SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 01 November 2002. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Infanrix penta is a combined vaccine which contains diphtheria toxoid (**D**), tetanus toxoid (**T**), three purified pertussis antigens (pertussis toxoid (**PT**), filamentous haemagglutinin (**FHA**) and pertactin (**PRN**; 69 kiloDalton outer membrane protein), and the purified major surface antigen (**HBsAg**) of the Hepatitis B virus (**HBV**). These components are adsorbed onto aluminium salts. In addition, it also contains three types of inactivated Polioviruses (**IPV** type 1: Mahoney strain; IPV type 2: MEF-1 strain; IPV type 3: Saukett strain).

In the following report, this combination vaccine will be referred to as "Infanrix penta" or as the "candidate vaccine".

All components of Infanrix penta have already been licensed, either individually or as combined vaccines in EU member states and are manufactured by the applicant (e.g. Infanrix HepB: D, T, Pa and HBV; Infanrix IPV: D, T, Pa and IPV). Infanrix penta is thus a new combination of known and approved components.

The rationale for the development of this combination vaccine is: to facilitate the universal vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis, in countries recommending the use of inactivated poliovirus vaccine and universal vaccination against hepatitis B in infancy by simplifying vaccine delivery. Incorporation of the hepatitis B and poliovirus vaccines in a multivalent formulation with DTPa is logical because the three vaccines are administered by the intramuscular route and that their administration schedule includes multiple doses during the first year of life.

The therapeutic indication for Infanrix penta is "for primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis".

2. Part II: Chemical, pharmaceutical and biological aspects

Composition

The composition of Infanrix penta is given in Table 1.

To potentiate the immune response, D, T, pertussis antigens (PT, FHA and PRN) and HBsAg are adsorbed on aluminium hydroxide and aluminium phosphate. Both aluminium salts are well-known and universally accepted immunopotentiating agents. The IPV component, although not pre-adsorbed for formulation, does adsorb when mixed with the other antigens.

An antimicrobial agent (2-phenoxyethanol) is added since it is not possible to terminally filter the final vaccine and the cloudy appearance of the suspension could mask microbial contamination. This is in accordance with the CPMP Note for Guidance on the Pharmaceutical and Biological Aspects of Combined Vaccines (CPMP/BWP/477/97). Sodium chloride is added to establish isotonicity and Medium 199 is used as a stabiliser during production of IPV component.

Table 1: Composition of Infanrix penta

Ingredients	Quantity/dose (0.5 ml)	Function
Active substances		
1. Diphtheria toxoid, adsorbed (D)	not less than 30 IU	Immunogen
2. Tetanus toxoid, adsorbed (T)	not less than 40 IU	Immunogen
3. Pertussis toxoid, adsorbed (PT)	25 µg	Immunogen
4. Filamentous haemagglutinin, adsorbed (FHA)	25 µg	Immunogen
5. Pertactin (69kDa Outer Membrane Protein - PRN adsorbed)	8 µg	Immunogen
6. r-DNA Hepatitis B surface antigen, adsorbed (HBsAg)	10 µg	Immunogen
7. Inactivated Polio Virus (IPV) Type 1	40 DU	Immunogen
8. Inactivated Polio Virus (IPV) Type 2	8 DU	Immunogen
9. Inactivated Polio Virus (IPV) Type 3	32 DU	Immunogen
Excipients		
1. 2-Phenoxyethanol	2.5 mg	Preservative
2. Sodium chloride (NaCl)	4.5 mg	For isotonicity
1. Medium 199 (M199) (including aminoacids)	1.15 mg (0.09 mg)	IPV stabiliser
2. Water for injections q.s.ad	0.5 ml	Solvent
Adjuvants		
Aluminium 0.5 mg as aluminium hydroxide ($Al(OH)_3$) 0.20 mg as aluminium phosphate ($AlPO_4$)	0.70 mg	Adjuvant

Infanrix penta is presented as 0.5 ml mono-dose preparations in 1 ml pre-filled glass (Type I, Ph. Eur.) syringes, either presented with separate needles or without needles. Syringes without needles are fitted with grey butyl rubber tip caps. Separate needles are fitted with grey butyl rubber shields. Plunger stoppers are of grey butyl rubber. Needles 23G1", 25G5/8" or 25G1" can be used for needle-less syringes.

Infanrix penta is to be administered by intramuscular injection.

