U.S. Department of Health & Human Services

U.S. Food and Drug Administration

Inspections, Compliance, Enforcement, and Criminal Investigations

Commonwealth Serum Laboratories (CSL), Ltd. 6/15/11

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

JUN 15, 2011

CBER-11-02

EXPRESS MAIL

Brian McNamee
Chief Executive Officer (CEO)
CSL Biotherapies
45 Poplar Road
Parkville, Victoria 3052
Australia

Dear Mr. McNamee:

The Food and Drug Administration (FDA) conducted an inspection of CSL Biotherapies, located at 45 Poplar Road, Parkville, Victoria 3052, Australia, between March 21 and March 31, 2011. During the inspection, FDA investigators documented deviations from current good manufacturing practice (CGMP) requirements in the manufacture of licensed biological vaccine Afluria and monovalent influenza bulks. Deviations from CGMP include the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), Section 351(a) of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210, 211, and 600-680.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your facility's compliance with CGMP. Significant deviations observed during the inspection include, but were not limited to, the following:

1) You failed to thoroughly investigate any unexplained discrepancy, or the failure of a batch or any of its components to meet any of its specifications, and failed to extend the investigation to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. For example:

A) The April 2010, investigation initiated to determine a root cause for Adverse Events for fever and convulsions in children is inadequate in that:

i. There is no documentation of the Adverse Event investigation. SOP # **(b)(4)** 11209 titled "Corrective and Preventive Action," requires documentation of actual or potential problems which may affect the quality and reliability of products, processes or quality systems. The procedure requires that activities and decisions are to be documented such that there is traceability of Corrective and Preventive Actions (CAPA) from the initial identification of problems to the implementation of solutions and the follow up to evaluate effectiveness.

ii. There was a limited analysis of the manufacturing process to determine why there was a substantial increase in Adverse Event reports of fever and convulsions in the 2010 Southern Hemisphere influenza season in comparison to previous seasons. There was no analysis of all critical parameters and critical processing steps to try to determine differences in the 2010 lots associated with Adverse Event reports compared to lots from previous seasons. For example:

a) Raw material lots, virus inactivation, virus splitting, yield and quality of product at each production step were not compared for lots associated with Adverse Events and lots prepared the previous season.

b) The Quality Review Report detailing the outcome of the manufacturing investigation indicates that batch records were reviewed for trivalent bulk formulation, filling and packaging but there was no discussion of evaluation of upstream processing **(b)(4),** inactivation, virus splitting, **(b)(4).**

iii. The Quality Review Report indicates that the A/California/7/2009 (H1N1) strain appears to have a **(b)(4)** content, which could have contributed to the Adverse Events. The information was received in July 2010. You confirmed that A/California/7/2009 (H1N1) had a **(b)(4)** level of **(b)(4)**, but have not initiated testing of the 2010 influenza vaccine lots to determine differences in **(b)(4)** content compared to 2009 strains.

iv. There was no evaluation of the testing of raw material, and potential impact on manufacturing, of **(b)(4)** lots of Sodium Taurodeoxycholate (TDOC), which failed ID tests performed via **(b)(4)** but were accepted for use. An investigation was not initiated to determine the reason for identification failures and the vendor was never contacted to inquire about the possible changes to TDOC lots. Without further investigation into possible changes to TDOC, the **(b)(4)** of the lots failing identification were included into the **(b)(4)** of acceptable **(b)(4)**

B) The April 2010, failure investigation initiated to investigate dark particles found in thimerosal containing multi-dose vials is inadequate in that:

i. The investigation focused on multi-dose vials only. This decision was based on a retrospective review of data for syringes, rather than an actual visual examination to determine that no dark particles have formed in syringes since release.

ii. A leachable study on product at the end of shelf life was initiated to determine if the container closure system contributed to dark particles found in influenza virus vaccine in multi-dose vials. Only one multi-dose vial lot and one syringe lot representing product distributed to the U.S. were included in this study. There is no statistical rationale for use of this sample size.

iii. The direct analysis of the particles indicates that they are discolored influenza split virus with the possible presence of **(b)(4)** mercury compounds that may contain **(b)(4)** and other inorganic compounds. You concluded that the dark particles are not foreign to the product. However, dark particles have not been linked to bulk lots and product in syringes (using different stoppers) and no rationale is provided for your conclusion.

