SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of HBVAXPRO. This scientific discussion has been updated until 01 September 2004. For information on changes after this date please refer to module 8B

1. Introduction

HBVAXPRO is a thiomersal free vaccine which is indicated for active immunisation against hepatitis B virus infection caused by all known subtypes in all age categories considered at risk of exposure to hepatitis B virus.

It is prepared by recombinant DNA technology, in yeast culture of *Saccharomyces cerevisiae*, permitting the large scale production of hepatitis B virus surface antigen (HBsAg) particles similar to naturally occurring particles; the manufacturing process minimises risk of contamination.

This vaccine induces specific humoral antibodies against HBsAg (anti-HBs). Development of an anti-HBs titre above 10 IU/l measured 1-2 months after the last injection correlates with protection against hepatitis B virus infection.

The rationale for the development of HBVAXPRO takes into account the EMEA´s public statement from July 1999 (EMEA/20962/99) on thiomersal containing medicinal products. It is currently licensed as the thiomersal-containing version in all member states as a MRP product, due to its former ex-concertation status.

2. Chemical, pharmaceutical and biological aspects

Composition
Hepatitis B Vaccine (Recombinant) is composed of highly purified hepatitis B surface antigen (HBsAg) adsorbed to an aluminum adjuvant. The antigen is produced from the fermentation of a recombinant strain of yeast, *Saccharomyces cerevisia*e. Following purification, the antigen is formulated and filled into one of three final container formulations. No thiomersal is added to the finished product.

The pharmaceutical form of this vaccine is a suspension for intramuscular injection and the final product is presented in a pre-filled syringe (with or without needle) or in a vial. The proposed shelf life is three years for the vial and syringe presentations when stored between +2°C and + 8°C.

The 3 mL glass vials are closed by rubber stoppers and capped with aluminum seals with plastic caps.

The 1.5 mL glass barrel pre-filled syringe is presented with or without an attached needle. The seal is a deep threaded grey butyl stopper and a polypropylene plunger rod is screwed into the stopper. Stopper and plunger rod specifications remain the same for both the fixed-needle and needleless images.
Syringes equipped with a fixed needle: Needlelength=5/8 inch. A needle guard is placed over the needle and a polypropylene needle shield is placed over the needle guard.
Syringes without a needle: Glass container is a Luer Tip syringe with a plastic Luer-Lok™ Adapter and gray E-Z grip tip cap. The needleless syringe barrel is composed of identical material, but lacks the fixed needle. A Luer-Lok™ adapter covered with a rubber tip cap maintains sterility and allows flexibility in needle gauge and length chosen for administration.

Active substance
HBVAXPRO contains Hepatitis B virus surface antigen (HBsAg). This is a hydrophobic 24 kDa membrane proteine called the S protein which is the active immunogen in the vaccine.

Expression system and cell banks
The biosynthesis of the HBsAg utilizes a recombinant plasmid expressed in the host cell Saccharomyces *cerevisiae* The plasmid codes for a 24 kDa membrane protein called the S protein. The Pre-Master, Master, and Working Seed lots were prepared according to the same procedure consisting of re-suspension in a medium containing 17% glycerol. The cultures obtained were aliquoted, frozen and stored at a temperature of ≤ -60 °C.

Fermentation and Purification
The fermentation process yields approximately 2100 L of final culture. The yeast cells are concentrated and diafiltered to produce an approximately 40% cell suspension. The purification process includes two phases, Phase 1 Purification (from cell lysate to Concentrated Silica Product, CSP) and Phase 2 Purification (from CSP to Sterile Filtered Product, SFP). The formulation process also includes two phases, Formaldehyde Treatment (from SFP to Final Aqueous Product, FAP) and Alum Co-precipitation (from FAP to Bulk Alum Product, BAP).

Product development and finished product
In July 1999, the EMEA made a public statement on thiomersal containing medicinal products (EMEA/20962/99) recommending the promotion for general use of vaccines without thiomersal and other mercurial containing preservatives, particularly for single dose vaccines, and this within the shortest possible timeframe. Merck & Co., Inc. therefore eliminated thiomersal from the monovalent Hepatitis B vaccine. The preservative free product is manufactured using the same intermediate, thiomersal free 40 µg Bulk Alum Product, already licensed and used in the preservative free vaccines, PROCOMVAX and HEXAVAC. For Hepatitis B Vaccine (Recombinant), this intermediate will be diluted to obtain the concentration of 10 µg/ml for the final product (for the 5 µg/0.5 ml and 10 µg/1.0 ml formulation) or used undiluted for the 40 µg/1.0 ml formulation.