Development pharmaceutics

Compatibility studies

The compatibility between D, T, Pa and HBV and between D, T, Pa and IPV have been established technically and clinically via licensed formulations containing these antigen combinations (Infanrix Hep B and Infanrix IPV). The compatibility of all of the components in a single combination has also been demonstrated.

Method of preparation

Finished product

For the preparation of the finished product, the sterile adsorbed DT, PT, FHA, PRN and HBsAg concentrates and the IPV component (trivalent bulk) are mixed with a sterile solution of sodium chloride and with water for injection. A sterile solution of 2-phenoxyethanol is added. The adsorbed DTPa-HBV-IPV vaccine is distributed aseptically in sterile glass (type I, Ph. Eur.) syringes.

In-process control consists of checking pH during formulation. During filling, homogeneity of the suspension and filled volume are checked. Environmental monitoring and counting of non-viable particles is carried out. Humidity and temperature of the filling room is monitored.

The aseptic filling system is validated by media fill studies. The entire process is carried out in aseptic conditions that ensure that the final product is sterile.

The formulation process has been adequately described and validated. ELISA tests showed that, within the detection limits of the tests, all the antigens engaged in the formulation process are adsorbed on aluminium and remain bound to the carrier over time. The IPV component, which is not pre-adsorbed for formulation, does adsorb on aluminium when mixed with the other antigens. Consistency of the production process is highlighted by the results of QC testing on routine production lots.

GMP inspection status

The adsorbed DT concentrate is prepared by Chiron-Behring (formerly Behringwerke), Postfach 1140, D-3550 Marburg 1, Germany. The adsorbed PT, FHA, PRN, HBsAg concentrates and IPV concentrates are prepared by SB Biologicals at Rixensart, Belgium. Both sites have active manufacturing authorisations demonstrating compliance with GMP.

During its meeting on 19-21 October 1999, the CPMP agreed that a GMP inspection of the manufacturing sites was not necessary.

Control of starting materials

D and T

Diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified Corynebacterium diphtheriae and Clostridium tetani toxins. The toxoids are produced and controlled by Chiron-Behring, Marburg, Germany as previously described and approved for Infanrix HepB.

PT, FHA and PRN

The acellular pertussis vaccine components are obtained by extraction and purification from phase I Bordetella pertussis cultures, followed by irreversible detoxification of the pertussis, and treatment of FHA and PRN. The antigens are produced according to the methods approved for Infanrix HepB. They comply with the specification limits and are tested as approved for Infanrix HepB.

The pertussis antigens comply with the requirements of the Ph. Eur. monograph 1356 (1999 supplement).

Elimination of adenylate cyclase, tracheal cytotoxin and dermonecrotic toxin was demonstrated for all the production scales validated. Absence of residual pertussis toxin is shown on each lot of the three antigens using the CHO cell test. The histamine sensitisation test in mice is not carried out at that stage but is performed on the finished product.

Elimination of detoxifying agents and other reagents has been validated. Polysorbate 80 is the only quantifiable reagent that remains in the bulk antigens (approximately 40 µg/dose).

HBV

The surface antigen of the HBV is produced by culture of genetically-engineered yeast cells (Saccharomyces cerevisiae) which carry the gene coding for the major surface antigen of the HBV. The HBsAg is expressed in yeast cells and purified by several physico-chemical steps. The HBsAg assembles spontaneously, in the absence of chemical treatment, into spherical particles of 20 nm in average diameter containing non-glycosylated HBsAg polypeptide and a lipid matrix consisting

mainly of phospholipids. Extensive tests have demonstrated that these particles display the characteristic properties of the natural HBsAg.

The final HBsAg bulk is tested for sterility, HBsAg identity, protein content and mercury content.

IPV

The inactivated polio vaccine component is produced on the Vero cell line using poliovirus strains Mahoney (type 1), MEF-1 (type 2) and Saukett (type 3) as seed materials. The origin and history of the polio virus strains are known. Identity was confirmed by seroneutralisation, infectivity measured and microbiological purity demonstrated (tests for mycoplasma, bacteria, fungi and extraneous agents in animals). A test in guinea pigs for the detection of Marburg virus was also performed.

Production and controls follow the requirements of WHO and Ph. Eur. Production is based on the seed lot principle: each production starts with inoculation of Vero cells expanded from one ampoule of the manufacturers working cell bank with one ampoule of the virus working seed lots.
The seed lot and cell banking system has been adequately established and characterized.