Additionally, significant deviations in the manufacture of your monovalent influenza bulks were observed during the inspection. These deviations violate Section 501 (a)(2)(B) of the FD&C Act and Section 351(a) of the PHS Act. Specific areas of concern include, but are not limited to:

PRODUCTION AND PROCESS CONTROLS

2) You failed to establish and follow written production and process controls for the execution of various production and process control functions. For example:

A) You failed to determine optimal splitting conditions for new virus strains before the strains are used in production. For the change to influenza virus strain A/Victoria/210/2009 for the 2010/2011 Northern Hemisphere, a concentration of **(b)(4)** TDOC was assigned to A/Victoria/210/2009. However, upon manufacture of the first two monovalent lots (**(b)(4)**), the **(b)(4).** A small scale study was then performed to determine the TDOC concentration required for optimal disruption of virus. The study determined that a concentration of **(b)(4)** TDOC, not **(b)(4)** should be used for manufacture of A/Victoria/210/2009. Nevertheless, the lots manufactured at **(b)(4)** TDOC concentration were released for further processing.

B) You failed to follow written production and process control procedures in that you failed to review, on a seasonal basis, the presence of Haemagglutinin Antigen (HA) in **(b)(4)** as stated in SOP # **(b)(4)** 9547, titled "**(b)(4)** of Influenza Vaccine **(b)(4)**

C) You failed to establish a procedure which ensures the completeness of virus splitting. The SOP for **(b)(4)** evaluation of **(b)(4)** 8803, titled "**(b)(4)** of Influenza Virus **(b)(4)** and Influenza Virus **(b)(4)**" does not define "Pass" acceptance criteria.

FAILURE INVESTIGATIONS

3) Investigations into the failure of a batch or any of its components are inadequate. For example:

A) Deviation # PRD-3470 was initiated in June 2010 due to the atypical appearance of Monovalent Pooled Harvest (MPH) lot # **(b)(4)** during the **(b)(4)**. Suspended white agglomerate material was present in Quality Control samples. The associated sister lot did not have the same problem. Investigation found that a **(b)(4)** was **(b)(4)** for lot # **(b)(4)**. There was no investigation into the possible failure of **(b)(4)**. The vendor was not notified and the **(b)(4)** were not further analyzed.

B) A series of **(b)(4)** lots exceeded bioburden alert/action limit at the **(b)(4)** between October 16, 2010, and December 4, 2010. There has been no effort to determine if the contamination could be isolated to specific **(b)(4)** or if all **(b)(4)** were implicated. The failure investigation did not evaluate the effectiveness of cleaning of the **(b)(4)**. The **(b)(4)** cleaning re-validation failed in July 2010.

CONTROL OF COMPONENTS

4) You failed to reject a lot of components which failed to meet appropriate written specifications. **(b)(4)** lots of Sodium Taurodeoxycholate (TDOC), used to disrupt influenza virus to make a split virion vaccine, were delivered in 2010. **(b)(4)** fifteen lots failed the ID test performed **(b)(4)** but the lots were accepted for use. An investigation was not initiated to determine the reason for identification failures and the vendor was never contacted to inquire about the possible changes to TDOC lots. Without further investigation into possible changes to TDOC, the –b(4)-- of the lots failing identification were included into the **(b)(4)** of acceptable **(b)(4)**

LABORATORY CONTROLS

5) The tests used to evaluate the completeness of virus splitting are deficient in that:

A) Neither the **(b)(4)** Assay **(b)(4)**-9547, **(b)(4)** of Influenza Vaccine **(b)(4)** are validated for their ability to discriminate between split and whole virus.

