

In your response, your firm describes the enhancement of the investigation process with quality oversight and management controls, reexamination of previously conducted investigations, and the implementation of a comprehensive investigation process. However, your response is inadequate because you fail to determine the root causes of the other particulates identified in your products. In the absence of a root cause determination and the lack of implemented corrective action, other

products could contain particulate matter contaminants. An analysis of the potential impact of the particulates observed in your marketed lots should be included in your response to this letter.

Lack of thorough particulate and product failure investigations are repeat violations from October 2010, October 2009, and November 2008 inspections.

3. Your firm failed to withhold containers from use until each lot of components, drug product containers, and closures had been sampled, tested, or examined, as appropriate, and released by the quality control unit [21 C.F.R. § 211.84(a)]. Your firm also has not established the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals for the drug product containers [21 C.F.R. § 211.84(d)(3)]. For example:

- a. Your firm failed to withhold from use, until after quality control testing and release, numerous lots of glass vials. These lots were conditionally released in accordance with your SOP 804.13, **(b)(4)** which allows for this inappropriate practice. In addition, these glass vial lots were provided by non-certified supplier locations.

- b. You have not established the reliability of the supplier's analyses for containers at appropriate intervals. Your practice also violates your SOP 303.01, "Inspection and Release of Packaging Components," for the (b)(4) glass vials, which states that you will conduct USP and Functional & Dimensional testing (b)(4).

Your response is inadequate because you did not address the corrections to your supplier computer software that will identify the manufacturing location for each lot of glass received to ensure that appropriate testing is conducted. Your response also fails to address a global review of all components to ensure that all components, drug product containers, and closures are appropriately tested to ensure the reliability of the supplier's analyses.

4. Your firm has failed to routinely calibrate, inspect, or check automatic equipment in accordance to an adequately written program designed to assure proper performance [21 C.F.R. § 211.68(a)].

For example, the SOP, SOP 601.23, Validation of the (b)(4) for the annual qualification of the (b)(4) does not include a requirement to evaluate contamination particle sizes discovered in your products from past investigations or recovered from an external forensic laboratory. The (b)(4) are qualified to identify particle size ranges (b)(4) and (b)(4). However, past investigations have identified particles less than (b)(4) and greater than (b)(4). In some cases, the (b)(4) have only been qualified to evaluate (b)(4) particle size. For example, (b)(4) has been qualified only with (b)(4) sized particles in the most recent validation dated 10/21/10.

Your response fails to provide assurance that the annual qualification of the (b)(4) demonstrate they can effectively remove vials with particulate matter, and do so across sufficiently representative vial sizes and types. We also note that your response, which states that an (b)(4) rejection rate of test vials on the (b)(4) is acceptable performance, contradicts the qualification acceptance criteria in your SOP 601.23, "(b)(4)," that requires (b)(4) to reject (b)(4) or more test vials with particulates.

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 compliance 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 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 drug applications listing your facility, until the above violations are corrected. FDA may re-inspect to verify corrective actions have been completed.

If, as a result of receiving this Warning Letter or in general, you are considering making a decision that will result in a decreased number of finished drug products or active pharmaceutical

ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov in order to ensure that your action(s) does not adversely affect the public health.

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct violations. Include an explanation of each step being taken to prevent the recurrence of violations and copies of supporting documentation. If you cannot complete corrective action within fifteen working days, state the reason for the delay and the date by which you will have completed the correction. Additionally, your response should state if you no longer manufacture the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address: U.S. Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433. Attention: Lillian C. Aveta, Compliance Officer.

Sincerely,
/S/
Ronald M. Pace
District Director
New York District