The formulation of Hepatitis B Vaccine (Recombinant) used in clinical studies contained the preservative, thiomersal (1:20,000). The formulation of the vaccine proposed for marketing does not contain thiomersal. With the exception of the absence of thiomersal, the formulation for the finished recombinant vaccine is the formulation developed for the Hepatitis B vaccine currently marketed by Aventis Pasteur MSD.

Status of GMP inspection
Manufacture of the hepatitis B vaccine is in compliance with GMP regulations. Current production facilities have been inspected by EEC inspectors during the past 2 to 3 years. As a follow up measure the Rapporteur has requested inspection of the bulk manufacturing and filling facilities which have not yet been inspected.

Product characterisation and process validation
An extensive characterization was performed on products from four demonstration lots. The same tests and procedures used to characterize the demonstration lots were used for the previous analysis of the pilot lots described in the Type II variation n° FR\H\23\01-05\W13.
The process was validated using critical process parameters (CPP) and critical quality attributes (CQA) based on historical data

The high level of product purity was supported by the characterization studies. In addition, process validation was used to show the decrease in levels of cell-derived biomolecules through the purification. Release testing monitored the clearance of any reagents added during processing. It was concluded from these analyses that product purity was high and consistent.

In addition, preclinical studies in C3H mice showed that the BAP was equivalent in potency to a process standard.

Control of the Finished Product
Specifications and routine testing are performed on each batch of final container product. Testing includes: sterility, fill volume, LAL, Identity, In Vitro Relative Potency, aluminum, pH, and sodium chloride.

Stability of the Product
Both real time data (2-8 □Çand data from accelerated stability studies (25 □C) are provided on Preservative Free BAP stability lots.

To date, test results for In Vitro Relative Potency, pH, sterility, and LAL all remain within release specifications for all three lots stored at 4 □C. Stability studies are ongoing.
Stability data from an accelerated study show a stability profile which is consistent with historical stability data for Thiomersal Containing final container product stored at 25 □C. Therefore, the presence or absence of thiomersal is not considered to have an impact on the stability of HBsAg.

In addition, historical data are provided to demonstrate consistently stable potency of the active ingredient when stored at 4 □C by comparing Preservative Free and Thiomersal Containing BAP. Statistical comparison shows that there is no evidence of a difference in IVRP, level of response or degradation profile among formulations (Preservative Free versus Thiomersal Containing).

Based on the satisfactory real time stability data from the three Preservative Free BAP lots and that there are ongoing stability studies, a 36 month shelf life is warranted. This dating is supported by the fact that accelerated data on these three BAP lots are consistent with Thiomersal Containing product and that historical stability database provides no difference in level of response or degradation profile for Preservative Free or Thiomersal Containing BAP.

3. Toxico-pharmacological aspects

Most of the data presented are derived from studies conducted on the applicant´s currently licensed, thiomersal-containing, hepatitis B vaccine, hereafter referred to as HBVAX or RECOMBIVAX.

Potency
The manufacturer performed preclinical studies comparing HBVAXPRO with their currently licensed thiomersal-containing recombinant hepatitis B vaccine. All 4 tested lots had ED50 values that were lower (i.e., more potent) or equivalent to those of the control vaccine.

ED_{50} Results for BTMC Demonstration Lots of HBVAXPRO and Current Process HBVAX Tested in C3H Mice

Demo-Lot No.	†IVRP	ED50	95% CI	Control (2036610)	95% CI ED50
2066410	3.04	0.19	(0.14, 0.25)	0.52	(0.36, 0.96)
2068061	2.91	0.38	(0.25, 0.74)	0.36	(0.25, 0.63)
2069429	2.13	0.14	(0.10, 0.19)	1.28	(0.76, 2.14)
2069710	2.14	0.15	(0.12, 0.20)	0.90	(0.47, 4.34)

† IVRP of the control lot was 1.47.

Toxicology
The tested substance was Hep B Thiomersal-Free Bulk Vaccine as Part of HEXAVAC development which was carried out in accordance with the current guideline (CPMP/SWP/465/95) for preclinical pharmacological and toxicological testing of vaccines. Its assessment included acute toxicology and repeat dose toxicology studies.

