Australian Government

Department of Health

Therapeutic Goods Administration

Advisory Committee on the Safety of Vaccines

Meeting statement

Meeting 8 – Thursday 11 June 2015

Role of the Advisory Committee on the Safety of Vaccines (ACSOV) in the TGA's regulatory decision making process

The ACSOV is a statutory advisory committee established by the Therapeutic Goods Regulations 1990.

The TGA currently has ten statutory advisory committees from which it can obtain independent expert advice on specific scientific and technical matters to aid the TGA's regulatory decision making and other regulatory processes.

The ACSOV provides advice to the TGA and the Office of Health Protection (OHP) on, amongst other things, matters relating to the safety, risk assessment and risk management of vaccines supplied in Australia.

How this statement should be read

The advice provided by the ACSOV is an important element in the undertaking of the regulatory functions of the TGA. However, it forms only one part of the total body of information that is available to, for instance, a TGA delegate making a regulatory decision under the *Therapeutic Goods Act 1989* ('the Act'). Therefore, while appropriate consideration will be given to such advice, it is important to note that neither the TGA nor a TGA delegate is obliged to follow it.

It should also be noted that details of the committee's advice may not become publicly available for some time after the committee has provided that advice. The purpose of this Meeting Statement is to describe in general terms the matters considered by the committee at each meeting and for it to be available as soon as reasonably practical after the relevant meeting.

Additionally, following publication of this statement, it is most likely that further work will be undertaken by the TGA to investigate, monitor and/or evaluate the vaccines considered by the ACSOV; and this will continue for some time into the future. It is therefore possible that further information about the vaccines will become publicly available at a later time and this will be pursuant to a regulatory decision under the Act being made and following further consultation with the vaccine's sponsor and/or manufacturer.

Overview of the safety reviews and therapeutic goods referred for advice

The TGA continually monitors therapeutic goods supplied in Australia to ensure their ongoing safety, efficacy and quality. As part of this process, the TGA routinely undertakes safety reviews of therapeutic goods.

At this meeting, the committee's advice was sought on the following safety reviews and adverse event investigations.

Preliminary assessment of the safety of aluminium adjuvants given at birth to premature or low birth weight neonates

In late 2014, the TGA received an enquiry raising concern regarding the aluminium (Al) level in hepatitis B vaccinations given to preterm infants at birth. Some 500 g babies would be administered 250 µg doses of aluminium (as hydroxide) at birth as per the immunisation schedule, equivalent to 500 µg/kg for low weight premature infants. In comparison, healthy newborns receiving the same vaccines would be receiving 70 µg/kg of aluminium.

The TGA undertook a search of recent overseas regulatory actions and literature to gauge the status of aluminium adjuvant safety; and identified several limitations in the strength and reliability of the data for the premature infant patient group. The TGA concluded that the weight of the international regulatory advice and identified publications to date suggested a lack of data supporting toxicity concerns with aluminium adjuvants. The proposed safety of aluminium adjuvants was instead supported by the history of use and reported adverse events, mainly sensitivity and local reactions.

Following this preliminary review, the TGA sought ACSOV's advice on the strength of the evidence of a potential signal and whether it justified the undertaking of a full safety review. The committee was asked whether it agreed with the approach proposed by the TGA i.e. that no further review is recommended; and approached this question by considering multiple aspects of a risk assessment for the safety of aluminium adjuvants administered at birth to premature or low birth weight neonates.

As well as the limitations in the available data identified by the TGA, ACSOV also noted that some of the published literature studies were potentially affected by the authors' conflicts of interest and a lack of robustness in the statistical methods used.

The committee also noted the stated positions of overseas regulatory agencies. In 2010, the European Medicines Agency concluded that spontaneous surveillance of adverse events had not revealed safety concerns regarding aluminium in allergen immunotherapy, and that it was acceptable to use allergen products containing up to 0.5 mg aluminium per subcutaneous dose in children. In 2011, the United States Food and Drug Administration's position was that there was little risk for aluminium toxicity following immunisations for either median or low-birth weight babies.

Following this consideration, ACSOV advised that recent reviews do not support the necessity for a full safety review on the association between aluminium-containing vaccines and increased risk to low birth weight / preterm infants. There was no indication of an increased risk of unanticipated adverse effects.