Production of the vaccine includes the following steps: preparation of cell substrate, virus inoculation, virus harvest, virus purification, virus inactivation, sterile filtration and pool of the monovalent bulks to obtain a trivalent concentrate.

Results of in process and quality control tests indicate that the production process is adequate. Virus yield after culture is reproducible. Purification gives a product of consistent quality from which proteins and VERO cell DNA are virtually eliminated.

Inactivation is performed in standard conditions using formaldehyde and effective inactivation is consistently achieved.

For quality control, all the tests recommended by WHO and Ph. Eur. are performed.

Control of intermediate products

Intermediate products are prepared in advance and a shelf life is claimed for them. These are the adsorbed DT concentrate, the adsorbed PT, FHA and PRN concentrates and the trivalent polio concentrate. As the adsorbed DT concentrate is prepared at Chiron-Behring, Marburg, Germany, the product is released by them and re-tested at SB Biologicals prior to use.

Each lot of DT concentrate is tested for aluminium, formaldehyde, sodium chloride and 2-phenoxyethanol content, for pH and sterility, for potency in animals, specific toxicity and for absence of blood group substances. Batch analysis data show consistency of production and quality.

The adsorbed Pa antigen concentrates are prepared at SB Biologicals and are in process tested for pH and sterility after adsorption and prior to use. The trivalent polio concentrate is tested in conformity with the Ph. Eur. requirement for absence of infectious poliovirus, sterility, antigen content and polysorbate 80 content.

Control of finished product

For the control of the finished product, tests can be performed either on the final bulk or on the final container. Several final container lots can be filled from the same final bulk. Therefore, tests, which involve animals, are carried out on the final bulk in order to avoid unnecessary use of animals. This principle is considered acceptable for Infanrix penta.

The following in vivo and in vitro tests are carried out:

- Specific toxicity test for diphtheria and tetanus performed according to Ph. Eur. 444.
- Potency for diphtheria and tetanus, performed according to Ph. Eur. requirements 2.2.7 and 2.2.9 respectively.
- Potency for pertussis antigens in mice (in-house method based on Ph. Eur. 214, supplement 1999).
- Test for residual pertussis toxin activity in mice (in-house method).
- Potency for IPV component in rats (in house method).
- In vitro potency assay for IPV component by ELISA (final bulk).
- In vitro potency assay for HBV component.

The other tests performed on each final bulk vaccine are pH, sterility, 2-phenoxyethanol content and formaldehyde content. Each final container lot is tested for appearance, identity for all antigens, volume, pH, aluminium content and as indicated above, for HBV and IPV content (in vitro potency). Validation data for these methods are presented in the application. The specification limits and tests performed are in accordance with Ph. Eur. monograph 153 (1999 supplement) "Vaccine for Human use", where applicable.

Stability

Stability tests on active substances

Infanrix penta is formulated using the same bulk antigens as for other licensed DTPa-based combination vaccines (Infanrix DTPa, Infanrix Hep B and Infanrix IPV). Therefore the applicant has made reference to the data generated on the above mentioned vaccines to support the shelf-life claimed for the active ingredients.

The stability data presented in the application support all agreed storage periods for the active ingredients.

Stability tests on the finished product

Three vaccine lots presented as mono-dose vials and three lots presented in pre-filled syringes are included in the stability studies.

The potency of the vaccine (Ph. Eur. assay for D, T & Pa, mouse immunogenicity for HBV and rat immunogenicity for IPV), through the whole shelf-life, meets the specifications applied to routine quality control tests conducted before each vaccine lot release. After 24 and 36 months of storage, the vaccine is also tested for appearance, identity, volume, pH, aluminium content, 2-phenoxyethanol, formaldehyde, endotoxin, sterility, general safety, D and T specific toxicity and residual pertussis toxin activity. Antimicrobial effectiveness was performed after 12 months and will be done after 36 months.

24 months stability studies are presented in the dossier. The results indicate that a shelf life of 24 months with storage at +2°C to +8°C is acceptable.

TSE risk assessment

Comprehensive information on the origin and preparation of substances of animal origin used in master and working seed lots and in routine production is included in the dossier. The applicant has switched when possible from materials of bovine origin to materials of either synthetic or non-ruminant origin.

