CMC Review - AFLURIA

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Memorandum

Date:

September 11, 2007

To:

Rakesh Pandey, Ph.D., DVRPA/OVRR

From:

Galina M. Vodeiko, Ph.D., DVP/OVRR

Through:

Jerry Weir Ph.D., DVP/OVRR

Subject:

CMC Review - BLA (STN 125254) Afluria, Influenza Virus Vaccine

Sponsor:

CSL Limited
45 Poplar Road,
Parkville 3052,
Victoria, Australia

SUMMARY AND RECOMMENDATION

Afluria[R], an intramuscularly administered vaccine, is a trivalent split virus produced from influenza virus infected embryonated hens' eggs. Each of the three virus strains is produced and purified separately. The viruses are concentrated by Tandenital Flow Filtration (TFF) and Zonal Ultracentrifugation (ZC), inactivated by Beta-Propiolactone (BPL) followed by detergent disruption with Sodium Taurodeoxycholate (TDOC), and Sterile filtration, purified by -----
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standardized according to USPHS requirements for each successive influenza season and is formulated to contain 15 mcg of hemagglutinin (HA) for each of the three strains recommended for a given Northern Hemisphere influenza immunization campaign. Afluria® is a sterile, suspension of inactivated and split influenza virus types A and B in phosphate-buffered saline solution without preservatives, or containing 0.01% thimerosal (25 mcg of mercury per dose) as a preservative, and trace residual amounts of egg proteins, and sodium taurodeoxycholate(----- ppm per dose). Antibiotics are used in the beginning of manufacturing, but not present in Afluria®. Afluria® is supplied in two presentations: a thimerosal-free 0.5 mL single-dose prefilled syringe and a thimerosal-containing 5 mL multi-dose vial.

There are no major CMC issues related to Afluria® produced using current manufacturing process. However, some of the studies, such as the stabilities of monovalent bulk and final product, are currently ongoing. The continuation of these studies will be the post marketing commitments. BLA (STN 125254/0), Afluria®, Influenza Virus Vaccine, is recommended for approval.

INTRODUCTION

CSL Limited of Australia submitted the BLA for Afluria® to CBER on March 30, 2007 seeking licensure in the US. Afluria® is a trivalent split virus vaccine administered intramuscularly and produced from influenza virus infected embyonated eggs. Afluria® vaccine is not currently licensed in US, but is licensed in Australia, New Zealand, Europe, South Africa, South East Asia and South America, total in more than 20 countries.

Afluria® is proposed for active immunization of adults 18 years old and older against influenza disease due to the influenza A and B viruses contained in the vaccine. Afluria® provides active immunity against three influenza virus strains anticipated to circulate in the Northern Hemisphere during the upcoming winter season. Although multiple immune mechanisms, including cellular immunity, may contribute to vaccine-induced protection against influenza, the humoral component of the immune response, in particular antibodies against viral HA and neuraminidase (NA) antigens, is best understood. Vaccine-induced antibodies to both proteins may be protective, but hemagglutination-inhibiting (HAI) antibodies to HA appear to play the dominant role. Specific levels of vaccine-induced HAI antibodies that protect against influenza disease have not been established in randomized, controlled trials. Human challenge studies have suggested that HAI antibody titers of ≥1:40 are associated with reductions in influenza illness. The effectiveness of inactivated influenza vaccines is also influenced by the age and immunocompetence of the vaccinee and the degree of similarity between the virus strains used to prepare the vaccine and those circulating in the population.

We have reviewed CMC section of the submission and have focused on Module 3-Drug Substance (section 3.2.S, vol.1,2); Drug Product (Thimerosal-Free), which includes Drug Product (Thimerosal-Free) (section 3.2.P, volumes 3-5), Drug Product

(Thimerosal-Containing)(section 3.2.P, volumes 6,7); Adventitious Agents Safety Evaluation (section 3.2.A.2, vol. 20) and Executed Batch Records (section 3.2R.1, vol.21-24); Method Validation Package (section 3.2.R.2, vol.25-29), and Comparability Protocols/Reports (section 3.2.R.3, vol.29). This review also covers the BLA amendments provided by CSL including consistency lots for the trivalent final bulk and final filled vaccine for 2007-2008 and the sponsor's responses to our CMC comments.

STN 125254/0 Response to FDA 06 July 2007 request for additional information, received 08/01/2007.
STN 125254/0.4, received 07/10/2007
STN 125254/0.6, received 08/06/2007
STN 125254/0.8, received 08/07/2007

CHEMISTRY, MANUFACTURING AND CONTROLS

3.2.S ----------

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