U.S. Department of Health & Human Services

FDA U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Lilly del Caribe, Inc. (PR05) 2/5/10

Department of Health and Human Services

Public Health Service
Food and Drug Administration
San Juan District
Compliance Branch
466 Fernandez Juncos Avenue
San Juan Puerto Rico 00901-3223
Telephone: 787-474-9500
FAX: 787-729-6658

February 5, 2010

WARNING LETTER
SJN-2010-03

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

John C. Lechleiter, Ph.D
Chairman President and CEO
Eli Lilly & Company
Lilly Corporate Center
Drop Code 2622
Indianapolis, IN 46285

Dear Mr. Lechleiter:

This is regarding our July 08 - 31, 2009 inspection of your active pharmaceutical ingredient (API) manufacturing facility, Lilly del Caribe located at Carretera #3 Km 12.3, Carolina, PR 00986. The inspection identified a significant deviation from the Current Good Manufacturing Practice (CGMP) requirements for the manufacture of APIs. This deviation causes your API, Lyspro Insulin Zinc Crystals, 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 reviewed your firm's response of August 21, 2009, and note that it lacks sufficient corrective actions.

The specific deviation observed during the inspection includes, but is not limited, to:

Your firm failed to adequately investigate critical deviations or a failure of a batch to meet its specifications or quality standards.

For example, your investigation TR# **(b)(4)** determined the disposition of 36 API batches based on the results obtained using a test method that was not validated for its intended use. The investigation evaluated the quality impact of 36 batches of **(b)(4)** that exhibited **(b)(4)**. This **(b)(4)** process of the API. Your investigation determined the affected API batches showed an increase **(b)(4)** which can cause **(b)(4)** that affect the quality of the API. As part of the investigation, you tested 36 API batches using the **(b)(4)** to determine if the batches underwent **(b)(4).** You released 24 of the 36 API batches based on the test results despite your failing to validate the test method and your knowledge of a similar **(b)(4)** event at one of your sister plants (as indicated during the inspection). This event resulted in that facility's rejection of the material and the extensive cleaning of the **(b)(4)** unit.

The **(b)(4)** can be used to determine the relative propensity of the API to form gel using the **(b)(4)**. However, we object to your use of the **(b)(4)** as a determinative part of the final disposition of the finished API, especially when you initially had only validation data to support the use of the test method as a limit test (i.e., yes/no for the presence of **(b)(4)**. Your investigation concluded that 24 batches, with **(b)(4)**, were suitable to release for production of the finished drug product Humalog. These batches were released from December 2007 to March 2008. In April 2008, you conducted additional studies that determined the test method **(b)(4)** was not linear. The data shows a gel number of **(b)(4)**. Similarly, a gel number of **(b)(4)**. Therefore, there is no assurance of the actual percentage of present in batches associated with the **(b)(4)** event. Despite the results of these studies showing lack of linearity, you failed to assess all affected batches of the APIs that were released for further processing using this **(b)(4)** number.

We acknowledge your response dated August 21, 2009, where you commit to: 1) stop using the **(b)(4)** as an additional criteria to recommend forward processing; 2) enhance cleaning activities to prevent **(b)(4)** and 3) enhance the visual appearance inspection to readily detect the presence of **(b)(4)** material (if **(b)(4)** occurs). However, your response does not address the specific changes that you have made to your cleaning procedures and visual appearance inspection, or whether upstream detection of **(b)(4)** will be possible using current process controls.

In addition, your firm indicated during the inspection that the **(b)(4)** may cause the finished drug product to be subpotent and have an atypical visual appearance. Your firm's indication that stability data for affected batches are comparable to normal batches appears insufficient to support safety and efficacy. Data submitted in your response does not appear to show correlation between lots known to have high levels of **(b)(4)** and subpotency or atypical visual appearance. Your response is inadequate because you have not provided your evaluation to adequately demonstrate why 24 API released batches are suitable for their intended use. Your evaluation should include the following:

- The rationale and methods for determining whether further insulin **(b)(4)** occurred in each batch.
- The particle size distribution of the **(b)(4)** and the impact to the finished drug product Humalog.
- The percentage of **(b)(4)** in the finished product Humalog, which could result in an adverse clinical outcome.
- Your current and plans beyond visual appearance inspection to improve in-process controls and finished API testing to enhance detection of **(b)(4)**

Also please provide the following:

- Copies of the safety reports that you referenced in your July 16, 2009 "Patient Safety and Consultation Report."
- An updated summary of complaints received for potentially affected finished product lots.
- All additional information gathered after the investigation of the **(b)(4)** event that evaluated whether correlation exists between the **(b)(4)** and product quality and stability. Your firm indicated on page 3 of your written response that no correlation exists.

The deviation cited in this letter is not intended to be an all-inclusive statement of deviations that exist at your facility. You are responsible for investigating and determining the causes of the deviation identified above and for preventing their recurrence and the occurrence of other deviations. is your responsibility to assure compliance with all requirements of federal law and FDA regulations.

You should take prompt action to correct the deviation cited in this letter. Failure to promptly correct the deviation 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 deviation is corrected. FDA may re-inspect to verify corrective actions have been completed.

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 the deviation. Include an explanation of each step being taken to prevent the recurrence of the deviation 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 or distribute API Insulin Lyspro Zinc crystals manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

Your reply should be sent to the following address: The Food & Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, PR 00901-3223, to the attention of Margarita Santiago, Compliance Officer.

Sincerely,
/S/

Maridalia Torres

District Director
San Juan District Office

Enclosure: FDA 483
cc: Sandra I. Galindez Feliciano, Plant Manager
Lilly del Caribe, Inc. (PR05)
PO Box 1198
Carolina, PR 00986-1198

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