Animal derived material used in the manufacture of Infanrix penta complies with the requirements of the CPMP Note for Guidance for minimising the risk of transmitting animal spongiform encephalopathy via medicinal products (Revision April 1999, CPMP/BWP/1230/98).

Conclusion on chemical, pharmaceutical and biological aspects

Infanrix penta is prepared according to Good Manufacturing Practices Rules and meets the World Health Organisation requirements for manufacture of biological substances, of diphtheria, tetanus, pertussis and combined vaccines, of hepatitis B vaccines made by recombinant DNA techniques and of inactivated poliomyelitis vaccines.

Starting materials of known origin of adequate quality are used. Consistency of production is demonstrated. Infanrix penta complies with approved specifications and is tested according to Ph. Eur. methods, where applicable. Methods developed in house are validated.

Packaging materials are the same as those used for other liquid vaccines manufactured by the applicant. Compatibility between the vaccine components has been shown. A shelf life of 24 months with storage at +2°C to +8°C has been accepted.

Several outstanding quality issues will be addressed by the applicant on an ongoing (post approval) basis.

3. Part III: Toxico-pharmacological aspects

Toxicology

As indicated in the CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines (CPMP/SWP/465/95), studies on reproductive function, embryo/foetal and perinatal toxicity are not necessary for paediatric vaccines and studies on mutagenicity and carcinogenicity are normally not needed for vaccines. The absence of perinatal toxicity data in the application is thus justified on the basis that Infanrix penta is intended for paediatric use only. The absence of mutagenicity and carcinogenicity data in the application is justified on the basis that the product is a vaccine and none of the active ingredients or excipients are novel or known to induce mutagenic or carcinogenic effects.

The preclinical testing included a repeated dose toxicity study reflecting the clinical use of the vaccine. The study was performed using Infanrix penta combined with an additional vaccine component containing adsorbed Haemophilus influenzae type b PRP-T conjugate. Since the addition of this component means that the study was conducted under more stringent conditions, the data generated can be accepted as being applicable to Infanrix penta. The vaccine was well tolerated and no significant toxicological reaction was observed.

Data were presented from in vivo safety studies for inactivated trivalent polioviruses demonstrating the safety of these components.

Other data, which provide assurance with respect to the safety of the vaccine, come from routine release in vivo tests. These are the specific toxicity testing for diphtheria and tetanus (Ph. Eur. 444) and the test for residual pertussis toxin activity (histamine sensitisation test). General safety (abnormal toxicity) testing is no longer required by Ph. Eur for routine release however, data were presented in the application. All lots met the requirements of this test.

In addition, the applicant addressed the question of potential toxicity and/or potential allergenicity for 2-phenoxyethanol, which is contained as a preservative in Infanrix penta (2.5mg/dose). The same preservative is used at the same concentration in other vaccines manufactured and commercialized by the applicant. The results of a comparison of the adverse event profile of a vaccine containing 2-phenoxyethanol and another vaccine without 2-phenoxyethanol gave no reason for concern.

Pharmacology (Immune response in animals)

The applicant only presents primary pharmacodynamic data. The absence of secondary pharmacodynamic data (safety pharmacology) is justified because all the vaccine components are well

known and are described in either Ph. Eur. or WHO monographs. Furthermore, any undesirable pharmacological activities would have been revealed in the repeated dose toxicity study, the safety studies for IPV or other routine toxicity tests.

It is indicated in the CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines that pharmacokinetics studies (e.g. determining serum concentrations of antigens) are normally not needed and this is considered to be the case for Infanrix penta.

Potency tests for diphtheria and for tetanus demonstrated a satisfactory potency response for the concerned components. A satisfactory immune response for the IPV component was demonstrated in immunogenicity tests. The vaccine elicited a satisfactory immune response for the HBV component in an in vivo immunogenicity test. For the pertussis component, the immunogenicity has been demonstrated in mice. The protective capacity of the anti-pertussis antibodies was demonstrated using a lung clearance activity test in a Bordetella pertussis intranasal challenge model of infection in mice.

Environmental Risk Assessment

The applicant has indicated that although the hepatitis B component of the candidate vaccine is derived from a genetically modified yeast strain, the final vaccine preparation does not contain any genetically modified organisms as the HBsAg undergoes extensive purification following its extraction from the yeast. With respect to the risk associated with use of the vaccine, the applicant has stated that no drug substance or identifiable metabolite will be introduced into the environment in quantities that merit concern.

