U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Lonza Biologics, Inc. 9/1/2011

Department of Health and Human Services

Public Health Service
Food and Drug Administration
New England District
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Stoneham, Massachusetts 02180
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NWE-27-11W

VIA UNITED PARCEL SERVICE
OVERNIGHT DELIVERY

September 1, 2011

Stephan Kutzer
Chief Operating Officer
Lonza Biologics, Inc.
101 International Drive
Portsmouth, NH 03801

Dear Mr. Kutzer:

During our April 4, 2011 to May 6, 2011 inspection of your pharmaceutical and active pharmaceutical ingredient (API) manufacturing facility, Lonza Biologics, Inc., located at 97 South Street, Hopkinton, MA, 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, and from CGMP for the manufacture of APIs. These violations cause your drug product(s) and APIs 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 May 26, 2011, and note that it lacks sufficient corrective actions.

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

CGMP Violations of Drug Products and Components:

1. 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 [21 C.F.R. § 211.192].

For example, your firm failed to conduct an investigation for ONTAK **(b)(4)** after an unidentified peak was observed co-eluting with the primary product peak at the **(b)(4)** and **(b)(4)** month stability time point **(b)(4)** analyses.

In your response, your firm states that you did not conduct an investigation for this lot because the same co-eluting peak is routinely observed in both the sample and reference chromatograms. Your firm indicates that the occurrence of co-eluting peaks in the **(b)(4)** method has been investigated and established that the method resolution observed was "sufficient to a varying degree." Your response, however, fails to provide an adequate scientific rationale to describe the reason why the co-eluting peak is significantly larger in this lot (as compared to the reference chromatogram), address the impact of the overlap of larger peaks, and evaluate how the method can be refined to prevent overlapping peaks.

CGMP Violations of Active Pharmaceutical Ingredients:

1. Inadequate or lack of an investigation of critical deviations or a failure of a batch to meet its specifications or quality standards.

For example, your firm failed to conduct an investigation after a number of ONTAK Drug Substance Lots **(b)(4)** failed to meet release specifications for residual **(b)(4)**.

In your response, your firm states that the lots described above were manufactured in 2009 after **(b)(4)** had suspended DNA testing due to on-going DNA method investigations. Your firm also states that **(b)(4)** did not communicate to you their commitments to the FDA until May 2010 in which, **(b)(4)** planned to conduct a minimum of **(b)(4)** independent tests for residual DNA until the assay variability was resolved. Thus, your firm initiated and documented a planned deviation, and began testing batches from the 2009 campaign in June 2010 with results received in December 2010 and January 2011. Your response, however, is inadequate because your firm has yet to address the failure to investigate the Out-of-Specification (OOS) results and identify a root cause.

2. Failure to validate analytical test methods used for API for potency testing.

For example, your firm failed to validate the ONTAK **(b)(4)** to quantify Peak A for potency and robustness. For example, only **(b)(4)** chromatographic columns were able to adequately separate **(b)(4)** and **(b)(4)**. Your firm has been unable to determine why the chromatographic columns of the same make and model had variability and could not provide adequate separation.

In your response, your firm states that the same RPLC column type has been used for 15 years for the **(b)(4)** method. In the last 2 years, there has been a change in the resolution (i.e., column-to-column variability outside the previously observed range). **(b)(4)** out of **(b)(4)** columns of the same model number, produced by the same vendor used in this analytical methodology, provided adequate resolution of **(b)(4)** from **(b)(4)**. Your firm states further that **(b)(4)** is making significant progress with both the **(b)(4)** and the **(b)(4)** column approaches, which may address both the **(b)(4)** peak issues. **(b)(4)** Your response, however, is inadequate because there is no assurance that the current columns are providing acceptable separation.

3. Failure of your quality unit to exercise its responsibility to ensure that APIs manufactured are in compliance with CGMP, including meeting established specifications for quality and purity. For example:

a. Your firm's quality control unit (QCU) failed to ensure that all released lots and any lots still in inventory of ONTAK API meet revised specifications for the level of **(b)(4)** (lot #**(b)(4)**), a chemical used during the **(b)(4)** step in the API manufacturing process. Specifically, your firm released a lot of ONTAK API to the sponsor's site in December 2010 with a concentration level of **(b)(4)**, although your firm had already implemented the required change to the **(b)(4)** release specification (implemented on March 16, 2010).

In your response, your firm has committed to providing an adequate Standard Operating Procedure (SOP) that requires generating interim Certificates of Analysis, comparing the interim Certificate of Analysis to the current approved specification, and keeping lots in quarantine until you have confirmed that specifications are met. Your response, however, is inadequate because it is unclear whether you will evaluate all lots of ONTAK API to ensure that the lots meet required specifications.

b. Your firm failed to reanalyze five production lots of ONTAK **(b)(4)** originally analyzed using a general DNA **(b)(4)** method not specifically validated for ONTAK, although a more specific validated DNA **(b)(4)** Method was approved.

In your response, your firm states that you had implemented the use of the general **(b)(4)** method per client request. Your firm tested and released product using this method prior to any communication from the FDA to the license holder requesting further validation of the more specific **(b)(4)** method. Your response is inadequate because there is no assurance from your firm or the license holder that the initial DNA analytical results were valid.

c. Your firm issued an outdated Certificate of Analysis for ONTAK (Lot #**(b)(4)**) that was manufactured on September 4, 2009, after receiving the DNA test results on March 3, 2011. The outdated Certificate of Analysis did not include a revised purity specification for the **(b)(4)** as required by the BLA**.**

In your response, your firm states that you agree that there was a failure to check the amended Certificate of Analysis against the current specification as required by your disposition procedure, **(b)(4)**. This failure was due to human error and your firm will retrain appropriate staff on this aspect of the procedure. Your response, however, is inadequate because there is no assurance that other staff did not use the outdated Certificate of Analysis.

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. It is our expectation that the corrections implemented to address the violations are sustainable and that these corrections are applied to all products currently manufactured and any products marketed in the future (e.g., Increlex). 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.

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 or distribute the drug product(s) manufactured at this facility, and provide the date(s) and reason(s) you ceased production.

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 bulk drug substances 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.

Your response should be sent to: Lori A. Holmquist, Compliance Officer, Food and Drug Administration, 330 Civic Center Drive, Suite 1, Box 4, Augusta, ME 04330. If you have any questions about the content of this letter please contact: Lori A. Holmquist at (207) 622-8268 x 13.

Sincerely yours,
/S/
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District Director
New England District

Cc: Ian Elvins
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(b)(4)

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