Media Release

Wednesday 11 June 2014

International Medical Journal Publishes bioCSL's Fluvax® Investigation Findings

- **Journal *Vaccine* publishes findings of root cause investigation into adverse events associated with the bioCSL 2010 influenza vaccine, Fluvax®.**
- **Manufacturing process modifications adopted based on findings.**
- **Clinical development program initiated to confirm the safety of modified Fluvax® in young children.**

The findings of bioCSL's multi-year investigation into the cause of the unexpected adverse events associated with its Fluvax® influenza vaccine in 2010 were today published in two separate papers in the peer-reviewed journal *Vaccine.*

The publications describe an extensive and highly complex investigation that involved international collaborators and was closely monitored by the TGA and the FDA. The findings have led bioCSL to modify its manufacturing process for Fluvax® and to initiate a clinical development program to confirm the safety of the modified vaccine in young children.

During the influenza season of 2010, Fluvax® was associated with a significant increase in reports of fever-related (febrile) convulsions in young children compared to previous seasons. Fluvax® has not been licensed for use in children under 5 years of age since these events. In response, bioCSL undertook a comprehensive, multifaceted investigation comprising clinical data analyses, manufacturing reviews and scientific studies involving over 200 separate laboratory experiments.

The investigation found that as a result of bioCSL's standard method of manufacture, virus components contained in the 2010 formulation of Fluvax® combined to overstimulate the immune system of some young children, triggering increased fever and fever-related convulsions. Further, these laboratory studies showed that increasing the levels of virus splitting agent used in the bioCSL manufacturing process addresses the potential for Fluvax® to generate excessive febrile reactions.

After successfully manufacturing Fluvax® using increased levels of virus splitting agent, bioCSL conducted a clinical study in adults which confirmed this modification had no negative impact on the immunogenicity of the vaccine. Following consultation with regulators, bioCSL has now implemented increased levels of virus splitting agent into its standard method of manufacturing for Fluvax®.

"As Australia's only onshore manufacturer of influenza vaccine, we know how important it is for us to be able to produce a seasonal flu vaccine that can be safely used in all age groups," said Dr John Anderson, General Manager of bioCSL.

"This is why we have continued to work to solve the problem and have now implemented the manufacturing changes we believe will ultimately address the safety concerns associated with the use of bioCSL's Fluvax® in children."

"The next step is proving our scientific findings through clinical studies, and until that happens, I want to stress that bioCSL's Fluvax® must not be used in children under 5 years of age and that restrictions also remain in place for the use of Fluvax® in those aged 5 to 9 years."

"We recognise that the events that took place in 2010 and the ongoing uncertainty about the cause have been very concerning to the public. The investigations have been extremely complex and it is of some relief to have reached this point. Our conclusions now give us a clear path forward which we intend to pursue to the fullest," Dr Anderson said.

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Current age restrictions for Fluvax[1]
Fluvax® must not be used in children under 5 years of age.
Fluvax® should only be used in children aged 5 to under 9 years based on careful consideration of potential benefits and risks to the individual and if no alternative is available.
Fluvax® continues to have an acceptable safety profile in people aged 10 years and over.

References:

1. ATAGI Clinical advice for immunisation providers regarding administration of 2014 seasonal influenza vaccines, March 2014. Available at: http://www.immunise.health.gov.au/internet/immunise/Publishing.nsf/content/40E9F669E3096146CA2579BA00097533/$File/ATAGI-clinical-advice-March14.pdf

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About *Vaccine*

Vaccine is the pre-eminent journal for those interested in vaccines and vaccination. It is the official journal of The Edward Jenner Society, The International Society for Vaccines and The Japanese Society for Vaccinology. www.elsevier.com/locate/vaccine

About bioCSL

bioCSL manufactures, markets and distributes seasonal and pandemic influenza vaccine worldwide. In Australia and New Zealand, bioCSL markets a comprehensive range of vaccines and pharmaceutical products. It also manufactures products of national significance for Australia, including antivenoms and Q-Fever vaccine, and supplies diagnostic reagents in the Australasia region. bioCSL's cold-chain logistics business ensures the integrity of CSL products, as well as those of our customers, as they are safely delivered across Australia.

bioCSL is part of the CSL Group which is headquartered in Melbourne Australia. The CSL Group includes CSL Behring, CSL Plasma and bioCSL. With major facilities in Australia, Germany, Switzerland and the US, CSL has over 12,000 employees working in 27 countries.

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PBS Information: This product is listed on the National Immunisation Program (NIP) Schedule. Refer to the NIP Schedule.

WARNING: This season's vaccine is indicated for use only in persons aged 5 years and over. It must not be used in children under 5 years (see Contraindications). It should only be used in children aged 5 to under 9 years based on a careful consideration of potential risks and benefits in the individual (see Precautions).

Before prescribing, please review product information available at www.biocsl.com.au/PI.

MINIMUM PRODUCT INFORMATION: Fluvax® Inactivated influenza vaccine (split virion). For winter 2014, antigens representative of types: A/California/7/2009 (NYMC X-181) (A/California/7/2009 (H1N1) – like), A/Texas/50/2012 (NYMC X 223)) (A/Texas/50/2012 (H3N2) – like) and B/Massachusetts/2/2012 (NYMC BX-51B) (B/Massachusetts/2/2012 – like); 15µg haemagglutinin of each per 0.5mL dose. **Indication**: Prevention of influenza caused by Influenza Virus, Types A and B. For the 2014 season, Fluvax is indicated for use only in persons aged 5 years and over. **Contraindications**: Must not be used in children under 5 years. Anaphylactic hypersensitivity to previous influenza vaccination or to eggs, neomycin, polymyxin B sulphate or any other constituents or trace residues of the vaccine. Postpone immunisation in people with febrile illness or acute infection. **Precautions**: During the 2010 Southern Hemisphere influenza season, there was an unexpected increase in reports of fever and febrile convulsions in children aged less than 5 years following seasonal influenza vaccination. The vaccine is only indicated in persons aged 5 years and over. Febrile events were also observed in children 5 to under 9 years. Therefore a decision to vaccinate this age group should be based on careful consideration of potential benefits and risks to the individual. Treatment for anaphylactic reactions should be available. In immunocompromised patients antibody response may be lower. History of Guillain-Barré Syndrome within 6 weeks of previous influenza vaccination. **Interactions**: Corticosteroid or immunosuppressant treatment may diminish immunological response. **Pregnancy**: Category B2. **Adverse Effects**: Adults: pain, erythema, ecchymosis; malaise, chills/shivering. In children: pain, erythema, swelling; irritability, rhinitis, fever, cough, loss of appetite, vomiting/diarrhoea, headache, myalgia, earache, sore throat, wheezing/shortness of breath. **Post-marketing surveillance**: Transient thrombocytopenia; allergic reactions including anaphylactic shock; neuralgia, paraesthesia and convulsions (including febrile convulsions); encephalitis, neuritis or neuropathy and Guillian- Barré syndrome; vasculitis with transient renal involvement; pruritus, urticaria and rash; cellulitis and large injection site swelling. **Dosage and Administration**: Intramuscular or deep subcutaneous injection. Adults and children from 5 yrs: 0.5 mL; For children aged 5 to under 9 years who have not previously been vaccinated 2 doses should be given at least 4 weeks apart.**Presentation**: 0.5mL single-use syringe. **Storage**: Store at 2-8 C; protect from light; do not freeze. Based on TGA Approved Product Information 24 October 2013.