Conclusion on toxico-pharmacological aspects

In conclusion, the applicant has performed adequate preclinical toxicity testing in accordance with the CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines. The testing shows that the vaccine was well tolerated in animals with no significant toxicological reaction or abnormality.

The applicant has provided adequate primary pharmacodynamic data to demonstrate that Infanrix penta elicits a satisfactory potency/immunogenicity response in animals with respect to all the vaccine components. The pharmacological properties of all the vaccine components have been shown to be satisfactory.

No environmental hazard meriting concern has been identified as being associated with use of this vaccine.

4. Part IV: Clinical aspects

Overview of clinical documentation

Complete reports of 24 clinical studies and 1 interim report are presented in this application:
16 primary vaccination studies and 9 booster trials.

A total of 10,078 subjects were enrolled in the primary vaccination studies, of which 7,549 were vaccinated with the candidate vaccineand were included in the ATP cohort for analysis of reactogenicity, with 2,403 subjects included in the ATP cohort for analysis of immunogenicity. Eleven different production lots of the candidate vaccine were used in the primary vaccination studies.
The overall objective of the primary vaccination trials was to demonstrate safety and immunogenicity when administered as a three-dose primary series in infants. Another important objective was to demonstrate that production lots (i.e. lots produced at commercial scale) of the vaccine achieve consistent results with respect to reactogenicity and immunogenicity. A further objective was to show that Infanrix penta can be administered, simultaneously at separate sites, with other routinely administered vaccines of infancy such as Hib vaccine.

From a total cohort of 10,078 subjects who received a primary vaccination course with either the candidate vaccine or other vaccines, 4,381 children were enrolled in 9 booster trials to receive either the candidate or other vaccines. From the 4,381 children enrolled, 3658 were primed with the candidate vaccine and from these subjects, 714 received the candidate vaccine as a booster dose. 693 were included in the ATP cohort for analysis of reactogenicity and 182 were included in the ATP cohort for analysis of immunogenicity. Four other booster options have been examined to meet different national booster policies.

The overall objective of the booster vaccination trials conducted was to evaluate the immunogenicity and reactogenicity of the candidate vaccine when administered as a fourth dose in the second year of life. Four different production lots of the candidate vaccine were used in the booster vaccination studies. A change that was made to the manufacturing process during the vaccine development was validated with an appropriate bridging study.

The procedures used in these studies were in accordance with the Declaration of Helsinki. The protocols were designed according to the Good Clinical Practice guidelines.

Clinical efficacy

The immunogenicity of the candidate vaccine was evaluated by measuring the antibody response elicited by each vaccine component. All assays were performed blinded to vaccine treatment using validated procedures with adequate controls.

Descriptive analysis of each vaccine group was provided for all studies. The statistical methodology used in most studies to evaluate the immunogenicity and reactogenicity of the candidate vaccine was equivalence or non inferiority testing based on a 90% CI. The pre-specified limits for non-inferiority were defined by the sponsor prior to analysis.

Primary vaccination

Feasibility studies

Three feasibility studies were performed to evaluate the reactogenicity and immunogenicity profile of the candidate vaccine in a limited number of subjects. There was a low incidence of local and general reaction, and a good immunogenicity profile, warranting further development of the candidate vaccine.

Comparison of the candidate vaccine to the separate administration of individual vaccine components

The reactogenicity and immunogenicity of the candidate vaccine with a licensed Hib vaccine administered simultaneously but at different sites was evaluated in comparison with the separate administration of individual vaccine components (all commercial vaccines) according to the same schedule (2, 4 and 6 months) in an open randomized trial including 4 groups of 100 infants. There was no clinically relevant difference in tolerability between the candidate vaccine and the other vaccine regimen.

In terms of seroprotection or vaccine response rates, the candidate vaccine was as immunogenic as the commercial vaccines administered at different sites for all antigens other than FHA. For FHA the response rate was slightly lower and the upper limit of the 90% CI for vaccination difference was slightly exceeding the pre-defined limit of non-inferiority. The clinical expert stated that this difference is probably not clinically relevant. In terms of post-vaccination GMTs there was nostatistically significant difference between the candidate vaccine and the commercial vaccine administered separately.