Single dose toxicity
HEXAVAC® safety was evaluated in the mouse by subcutaneous route to mimic the human route of exposure (injected dose: 40 human dose/kg) and in the rat by intraperitoneal route to obtain a rapid bioavailability (injected dose: 12.5 human dose/kg). Both studies were performed according to Good

Laboratory Practices. The doses tested are relatively high considering that one human dose for a 6 kg infant is equivalent to 0.17 human dose/kg of human body weight.
No signs of toxicity were noted in both species through clinical observation and gross necropsy examination. The local reactions observed in the mouse at the subcutaneous injection site were as expected for an adjuvanted vaccine.

Repeat dose toxicity
The absence of toxicity was evaluated after repeated administrations in the rat according to treatment schedules mimicking a human vaccination scheme (i.e., 3 injections at monthly intervals).
The fourth dose which was administered 6 months to 1 year after the third dose in the human vaccination scheme for HEXAVAC® was not included in this toxicology study design. However, it is considered that the second and the third injections were sufficient to boost the immune response and to reveal potential adverse reactions. The subcutaneous route was considered equivalent in terms of bioavailability to the intramuscular clinical route and a dose level of 5 human doses per kg was tested (human dose level: 0.17 human dose/kg of human body weight). A control group only received aluminium adjuvant, while a reference group received, in an identical manner, a pentavalent adjuvanted vaccine lot which is already marketed (differs from HEXAVAC® by the presence of cellular (whole cell) pertussis antigens and the absence of HBs antigen). All clinical observations followed by gross and histopathologic examinations and blood assays (haematological and biochemical) at completion of treatment revealed changes attributed to the vaccine properties of the reference and tested vaccines. None of these findings had a toxicological significance.
Based on the design of this repeated dose toxicology study, no immuno-toxicological findings such as autoimmune reactions were observed. It is noted that this animal study revealed no kidney or vascular lesions justifying further examinations or indicating potential immune complex deposition.
No hypersensitivity reactions were noted after the second or the third administrations.

Discussion on toxico-pharmacological aspects
The comparative mouse immunogenicity test performed with the hepatitis B vaccine with and without thiomersal indicates that there is at least equivalent immunogenicity of both products. However, it is controversial to what extent these data can be extrapolated to humans.

There is no clinical evidence that increased immunogenicity is correlated with increased reactogenicity.

Pre-clinical data are considered to be sufficent. The data from the HEXAVAC and PROCOMVAX studies can be extrapolated to the monovalent, thiomersal-free hepatitis B vaccine. Separate studies would not provide any new knowledge on the pre-clinical safety profile of HBVAXPRO.

The thiomersal-free monovalent hepatitis B vaccine that is the subject of this application has been shown to be both safe and immunogenic in preclinical animal models.
The thiomersal-containing vaccine was shown to have no detectable acute toxicity in mice and rats and to pass the general safety test in guinea pigs. In addition, a special assay was run to test for possible anaphylactic reactions to potential yeast antigen contaminants of the HBs vaccine.
No anaphylactic reactions were detected when multiple lots of the vaccine were tested. In addition, recent studies with the thiomersal-free, hepatitis B-containing combination vaccine, HEXAVAC® showed no detectable toxicity in acute or repeated dose studies.

In-vivo potency testing in C3H mice showed the thiomersal-free vaccine to be highly potent and comparable to that of the thiomersal-containing formulation. Therefore, based on historic (indirect) and on product related data there is no scientific basis for contraindications to the use of HBVAXPRO.

4. Part IV: Clinical aspects

No formal clinical trial has been performed with HBVAXPRO in most of the target populations included in the proposed indications e.g. newborns of HBsAg positive mothers, infants, toddlers and adult persons at risk.

However, there are extrapolated clinical data on the efficacy, immunogenicity and safety of HBVAXPRO which are based on different sources:

PROCOMVAX pre- and post-authorisation safety and immunogenicity data (evaluated in the Centralized Procedure)
HEXAVAC pre-licensure data (idem)
Post-marketing surveillance data of the thiomersal-free vaccine in high risk infants in the U.S.
Post-marketing safety data of the thiomersal-free vaccine in the U.S.

A post-authorisation study will be performed in young adults to confirm non-inferiority of the thiomersal free vaccine towards the thiomersal containg regarding efficay and safety.