Influenza vaccines and increased immune system AEFI reporting

ACSOV was advised that the TGA had begun an investigation into an observed increase, compared to previous years, in reports of Immune System Disorders (ISD) following the

administration of the 2015 influenza vaccines. ISD reactions include anaphylaxis, hypersensitivity, urticaria, angioedema, wheezing and bronchospasm.

The percentage of reported ISD adverse events following immunisation (AEFIs) with the influenza vaccine compared to the total number of reported AEFIs following influenza vaccine had risen from 12% (2013) and 13% (2014) to 21% in 2015 (as at 8 May 2015).

Due to the delayed rollout of the 2015 National Immunisation Program (NIP), the TGA data (to 8 May 2015) only reflected the first three weeks of the NIP for the 2015 seasonal influenza vaccines. The observed increase in ISD AEFI was across all States and Territories and all vaccines for which there has been sufficient reporting to TGA to determine a change in reporting rate compared to previous years.

ACSOV advised that it was unclear whether there was an increase in ISD AEFI reports associated with the 2015 influenza vaccine. The limited data and analysis do not confirm a signal without further information and investigation.

The committee suggested a range of possible explanations for the observations, including an increase in ISD reports ('the numerator'), a decrease in overall AEFI reports ('the denominator') and a time-shift of the vaccination season leading to a changed relationship with seasonal respiratory illnesses.

In considering other information that should be obtained in investigating this issue, ACSOV suggested a number of additional analyses that could be undertaken with the existing data. The committee also suggested that discussion with the manufacturers regarding any changes to the manufacturing processes used in the 2015 vaccines, compared to previous years, may be useful. ACSOV also advised that interrogation of other State and Territory datasets would be useful, as there appeared to be mixed findings on whether ISD is elevated in the 2015 influenza season. It would also be useful to liaise with other southern hemisphere regulators on this matter.

As urgent program or regulatory action was not indicated, the TGA advised that it would undertake further analysis with more complete data and provide ACSOV with the results.

Risk Management Plans (RMP)

A Risk Management Plan (RMP) is a set of pharmacovigilance activities and interventions designed to identify, characterise and manage risks relating to a medicine or a vaccine. No RMPs were considered at this meeting.

Immunisation Program advice

ACSOV noted that the Australian Immunisation Handbook 2015 has been updated to recommend the administration of a DTPa (diphtheria, tetanus, acellular pertussis) booster vaccination at age 18 months to reduce pertussis notifications in infants aged 1–3 years and to reduce transmission to younger siblings. The 18 month booster dose of pertussis-containing vaccine had been discontinued from the NIP in 2003.

ACSOV provided advice on a Vaccine Safety Plan (VSP) which has been developed in support of the 18 month booster dose of pertussis-containing vaccine as part of the NIP. The VSP is based on advice from the Australian Technical Advisory Group on Immunisation (ATAGI), the TGA and the Pharmaceutical Benefits Advisory Committee (PBAC). It was noted that the reintroduction of the 18 month booster of DTPa followed by the 4 year booster was a similar vaccination protocol to that recommended in the USA.

With an adverse event of special interest, extensive limb swelling (ELS), known to follow 2% of pertussis-containing booster doses, it is necessary for enhanced surveillance to be undertaken to monitor for a likely increase in the overall incidence of ELS at 18 months and for any potential incremental effect on incidence of ELS following the 4 year old booster dose.

ACSOV noted that the VSP includes a range of safety surveillance activities. The active surveillance activities were expected to be for a minimum of three years, cover all States and Territories across approximately 24 sites, and recruit a minimum participation of 6500 children per year (about 2% of the population cohort). ACSOV advised that it agreed with the scope of the enhanced vaccine safety surveillance activities in the VSP, but the following activities should also be included:

- a retrospective surveillance element to collect baseline data on ELS;
- broadening participating sites to include council based immunisation services; and
- photographic documentation as part of follow up with participating parents/ carers to record AEFI for research and education purposes.

Further information

Meeting statements are made publicly available after each meeting.

For further information on the ACSOV, please visit the ACSOV webpage or contact the ACSOV Secretary: Mr Craig Davies on 02 6232 8641 (telephone) or via email: acsov@tga.gov.au