Lot to lot consistency studies

Two series of lots were used in the evaluation. The second series was studied due to a change in the manufacturing process during vaccine development. The lot-to-lot consistency in First Lot Series (3 lots) was evaluated in 2 double blind studies. The 3 lots were consistent in terms of reactogenicity in both studies. Due to the high rate of subjects eliminated from the ATP immunogenicity analysis in the second trial, no conclusions could be drawn. In the first study, the three lots were shown to be consistent with respect to immunogenicity.

The lot-to-lot consistency of the Second Lot Series formulated according to the final manufacturing process was demonstrated in a double blind study in which infants were randomized to receive vaccines from 3 lots of the Second Lots Series. To address the bridging of the manufacturing processes a fourth group of subjects was randomized to receive vaccines from the First Lots Series. There was no difference in the reactogenicity profile of the 3 Second Series lots. The 3 lots were highly immunogenic. The 3 vaccine lots were consistent in terms of seroprotection or vaccine response rates for all antigens (D, T, PT, HbsAg, polio 1, 2 and 3) except FHA and PRN. For both antigens, the upper 90% CI limit exceeded the pre-specified limit for equivalence. However there was an imbalance between groups in the number of subjects with high titres of maternal antibodies. Analysis of the post-vaccination titres in function of both vaccine lots and pre-vaccination titres showed that the 3 lots were equivalent in terms of post-vaccination titres. Therefore the observed lot-to-lot differences in immunogenicity have no clinical significance.

To compare the reactogenicity and the immunogenicity of the First Lot Series to that of the Second Lot Series, the results obtained with the Second Lots series were pooled. The overall incidence of solicited local and general symptoms was similar in pooled groups 1, 2 and 3 (Second Lots Series) and in group 4 (First Lots Series).

The 2 series were statistically equivalent in terms of seroprotection and vaccine response rates for all antigens except PRN. For PRN an imbalance in prevaccination titres between pooled groups 1, 2 and 3 (Second Lots Series) and in group 4 (First Lots Series) was found. Correction for this imbalance showed that the Second Lot Series is as immunogenic as the First Lot Series.

Pivotal phase III study for the assessment of safety and reactogenicity

In this open randomized study Infanrix penta was co-administered with 4 different commercial Hib-containing vaccines at the ages of 3, 4 and 5 months. After 1600 subjects had been enrolled, the study was amended to include a control group (group 5) which received the applicant's DTPa vaccine, an Hib vaccine and OPV. A total of 5472 healthy infants were included. The primary endpoint was the percentage of subjects with solicited grade 3 reactions over the study period. The results show that Infanrix penta is not inferior to the comparator vaccines.

Primary vaccination studies according to various vaccination schedules

The following schedules have been investigated:

- 2, 3 and 4 months (2 studies)
- 3,4 and 5 months (6 studies)
- 3, $4^1/_2$, and 6 months (2 studies)
- 2, 4 and 6 months (4 studies)
- $1^1/_2$, $2^1/_2$ and $3^1/_2$ months with one dose of HBV vaccine at birth (EPI schedule) (1 study)
- 3, 5, 11 months (1 study: evaluation of Infanrix penta mixed with Hib adsorbed)

Overall, one month after completion of the primary vaccination schedule, >98% of subjects had protective titres against diphtheria and tetanus, over 95% had protective anti-HBs titres, >94% had neutralizing antibodies to each of the 3 polio antigens, 97% had a vaccine response to PT, 89% to PRN and 86% to FHA. A schedule effect was seen for vaccine response rates and geometric mean titres: values tended to be higher for schedules in which the first dose of vaccine was given later in infancy and in which the interval between doses is longer.

Protective efficacy can thus be expected for all vaccine components for which a correlation exists between antibody titres and protection (D, T, HBV, Poliovirus).

For the hepatitis B component, the schedule effect impacts significantly on the protective efficacy when the EPI schedule ($1^1/_2$, $2^1/_2$ and $3^1/_2$ months), the most immunologically challenging schedule, is used. In a study conducted with another candidate vaccine (Infanrix penta combined before administration with a Hib vaccine adsorbed on aluminium phosphate), the rate of subjects reaching hepatitis B antibody titres $\geq$10 mIU/ml after vaccination was only 77.7%, whereas it reached >95% if the infants had received one dose of HBV at birth. This implies that the candidate vaccine should not be used according to the EPI schedule without a HBV dose given at birth. This is stated in the appropriate section of the SPC.

