SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLETS PRESENTED BY THE EMEA

INTRODUCTION

The EMEA published its initial review on the benefit/risk profile of hexavalent vaccines (EMEA/8519/03, EMEA/CHMP/5889/03) in April and December 2003, concluding that there was no change to the benefit/risk profile and therefore no changes to the conditions of use were recommended, for, among others, the following reasons:

- Vaccination offers benefits to the individual child and to the general population. The CHMP considered that the benefits of vaccination far outweighed possible risks of existing vaccines, including hexavalent vaccines, and that vaccination should be continued according to national vaccination schedules.

- The causes of death remain unexplained and on the basis of the available data, it is not possible to establish a cause and effect association with the hexavalent vaccines.

- The temporal relationship identified between 4 Sudden Unexpected Death (SUD) cases and hexavalent vaccination raises a possible signal for Hexavac vaccination and SUD, but there are some inevitable limitations of the data sources and methods used to calculate the expected numbers. In any case, the signal only raised a suspicion and did not prove a cause and effect relationship. Further studies are needed to establish whether or not there is a risk.

On 28 January 2005, Germany requested the suspension of the Marketing Authorisation for Hexavac (EU/1/00/147/001-8) based on the Article 18 of Council Regulation 2309/93 (EC).

Therefore, on 15 February 2005, the European Commission (EC) triggered the review procedure under Article 18 of Council Regulation (EEC) No 2309/93 for reasons related to the occurrence of Sudden Unexplained Deaths after administration of Hexavac in the 2nd year of life. The CHMP was requested to give an opinion as to whether the Marketing Authorisation (MA) for Hexavac should be maintained, varied, suspended or withdrawn.

The CHMP started the review procedure on 15 February 2005.
An expert meeting was convened on 21 March 2005 to scrutinise all available data and analyses on the occurrence of Sudden Infant Death Syndrome (SIDS) and SUD after administration of Hexavac and to discuss whether the administration of Hexavac can be considered as safe.

The risk assessment focused on epidemiological analyses of the cases of SUD, autopsy reports of the individual cases, all available data from the previous review and the results from the observed/expected analysis of Prof. Von Kries, as published in the *European Journal of Paediatrics*, 2005 (Eur J Pediatr 2005 Feb;164(2):61-69, Epub 2004 Dec 16).

Safety Issue

The CHMP had previously concluded that there is a *statistical* signal of an excess occurrence of cases of SUD within 24 hours of a booster vaccination with Hexavac during the 2nd year of life.

The signal had been identified in the observed/expected analysis (see above). The investigators regarded their data as evidence for "a strong risk signal for Hexavac booster vaccinations in the 2nd year of life and SUD". They find that chance is a very unlikely explanation of the finding, given the

fact that the lower confidence limits for both day 1 and day 2 were greater than unity, i.e. 3.8 and 4.8, respectively. The absolute risk (reporting rate) would correspond to 1 death due to SUD in 300,000-400,000 children in the 2nd year of life. On the basis of extensive analyses showing a remaining excess risk, i.e. sensitivity analyses, it was concluded that the findings were unlikely to be attributed solely to limitations of the data sources.
However, it is acknowledged that the calculations are based on a number of assumptions and may be affected by bias in the data, but the finding of an excess statistical occurrence of SUD seems to remain after testing for the influence of new and different assumptions.

The CHMP concluded, that the absolute risk was considered to be very small. In addition, the observed/expected analysis could not provide evidence for a cause and effect relationship between SUDs and vaccination with Hexavac. Additionally, there is no biologic explanation so far to support a causal link.

Meticulous expert scrutiny of individual reports of all known cases (3 cases from Germany and 1 case from Austria) of SUD in the 2nd year of life did not reveal any circumstantial evidence of a biological and causal link between Hexavac and the occurrence of SUD. Neither is there any hypothetical explanation regarding possible effects on the immune or autonomous nervous systems, on pro-convulsive mechanisms or by means of quality defects in the production of the multivalent vaccines.

The updated review of the individual cases did not identify any new safety issue for Hexavac. Additionally, no specific underlying mechanism could be identified to explain a causal link between Hexavac and an increased occurrence of SUD.
Different experts had previously assessed and discussed the quality aspects of Hexavac and no mechanistic support for an increased risk of SUD was identified. There is no inconsistency between batches and no quality deficiencies were identified.

Based on the available data, there is no possible link between an immunological reaction caused by the hexavalent vaccines and an increase of SUD occurrence.

Animal studies and animal models were thoroughly reviewed to analyse a possible relationship between SUD and Hexavac. However, there was currently no animal model available to investigate SUDs. Furthermore, the fact that no significant effects had been observed in the telemetry animal studies indicates that there is no support for a hypothesis that disturbances in the autonomic nervous system are responsible for the SUD occurrence associated with Hexavalent vaccines. Furthermore the EEG monitoring did not show proconvulsive effects related to the administration of vaccines.

Conclusion

In summary, it was found that no new relevant data has become available since previous discussions/conclusions by/of the CHMP.

The CHMP, upon review of the safety of Hexavac, acknowledged the finding of a statistical signal of an excess occurrence of SUD after Hexavac booster vaccination in the 2nd year of life, but also the inability to identify a biological mechanism in spite of meticulous expert considerations, and the initiation of epidemiological studies.

The CHMP reviewed the data submitted by the MAHs in relation to the signal of SUD in children and toddlers. The CHMP concluded that a signal does exist based on a statistical relationship, which may represent an artefact in the data, a random cluster of events, or a true biological effect. However, the strength of this signal is, in the absence of a convincing biological and causal link, weak, therefore the benefit-risk balance for Hexavac remains positive and no further regulatory action is necessary at this point in time.

The CHMP concluded that serious adverse events, particularly cases of SUD, shall be continuously and carefully monitored and assessed. Therefore the CHMP members recommended follow-up measures to further investigate the known cases and to initiate further studies

On the basis of the current data, the CHMP concluded that the safety profile of Hexavac is in line with the current SPC.

GROUNDS FOR MAINTAINING THE MARKETING AUTHORISATION OF HEXAVAC

WHEREAS

- The CHMP came to the conclusion that after the review of available data, the causes of death remain unexplained and it is not possible to establish a causal association with Hexavac.

- The CHMP members have, in line with the previous reviews, come to the conclusion that the signal does exist based on a statistical relationship, which may represent an artefact in the data, a random cluster of events, or a true biological effect. However, the strength of this signal is, in the absence of a convincing biological and causal link, weak.

- The CHMP concluded that no scientific rationale or convincing ethical considerations to take regulatory action have been presented. Therefore the benefit-risk balance for Hexavac remains positive and no further regulatory action is necessary at this point in time.

- The CHMP concluded that serious adverse events, particularly cases of SUD, shall be continuously and carefully monitored and assessed. Therefore the CHMP members recommended follow-up measures to further investigate the known cases and to initiate further studies