SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION OF THE MARKETING AUTHORISATION OF PROCOMVAX PRESENTED BY THE EMEA

INTRODUCTION

The approved indication of Procomvax is for vaccination against invasive disease caused by Haemophilus influenzae type b and against infection caused by all known subtypes of hepatitis B virus in infants 6 weeks to 15 months of age. The active substances of Procomvax consist of polyribosylribitol phosphate (PRP) purified from Haemophilus influenzae and chemically coupled to the outer membrane protein complex (OMPC) of Neisseria meningitidis, and the hepatitis B surface antigen (HBsAg) of the hepatitis B virus, derived from a recombinant strain of yeast. These non-infectious substances protect infants against invasive disease caused by Haemophilus influenzae type b (infection of brain and spinal cord tissues, infection of the blood, etc.) and against infection caused by all known subtypes of hepatitis B virus, by stimulating an immune response (immunogenic activity) against these infections.

Issues pertaining to the relatively low immunogenicity of the Hepatitis B (HepB) component contained in the vaccines containing the recombinant Hepatitis B component from, SPMSD have been assessed and extensively discussed by the CHMP and its Working Parties (Biotechnology Working Party, Vaccines Working Party).

On 26 May 2005, the CHMP agreed on the need to convene an Ad Hoc Expert Group Meeting on Hepatitis short and long-term protection afforded by recombinant Hepatitis B vaccines. The CHMP expressed concerns that there is evidence of unpredictable variability in Hepatitis B antibody response following vaccination with Hexavac. This variability seems to be related to currently uncontrollable variances in the manufacturing process of the recombinant HepB vaccine component. Concerns were expressed on the low immunogenicity of the HepB component of Hexavac and the potential consequences on long-term protection against Hepatitis B infection and boostability post primary course of vaccination with this vaccine.

Following the suspension of Hexavac due to reduced immunogenicity of the Hep B component in the vaccine, the MAH (Sanofi Pasteur MSD) was requested in September 2005 to provide further data and clarification on long-term immunological memory and protection against Hep B viral infection afforded by HBVAXPRO and PROCOMVAX, and the timelines of availability of further data.
In their January 2006 plenary meeting, the CHMP confirmed their concerns regarding the decreasing immunogenicity of the recombinant Hep B component contained in HBVAXPRO and PROCOMVAX. The CHMP debated the current lack of knowledge about the clinical significance of the findings and immune memory in general and agreed that these issues needed to be carefully explored before deciding on regulatory action.
The Committee also noted that the last study performed in infants below one year was completed in 2001. As a consequence the data obtained so far must be interpreted with caution since they were generated using the paediatric (5µg) dose of Hep B vaccine produced before 2001. There are some indications that the Hep B vaccine currently produced is less immunogenic than the vaccine produced in the 1990's. The reason for decreasing immunogenicity over several years remains still unidentified. It was considered that a decision will be taken according to the responses given on quality and clinical concerns. The clinical issues were discussed with the MAH at the Vaccine Working Party (VWP) during its February 2006 meeting, while the quality issues were discussed at the February BWP meeting.

On 13 February 2006, the European Commission (EC) triggered the procedure under Article 20 of Regulation (EC) No 726/2004, after the CHMP expressed concerns on the low immunogenicity of the HepB component of Procomvax. The CHMP was requested to give an opinion as to whether the marketing authorisation for Procomvax should be maintained, varied, suspended or withdrawn in the context of an Article 20 of Regulation (EC) No726/2004 procedure.

DISCUSSION

From the quality point of view, there are no technical, analytical or animal tools able to predict immunogenicity of recombinant hepatitis B components in man. Analytical tools can be used as consistency criteria, but not as correlates for safety and efficacy (immunogenicity) of Hepatitis B batches produced at SPMSD. As there is no *in vitro* or *in vivo* system suitable to predict acceptable immunogenicity in man, it is important to note at this stage that the C3H mouse model suggested by the MAH appears to be able to discriminate between Hepatitis B lots which are acceptable and those who are not. Notwithstanding, the new proposed model will have only predictive value once it has been fully validated and has shown to be able to discriminate batches of the Hepatitis B component that have elicited a high vs. a low immune response during clinical trials.

Although the root cause for reduced immunogenicity during the past 5 years is still not ascertained, evidence was provided that the manufacturing process seems now to be better controlled. The MAH developed an upgraded manufacturing process to increase immunogenicity. The interim outcome of a clinical trial with the 'process upgraded' recombinant Hepatitis B batches confirms that the immunogenicity of the current PROCOMVAX vaccine is at the historic standard, and provides evidence for a consistent trend to higher GMTs with PROCOMVAX manufactured with the process modification.

The data reviewed by CHMP included data from 7 studies with HBVAXPRO and Procomvax, one of which is on-going at present. These trials were carried out in different risk groups and age categories, i.e. children born to Hepatitis B positive mothers, infants, healthy young adults and healthy subjects between 16-35 years of age.