B) There are no data to support the acceptance range for the **(b)(4)** that defines whether splitting is optimum for **(b)(4)**

The deficiencies described in the Form FDA 483 and this letter are an indication of your Quality Control Unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your monovalent influenza bulks and final drug products. Please describe in detail how CSL Biotherapies will attain CGMP compliance with regard to the above observations. Please include in that description how you will use all relevant information to conduct thorough investigations to ensure that adequate steps are taken to evaluate whether deviations impact product and to implement effective corrective and preventive actions.

We acknowledge receipt of your written responses dated April 18, 2011, and May 13, 2011, which address the inspectional observations on the Form FDA 483 issued at the close of the inspection, and we have reviewed their contents. Corrective actions addressed in your letter may be referenced in your response; however, we believe that your response did not provide sufficient detail to fully assess the adequacy of your corrective actions. In addition, we have the following comments regarding the corrective actions detailed below. The items are numbered to correspond to the observations listed on the Form FDA 483.

Observation 1 – General Comments –The deviations listed throughout 483 Observation #1, and in other 483 items, appear to suggest that a more global approach should be taken to evaluate your Quality System and how it interacts with all other parts of your manufacturing process. For example, your responses reference several new procedures and procedural changes which will enable you to perform more effective and complete investigations. It is of note, however, that the Untitled Letter (UL) issued to CSL on June 24, 2010 cited several inadequacies in your investigation into black particle formation in multi-dose vials of Influenza Virus Vaccine. These concerns have been reiterated in form FDA 483 observation #4. Your proposed corrective actions as a result of the 2010 UL should have included a comprehensive evaluation of your investigation process and should have driven corrective and preventive actions which could have prevented the deviations noted in this observation. Also, Observation #1E reads in part, "There was no evaluation of testing of raw material and potential impact on manufacturing." Your response indicates that you intend to update SOP **(b)(4)**-9254, titled "*5950 Identification and Qualification of Raw Materials Using the* **(b)(4)***,"* to provide instruction on performing an investigation in the event of a raw material acceptance test failure.

However, your response to this observation does not take the more global approach and look at all raw materials used during manufacture which should be part of an effective investigation.

Observation 1I
We acknowledge the commitments made in your response, however, we note that you do not address the fact that the change to **(b)(4)** the lot size limit of **(b)(4)** was not described in your annual report to FDA. Please be advised that all changes to currently approved procedures should be evaluated for potential reporting as per 21 CFR 601.12.

Observations 2B, 2C, 3A1, 3A2, & 3B – General Comments –Due to the complex technical nature and overlapping issues presented in these observations, we advise that you contact Maryna Eichelberger in CBER's Office of Vaccines Research and Review at 301-402-3846 in order to obtain input on your proposed corrective and preventive actions.

Observation 5 – Procedure **(b)(4)**-11147, titled "Procedure for Management of Deviations" appears inadequate in that it does not require lots to be placed on stability which are manufactured under conditions outside targeted limits, even if all final test specifications are met.

Neither this letter, nor the observations listed on the Form FDA 483 presented to your firm at the conclusion of the inspection, are intended to be an all-inclusive list of deviations that may exist at your facility. It is your responsibility as management to ensure that your establishment is in compliance with the provisions of the Federal Food, Drug, and Cosmetic Act, The Public Health Service Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological products so that they may take this information into account when considering the award of

contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions may include license suspension and/or revocation.

To facilitate your remediation efforts we request a meeting with you and other senior management at CSL Biotherapies to further discuss the issues cited in this letter and your proposed responses to address them.

Given the potential contributions of safe, pure, and potent vaccines to the public health, we encourage frequent interactions between your technical staff and FDA in an effort to help CSL Biotherapies move forward with corrective actions as rapidly as possible.

Please notify this office in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that corrective action has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the following address: U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448. To schedule a meeting at your earliest convenience, please contact Robert McElwain, Consumer Safety Officer, in the Division of Case Management at (301) 827-6196.

Sincerely,
/S/
Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc:

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