Clinical efficacy

Efficacy in high risk infants

- Surveillance data by New York City Department of Health (NYCDOH) on vaccination of high risk infants

Infants born to HBsAg positive mothers are vaccinated while their immune systems are premature. Therefore, the high risk infant population provides a stringent test of the effectiveness of a hepatitis B vaccine.
Surveillance data on the efficacy of the thiomersal-free hepatitis B vaccine in high-risk infants born to HBsAg positive mothers were provided by the New York City Department of Health (NYCDOH).
The NYCDOH provides services to over 7 million residents of New York with an annual birth cohort of approximately 125.000. The recommended vaccination regime is HBIG at birth plus a 3-dose course of vaccine beginning while the infant is in the hospital with subsequent doses at approximately 1 and 6 months of age. Serological assessment of hepatitis B antigen and antibody status in these high-risk infants is conducted 1 to 3 months after completion of the vaccine series. Thus, a high proportion of infants in the 2000 time period has not been serologically checked for hepatitis B antigen and antibody status.

Table 1: Surveillance data from the New York City Department of Health

	Period 1 1 Jan 99 – 31 Mar 99 with thiomersal- containing hepatitis B vaccine in use	Period 2 1 Jan 00 – 31 Mar 00 with thiomersal- free hepatitis B vaccine available
No. of risk infants tracked	335 (100 %)	401 (100 %)
No. of infants with documented vaccination regime as recommended*	282	297
No. of infants with available serological data	146	137
No. of documented HBsAg positive infants	5	3
No. of documented HBsAg negative infants & anti-HBsAg positive	141	131
No. of documented HBsAg negative infants & anti-HBsAg negative	Not Available	3
Calculated vaccine efficacy**	95.1 %	96.8%

* HBIG at birth plus a series of three 5-µg doses of hepatitis B vaccine
** assuming that 70 % of high risk infants would suffer from chronic HBV

Extrapolated studies

- Post-marketing study on PROCOMVAX (Preliminary assessment report September 2000) entiteld: "Safety, tolerability and immunogenicity probe study of COMVAX using various levels of PRP in South African infants" (study protocol 10)

PROCOMVAX Protocol 10 was a single-blind, randomised, single-centre study of 4 formulations of Haemophilus influenzae type b/ hepatitis B combination vaccine to probe the immunogenicity of varying PRP dosage (0.5 µg, 1.0 µg, 3.75 µg and 7.5 µg (licensed formulation) in combination with 5 µg HBsAg. South African infants (4 to 8 weeks of age) were randomised to receive one of the four formulations. The formulations 1.0 µg and 7.5 µg PRP did not contain thiomersal. The preparations 0.5 µg and 3.75 µg were prepared as field mixes and contained 11.48 µg thiomersal/ 0.5 ml dose which is approximately half of the amount of in the paediatric formulation of the licensed monovalent hepatitis B vaccine, HBVAX. The vaccine formulations were administered at 6, 10, 14 and 36 weeks of age. Serum samples were obtained prior to and 4 weeks following dose 3 and prior to and 4 weeks following dose 4. Safety data were collected for 14 days following each dose of the study vaccine. The study was intended for infants born to non-carrier mothers. Between 51 and 53 vaccinees were enrolled per group.

As shown in the table, the anti-HBs responses (%≥ 10 mIU/mL and GMTs) appeared similar for the PRP dosage ranged from 0.5 µg to 3.75 µg with a very slight trend towards a lower immune response of the 1.0 µg formulation. After dose 4, 100 % of these subjects developed an anti- HBs response of 10 mIU/mL with GMTs ranging from 3177.2 mIU/mL to 3390.3 mIU/mL. However, the anti-HBs responses to the formulation with 7.5 µg PRP (thiomersal-free) appeared decreased compared to the other formulations. The post dose 4 anti-HBs response was 97.6 % with a GMT of 1566.2 mIU/mL.

PROCOMVAX protocol 10, anti-HBs response among infants who received vaccine at 6, 10, 14 and 36 weeks of age