In the studies conducted by the MAH to date with HBVAXPRO and Procomvax, seroprotective levels have been achieved in the large majority of vaccinees. There is no evidence that either short or long term protection has been impacted. Although in some of the trials conducted in the past 5 years, the GMTs of the hepatitis B vaccines were lower than responses observed in the early 1990's, the clinical data generated by the sponsor in the trials described above, demonstrate consistent, high anti-HBs seroprotective rates, which is the established correlate of effectiveness. In addition, a review of clinical performance as assessed by protection against disease as noted in the V121-018 trial supports the conclusion that the hepatitis B vaccines remain effective in decreasing hepatitis B infection and its serious sequelae.
Due to the relatively high risk of infection, the group of infants born to Hepatitis B positive mothers represents the population, which would be most vulnerable to a possible insufficient immunogenicity of the vaccine. As there are currently no reports on increased numbers of Hepatitis B breakthrough cases after PROCOMVAX vaccination, considering that the EU is a low endemic region, no immediate safety signal could be identified by the CHMP.

The most recent immunogenicity data comes from the interim analysis of the V232-054 trial, this is the third trial in the past few years to study the current product (from the BTMC manufacturing facility) in young adults using the same dosing schedule (the other two trials are V501-011 and V232-052). The results from these three trials with product manufactured in the current facility, confirm solid, reproducible performance based on these recent historical data and should also predict performance as expected in other populations as well. In the past experience, there has never been an instance when high performance in adolescents and young adults did not correspond with high performance in infants. Therefore, the results of this study provide evidence that the currently available product is providing the expected level of protective antibodies in all populations for which it is indicated.

In addition to the immunogenicity data generated in the past 5 years from clinical trials with the PROCOMVAX data, the acceptable performance of these vaccines are supported from findings of surveillance for hepatitis B cases in the United States and New Zealand and from an analysis of the trend in vaccine failures reported to the MAH safety database.

The CHMP requested the MAH to conduct studies regarding neonates, infants, older adults, renal dialysis patients, dose ranging and a booster study with the current formulation and the process upgraded product to further ensure that the vaccine provides a sufficient level of long-term protection against Hepatitis B.

In view of the lack of analytical tools to predict immunogenicity in man, the need for regular testing of recombinant HepB batches in clinical trials was considered, in order to ensure consistent high immunogenicity of PROCOMVAX produced in particular according to the new updated/improved process. The CHMP agreed with the MAH that in 4 years time, in the absence of ongoing clinical studies of immunogenicity with the MAH's hepatitis B antigen, the MAH will conduct a study of vaccine immunogenicity no less frequently than every four years to confirm that experience with manufactured product remains current and that clinical performance meets expectations.

The CHMP agreed with the MAH on revised product information for all presentations of PROCOMVAX, reflecting advice and suggestions made during the procedure. Revised SPCs and PLs provide updated information in relation to best use of the product considering latest clinical data. These changes, in principle, address the concerns raised by the CHMP and its Working Parties.

Pending the outcome of the studies, the MAH committed to amend the SPC section 5.1 in order to update this section with the latest results from clinical studies regarding anti-HBs responses in individuals previously vaccinated and not vaccinated with Hepatitis B Vaccine as well as anti-PRP responses.

CONCLUSION

The CHMP reviewed all the technical and clinical data available for PROCOMVAX extensively. The CHMP also considered the commitments given by the MAH in response to CHMP's requests to meticulously control the performance of PROCOMVAX from now on in a broad array of appropriate clinical trials including all age and risk categories. The CHMP concluded that the use of this vaccine will not pose an immediate risk to any of the target groups the vaccine is indicated for. Potential remaining risks will be minimised to an acceptable level by the fundamentally revised SPC. Information will be provided to health care professionals and will ensure that the vaccine will be correctly used in the different age and risk categories. The CHMP endorsed the new product information and agreed to finalise the article 20 procedure without any further regulatory action.

Considering all points raised, including time lines required to fully explore all issues related to low HepB immunogenicity following vaccination with PROCOMVAX and, further to the assessment of the data provided by the MAH, the CHMP concluded that the MA of PROCOMVAX should be varied in accordance with Article 5(2) of Regulation (EC) No 726/2004.

GROUNDS FOR THE VARIATION OF THE MARKETING AUTHORISATION OF PROCOMVAX

WHEREAS

The CHMP is of the Opinion that the Product Information of PROCOMVAX, should be varied in order to maintain the safe and effective clinical use for the following reasons:

- Considering the data on low immunogenicity available today, the CHMP identified the need for further studies to ensure long-term protection against Hepatitis B with the current vaccine in future.

- The CHMP identified that the decreased immunogeniticy of the HepB component released by the MAH seems to be due to variability in the production process for this component and that following extensive review of the manufacturing process the MAH has identified the current adjuvantation process as a potential root cause for decreased immunogenicity of the HepB vaccine component.

- The use of this vaccine will not pose an immediate risk to any of the target groups the vaccine is indicated for. Potential remaining risks will be minimised to an acceptable level by the fundamentally revised SPC.

- The CHMP considered that the benefit/risk balance of PROCOMVAX concerning protection against hepatitis B virus infection caused by all known subtypes in all age categories considered at risk of exposure to hepatitis B virus remains favourable.

The CHMP has recommended the variation of the Marketing Authorisations for PROCOMVAX in accordance with Article 5(2) of Regulation (EC) No 726/2004.