No correlation between antibody titres and protection has been demonstrated for pertussis. The applicant supports the efficacy of the acellular pertussis component of the candidate vaccine by stating that this component is identical to that of other authorised vaccines from the same company (e.g. Infanrix HepB), for which efficacy has been demonstrated in appropriate clinical trials. It can therefore be expected that the candidate vaccine will be efficacious. The applicant provided further support of this hypothesis by referring to the pertussis surveillance study currently ongoing in Sweden. During the observation period from the start of the pertussis vaccination in 1996 until Q3 1998, a DTPa vaccine (Infanrix) from the applicant has been used almost exclusively according to a 3,5 and 12 months schedule. A dramatic drop of 80 to 90% in disease incidence was observed within 3 years. This provides strong evidence of the field effectiveness of the Pa antigens

Although no issues specific to the Pa component of the candidate vaccine were identified, other than those already relevant for the licensed DTPa vaccines, the impact of genetic polymorphism of circulating strains on the protection provided by the vaccine should be further monitored. Therefore, surveillance of the variant strains will be carried out.

The 3, 5 and 11 months schedule was not investigated with this vaccine, but with another candidate vaccine (Infanrix penta combined before administration with a Hib vaccine adsorbed on aluminium phosphate). In that study, the hexavalent vaccine was not inferior to separately administered commercially available vaccines used as comparators. To support the use of data generated with the hexavalent vaccine, the applicant refers to 2 open randomized studies, in which the immunogenicity and safety of Infanrix penta administered with Hib vaccine in separate injections was compared to the hexavalent vaccine. The two vaccines were equivalent in terms of immunogenicity and reactogenicity. At the time of submission, only month 6 data (blood samples tested one month after the second dose) were reported in the registration file. As requested by the CPMP, the applicant provided further data on reactogenicity and immunogenicity obtained one month after the third vaccine dose, which confirmed the results obtained after 2 doses of vaccine.

Persistence of antibodies up to booster vaccination

Subjects from 7 primary vaccination trials participated in booster trials during the second year of life and had antibody titres measured before booster administration. One year after primary vaccination at 2, 4 and 6 months of age, over 96% of subjects had protective levels of antibodies against tetanus and the 3 serotypes of poliovirus. With respect to pertussis antigens, 75.8%, 95.2% and 100% of subjects were seropositive for anti-PT, anti-PRN and anti-FHA antibodies respectively. For antibodies against HBsAg, antibody persistence after vaccination with the candidate vaccine was in line with what was seen following vaccination with commercially available controls.
The persistence of antibodies was related to the magnitude of the response after primary vaccination, which was lower after the most immunologically challenging schedule (primary vaccination at 2, 3 and 4 months).

Booster vaccination

Five different booster options have been investigated as booster policies vary from country to country. In total, 2760 subjects primed with 3 doses of Infanrix penta were evaluable for safety of the booster

dose and 612 for booster immunogenicity. Among them, 693 subjects primed with 3 doses of Infanrix penta and receiving the same vaccine plus one of several Hib vaccines (administered at another site) as a booster were evaluable for safety and 182 for immunogenicity. There was a marked increase in seroprotection / vaccine response rates and geometric mean titres post booster administration. The four other booster options resulted also in a marked increase in post-booster antibody titres against all components included in the vaccines.

Clinical safety

The safety of the vaccine and the reactogenicity profile was evaluated on the day of the vaccination and on the 3 following days on the basis of a checklist of solicited local and general signs and symptoms. Non solicited symptoms could be recorded on the diary cards. The parents were instructed to immediately inform the investigators of the occurrence of any serious adverse event occurring during the study period and investigators had to notify the sponsor within 24 hours.

Primary vaccination

In one large comparative trial, local reactogenicity was reported in up to 50% of the children and systemic reactogenicity in more than 80% of infants, with similar incidences following the candidate vaccine or separately administered licensed DTPa, Hib and OPV vaccines. The applicant has emphasized that the reactogenicity data in the submitted dossier has been presented per subject rather than per dose which explains the relatively high rates.
In all of the studies, the local reactions were only infrequently severe or extensive. Virtually all symptoms reported resolved within the follow-up period, and all recovered without sequelae. In addition, as stated throughout each of the various sections, Infanrix penta was at least as well tolerated as the comparator vaccines.

Restlessness or fussiness appeared to be the most commonly reported solicited general symptom. Reports of grade 3 symptoms were infrequent. Virtually all symptoms reported resolved within the follow-up period, and all recovered without sequelae.