Formulation	Interval	N	Percent ≥10 mIU/mL (CI)		GMT mIU/mL (CI)	
0.5µg PRP/ 5µg HBsAg † (T+)	Post Dose 2	43	88.4 %	(74.9 %, 96.1 %)	46.0	(29.4, 72.0)
	Post Dose 3	51	98.0 %	(89.6 %, 100 %)	260.7	(169.0, 402.1)
	Pre Dose 4	49	100 %	(92.7 %, 100 %)	249.5	(185.5, 335.6)
	Post Dose 4	46	100 %	(92.3 %, 100 %)	3390.3	(2504.0, 4590.3)
1.0µg PRP/ 5µg HBsAg †† (T-)	Post Dose 2	45	73.3 %	(58.1 %, 85.4 %)	17.8	(10.5, 30.0)
	Post Dose 3	45	97.8 %	(88.2 %, 99.9 %)	162.7	(107.9, 245.3)
	Pre Dose 4	45	97.8 %	(88.2 %, 99.9 %)	123.7	(81.4, 188.0)
	Post Dose 4	40	100 %	(91.2 %, 100 %)	3177.2	(2189.7, 4609.9)
3.75µg PRP/ 5µg HBsAg † (T+)	Post Dose 2	45	77.8 %	(62.9 %, 88.8 %)	48.4	(27.7, 84.4)
	Post Dose 3	49	98.0 %	(89.1 %, 99.9 %)	198.3	(135.0, 291.1)
	Pre Dose 4	46	97.8 %	(88.5 %, 99.9 %)	112.1	(77.8, 161.4)
	Post Dose 4	42	100 %	(91.6 %, 100 %)	3223.1	(2126.2, 4885.7)
7.5µg PRP/ 5µg HBsAg †† (T-)	Post Dose 2	48	54.2 %	(39.2 %, 68.6 %)	7.6	(4.0, 14.7)
	Post Dose 3	48	83.3 %	(69.8 %, 92.5 %)	41.4	(22.6, 75.8)
	Pre Dose 4	47	80.9 %	(66.7 %, 90.9 %)	24.3	(13.7, 43.1)
	Post Dose 4	42	97.6 %	(87.4 %, 99.9 %)	1566.2	(921.0, 2663.2)

Notably, the formulations with 3.75 µg and 7.5 µg PRP appeared to be modestly more immunogenic after dose 3 than the formulations with lower PRP dosages. After dose 4, no clear dose effect could be observed. The applicant concluded that the GMT of the 7.5 µg formulation was less robust than the GMTs of the other formulations and that the trends observed seem consistent with a PRP dose effect as opposed to a thiomersal effect.

Interestingly, there were 4 infants (three in the groups with thiomersal-free hepatitis B vaccine) born to HBsAg positive mothers who were tested HBsAg and HBV-DNA negative at 40 weeks of age.

- Comparison of anti-HBs response to Hexavac and Primavax

The applicant presented a historical comparison of the anti-HBs immune response of the pivotal Hexavac study A3R08396 with the results of the pivotal PRIMAVAX study RDT 01194. The

applicant stated that the observed variability in the immune response of the hepatitis B component of these products is unrelated to the presence of thiomersal.

Anti-HBs post primary series and booster dose – comparison of thiomersal -free HEXAVAC and thiomersal-containing PRIMAVAX

Vaccine	HBsAg	Primary series-months of age (n)	GMT and % ≥10 mIU/mL	Booster dose-Months of age (n)	GMT Post-booster	% ≥10 mIU/mL
HEXAVAC	5 µg	2, 4, 6 (328)	434 96.6	12 – 15 (325)	932	96.6
PRIMAVAX	5 µg	3, 5 (203)	103 87.7	11 (187)	1309	98.4

Discussion on clinical efficacy

High risk infants
The NYCDH data do not indicate that the introduction and use of the thiomersal free monovalent hepatitis B vaccine has a negative impact on the effectiveness of vaccination to prevent HBV infection in a public health setting. However, the surveillance data are considered to be limited and subject of several biases (see CPMP/4167/00 adopted). Of some concern are the 3 infants who remained anti-HBsAg negative despite regular vaccination with the thiomersal-free hepatitis B vaccine (period 2).

A valid classification of the mothers' HBsAg status derived from the NYCDOH has not been possible due to the limited number of infants for which serological data could be obtained**.**

Extrapolated studies
Data from HEXAVAC and PROCOMVAX clinical documentation indicate

- a decrease of the immune response of anti-HBs with regard to lower GMTs
- a lower percentage of infants ≥ 10 mIU/mL just prior to the booster

Compared to the monovalent, thiomersal-containing, Hepatitis B vaccine.
Although there is no evidence that the thiomersal free vaccine would be less immunogenic than the thiomersal containing vaccine, clinical data from PROCOMVAX and HEXAVAC suggest a lower immune response of the hepatitis B component of the vaccines. Whether this is a result of an interaction with the Hib-component of the vaccines or due to the omission of thiomersal in the finished product is at present not known.

Although the PROCOMVAX study is difficult to interpret due to variable PRP dosage, variable thiomersal- content, low sample size per group and the different vaccination schedule it could suggest that there is both a PRP dose and a thiomersal effect in terms of a decrease of the immune response. If a possible lower immune response is only caused by an interaction with the PRP component or is also the result of the avoidance of thiomersal in the bulk alum product (BAP) of the HBsAg used in HEXAVAC and PROCOMVAX, is not known at present.

A possible lower immune response in infants and toddlers as seen within those combination vaccines is not considered to be of clinical relevance because infants and toddlers in the EU are not considered to be at high risk immediately after vaccination. However, the results raised some concern with regard to the persistence of the immune response. Notably, the immunogenicity data obtained with PROCOMVAX and HEXAVAC are from infants in their first and second year of life. It is not clear to what extent potential reduced immunogenicity of the thiomersal-free, monovalent hepatitis B vaccine may affect pre-maturely born infants, adolescents, adults, older persons, persons at risk and (pre) dialysis patients since no hard clinical efficacy/ immunogenicity data for the thiomersal-free formulation are provided for these populations.

For all reasons stated above, the proposed clinical study in younger adults is deemed necessary to adequately answer the question of comparability of the thiomersal- free hepatitis B vaccine with the currently licensed vaccine.

Clinical safety

- Post-marketing safety data of the thiomersal-free vaccine in the U.S.

The company's database was queried to determine if there is any difference in the number and type of reported suspected adverse drug reactions (ADR) with the thiomersal-containing and the thiomersal-free formulation of the applicant's hepatitis B vaccine (RECOMBIVAX). The time periods between 1 January 1999 to 31 August 1999 and 1 January 2000 to 31 August 2000 was chosen because they best reflect the reporting AEs with thiomersal-containing and thiomersal-free RECOMBIVAX HB formulations, respectively. Thiomersal-free RECOMBIVAX HB has been approval by the FDA in August 1999. All adverse experiences reported in patients less than 20 years with reported RECOMBIVAX HB lot number were identified. These inclusion criteria were selected because persons under 20 years are most likely to have received thiomersal-free hepatitis B vaccine. Notably, in 2000 both hepatitis B formulations were on parallel on the US market. The data are shown in Table 5:

Overview of spontaneous ADR reports between the thiomersal-containing and thiomersal-free hepatitis B vaccine in the US.

ADR reports in WAES database in US patients less than 20 years of age after RECOMBIVAX HB with a reported lot number	Period 01-Jan-1999 to 31-Aug-1999	Period 01-Jan-1999 to 31-Aug-1999
Number of ADR reports	26	16
Serious ADR reports	7	4
Number of doses distributed	> 6 million	> 7 million

The applicant concluded that the number of suspected ADR in the WAES database are low and that the data provide evidence that there is no evidence that the number and type of reported adverse experiences following the administration of the sponsors monovalent thiomersal-free vaccine is different from the recent formulation.

- Post-Marketing Safety Study of PROCOMVAX

Post-Marketing Safety Study of PROCOMVAX

PROCOMVAX Protocol 012, entitled "Post Marketing Evaluation of the Short Term Safety of COMVAX," assesses uncommon adverse experiences (i.e., those that might not be detected during pre-licensure clinical trials), which could be associated with this thiomersal-free, hepatitis B-containing combination vaccine. The study is being conducted at Group Health Cooperative of Puget Sound (GHC), a managed care plan that provides medical care for over 530,000 children and adults in Washington State. Study methods involve comparing adverse experience rates, as measured by diagnostic codes for hospital, emergency room, or outpatient visits, during different time periods following vaccination. Two types of control groups are presented in this study: self-comparison and historical. For the self-comparison control, the rates of medical events related to PROCOMVAX occurring in the 0, 1 to 5, 6 to 14, and 0 to 30 day risk periods were compared to the rate of the same clinical events occurring in a comparison time period 31 to 60 days post vaccination. The historical control group matches children who received Hib conjugate vaccine in the 2 years prior to the introduction of PROCOMVAX at GHC (Jul-1995 to Jul-1997) to recipients of PROCOMVAX according to birth month, shot month, and shot number. The rates of medical events occurring in the 0, 1 to 5, 6 to 14, and 0 to 30 day risk periods for PROCOMVAX were compared to the same time windows following Hib vaccination. A total of 11,680 doses of PROCOMVAX were administered to children 6 weeks to 36 months of age between Jul-1997 and Feb-1999. Of these, 6206 doses were first doses of PROCOMVAX, 4485 were second doses, and 979 were third doses. The analyses identified 4 main categories of elevated relative risks that were statistically significant at the $p<0.05$ level:
"Respiratory Abnormality, Not Elsewhere Coded" (Days 6 to 14 post-vaccination 1 and 2);
"Non-infectious Gastroenteritis" (Days 1 to 5 post-vaccination 3) and
"Viral Enteritis" (Days 6 to 14 post-vaccination 2);