The most common unsolicited events reported following vaccination were bronchitis (9.8%), upper respiratory tract infection (9.4%) and fever (6.7%). Only 1.8% of subjects reported unsolicited symptoms graded 3 in intensity. The incidence (percentage of subjects reporting at least one symptom) of unsolicited symptoms assessed with related, possibly related, probable or suspected relationship to vaccination was 15.9 %.

Booster vaccination

Reactogenicity with the candidate vaccine increased as compared with the reactogenicity reported for the same subjects during the primary vaccination.

In particular, there was a concern relating to the increase of incidence of high fever in a substantial number of infants after booster vaccination. The applicant was therefore asked to address this safety concern in an oral explanation. In particular, the applicant was asked to present a full distribution and size of the complete population experiencing high fever above 39°C. The company was asked to show that this high fever induced by the Infanrix penta in a substantial number of children is not a matter of concern and has no influence on the vaccine acceptability.

The applicant performed an analysis of fever after 4 different boosters (DTPw-IPV/Hib+HBV; Infanrix penta+Hib, DTPa-IPV/Hib+HBV; DTPa-IPV/Hib). The data were pooled regardless of priming. Furthermore, the duration of fever above 37.5°C was compared following 4 different boosters (DTPa+Hib; DTPa/Hib; DTPa-IPV/Hib; Infanrix penta+Hib). From the data it can be concluded that there was a similar incidence and distribution of high fever and a similar duration of fever episodes in the various booster groups.

The incidence of high fever above 39°C observed with Infanrix penta after boosting was also discussed in an Ad hoc Expert Meeting, which was convened at request of the CPMP and BWP in order to clarify the advantages and risks of new combination vaccines presently under CPMP evaluation. It was concluded that concerns are still present with reference to high fever, even though such reactions have been observed also with other licensed combined vaccines. Therefore, an appropriate statement should be present in the SPC. Further detailed evaluation of such severe adverse reactions is needed with post-marketing studies based on well-defined protocols and conformity in data measurements across study centres.

Serious adverse events

A total of 241 SAEs were reported by 219 subjects in the 16 primary vaccination studies; 185 occurred in 170 infants receiving Infanrix penta. Only 8 reports were considered as related, possibly or probably related to the vaccine. All resolved without medical intervention or sequelae.
In the booster trials, all but one of the 31 reported SAEs were assessed as unrelated to vaccination; one SAE was considered as possibly related to vaccination and resolved without medical intervention and sequelae.

Conclusions on clinical efficacy and safety

The clinical investigation of the candidate vaccine followed a well conducted programme developed according to comprehensive design. Infanrix penta has shown to be immunogenic in defined conditions of use (specific primary and booster vaccination schedules). No interference was detected between the components.

The safety profile of Infanrix penta has been acceptably documented, including the reactogenicity of a booster dose injected around one year after the primary immunization programme. Concerns relating to the incidence of high fever above 39°C are adequately addressed in the SPC.

5. Overall conclusions on quality, efficacy and safety and benefit/risk assessment

The quality of Infanrix penta has been acceptably documented. The applicant has agreed to solve remaining quality issues by providing additional data on an ongoing basis after approval.

Following evaluation of the toxicological/pharmacological documentation, it is concluded that the applicant has performed adequate preclinical toxicity testing in accordance with the CPMP Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines. The testing shows that the vaccine was well tolerated in animals with no toxicological significant reaction or abnormality. The pharmacological properties of all the vaccine components were shown to be satisfactory.

The clinical documentation presented by the applicant conforms to ICH guidelines and is adequate from a GLP and GCP point of view. Infanrix penta was shown to be immunogenic when administered according to a variety of vaccination schedules. Comprehensive data have been submitted to characterise the reactogenicity profile of Infanrix penta. The observed tendency towards higher reactogenicity of Infanrix penta (incidence of high fever after boosting) is not considered to be barrier to a positive opinion for this vaccine. However, the applicant is asked to further monitor severe adverse reactions and their impact on vaccine acceptability.

From the practical point of view, Infanrix penta is a further contribution to decrease the number of injections required for primary and booster vaccination in infants. The vaccine will assist in increasing vaccination compliance and in further simplifying vaccination schedules and programmes.

<u>Benefit/risk assessment</u>

Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile of Infanrix penta is favourable for the primary and booster vaccination of infants against diphtheria, tetanus, pertussis, hepatitis B and poliomyelitis.