”Unspecified Adverse Effect of Drug, Medicinal, and Biological Substance (Days 1 to 5 post-vaccination 2);”
and ”Pyrexia Unknown Origin” (Days 6 to 14 post-vaccination 1 and 3).

There were two categories with significantly decreased relative risks at the $p<0.05$ level:
”Convulsions (Days 6 to 14 post-vaccination 1)” and
”Non-infectious gastroenteritis (Days 6 to 14 post-vaccination 2).”

Specifically with respect to pyrexia (14/ 5703 infants), there was an increased rate of outpatient visits 6 to 14 days following shot 1 in the outpatient setting versus the historical control group but not versus the self-comparison group. There were no increased risks for serious adverse outcomes associated with pyrexia, such as emergency department visits or hospitalisation. Furthermore, there was no increased risk of outpatient visits for pyrexia following shot 2 or shot 3 compared to the historical control group. PROCOMVAX was associated with an increased rate for pyrexia 6-14 days after shot 3 compared to the self-comparison group but not when compared to the historical control group. Since shot 3 is generally given concomitantly with M-M-R®II at approximately 15 months of age, the analysis was stratified by concomitant M-M-R®II administration. Among children who received M-M-R®II with PROCOMVAX, there was an increased risk of outpatient visits for pyrexia 6-14 days after shot 3 compared to self comparison, but not when compared to historical controls. This suggests that the increased risk was due to concomitant M-M-R®II administration. Among children who received PROCOMVAX without M-M-R®II at shot 3, there was no statistically increased risk of health care visits for pyrexia.

While the data from this post-marketing study are preliminary, they reconfirm the excellent safety profile of the thiomersal-free vaccine PROCOMVAX and, by extension, the thiomersal-free monovalent hepatitis B vaccine.

Discussion on clinical safety

The PROCOMVAX-study revealed no evidence of any new safety signal but the data are considered preliminary and reporting will be continued.

The selection criteria for the analysis of spontaneous ADR reports have been accepted but the safety data provided for the thiomersal –free hepatitis B vaccines are considered limited and will be dealt with in an active PMS program.

5. Overall conclusions, benefit/risk assessment and recommendation

Quality
The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Batch to batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

Preclinical pharmacology and toxicology
Overall, the toxicology programme revealed that the thiomersal free Hepatitis B vaccine can be considered safe and immunogenic. Extrapolated study results from other thiomersal free vaccines have shown no acute and repeated dose toxicity. Animal reproduction studies have not been conducted. This information has been included in the SPC.

Efficacy and safety
Since no formal studies have been performed with the thiomersal free vaccine, the proposed post-licensure, randomised, double-blind study comparing the immunogenicity and safety of thiomersal-free and thiomersal-containing monovalent hepatitis B vaccines in healthy adolescents and younger

adults (16 to 35 years of age) is considered to be of inherent importance to ensure that the thiomersal-free vaccine is not-inferior to the thiomersal-containing vaccine.
Immunogenicity data obtained from the HEXAVAC and the PROCOMVAX file can be linked to the new application for infants (< 2 months of age) and toddlers. For ethical reasons no additional trial is deemed necessary in this particular age groups.
In the light of the conclusion of the CPMP (CPMP/4167/00 adopted) that there should be no further delay to provide the vaccine to the EU population taking into account the public health interests regarding thiomersal-free vaccines and the fact that no negative experiences with HBVAXPRO given to infants at risk in the U.S. the benefit/risk ratio is considered positive.

Safety
An active PMS program including surveillance on both effectiveness and safety of the thiomersal free vaccine is considered necessary.

Benefit/risk assessment

Recommendation
Based on the CPMP review of data on quality, safety and efficacy, the CPMP concluded that the benefit/risk profile of HBVAXPRO in the prophylaxis of Hepatitis B infection was favourable and therefore recommended the granting of the marketing authorisation.