SCIENTIFIC DISCUSSION

Name of the medicinal product:	Quintanrix
Marketing Autorisation Holder:	GlaxoSmithKline Biologicals S.A. 89 rue de I'Institut B-1330 Rixensart Belgium
Active substances:	Diphtheria toxoid, adsorbed Tetanus toxoid, adsorbed Inactivated *Bordetella pertussis,* adsorbed Hepatatis B surface antigen (rDNA), adsorbed *Haemophilus influenzae* type b polysaccharide (PRP) conjugated to tetanus toxoid (T), adsorbed
Common Name:	Diphtheria, tetanus, pertussis (whole cell), hepatitis B (rDNA) and Haemophilus influenzae type b conjugate vaccine (absorbed)
Pharmaco-therapeutic group (ATC Code):	Bacterial and viral vaccines combined ATC code: [proposed: under application]
Therapeutic indication(s):	Primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B and invasive disease caused by *Haemophilus influenzae* type b and for booster immunisation of young children during the second year of life

1. Introduction

Since the 1940's, diphtheria, tetanus and whole cell pertussis vaccines have been administered as combined vaccines (DTPw). In 1992, the World Health Organisation (WHO) 's Expanded Programme of Immunisation (EPI) set targets for incorporation of hepatitis B (HBV) vaccination into national immunisation programmes by 1995 for high, and by 1997, for low endemic countries. The WHO endorsed the development of the DTPw-HBV combination vaccines in order to facilitate the incorporation of HBV vaccination into the EPI. In 1998, the WHO recommended the incorporation of Haemophilus influenzae type b (Hib) into routine infant immunisation programmes as appropriate to national capacities and priorities. Because of the fact that Hib, DTPw and HBV vaccines share the same vaccination schedules in early childhood it is possible to co-administer these vaccines at the same time and even to administer them as a single combined vaccine.

Clinical data have shown that the liquid Tritanrix HepB (a combined diphtheria, tetanus, whole cell pertussis and HBV vaccine) can be used to reconstitute GSK's lyophilised Hib conjugate vaccine, Hiberix. These data indicated that the mix did not impair the immune response or reactogenicity when compared with the administration of Tritanrix HepB and Hiberix in separate injections.
The monovalent Hib conjugate vaccines, licensed during the early 1990's, contained 10 µg or more of polyribosyl-ribitol-phosphate (PRP) antigen. Since 1998, several studies have demonstrated that the PRP antigen content of these vaccines may be reduced while maintaining a similar immunogenicity. Therefore, GSK Biologicals developed a combined diphtheria-tetanus-whole cell pertussis-hepatitis B-adsorbed *Haemophilus influenzae* type b vaccine with a reduced PRP antigen content (DTPw-HBV/Hib_ads 2.5µg) and submitted an application for a marketing authorisation in accordance with Art 8.3 of Directive 2001/83/EC.

Quintanrix is a pentavalent vaccine against diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b developed on the basis of the combination of the existing diphtheria-tetanus-inactivated whole cell pertussis-hepatitis B vaccine (Tritanrix HepB) and a lyophilized adsorbed Hib vaccine (modified from the approved Infanrix Hexa). The primary vaccination schedule consists of three doses to be administered at intervals of at least 4 weeks within the first 6 months of life in accordance with local official recommendations. The first dose can be administered at 6 weeks of age.

2. Quality aspects

Composition

The finished product is presented as a vial with lyophilised *Haemophilus influenzae* type b and a vial containing a suspension of diphtheria, tetanus, whole cell pertussis and hepatitis B. After reconstitution, a suspension for deep intramuscular injection is obtained.

After reconstitution, 1 dose (0.5 ml) contains:

Diphtheria toxoid[1]	not less than 30 International Units
Tetanus toxoid[1]	not less than 60 International Units
Inactivated *Bordetella pertussis* [2]	not less than 4 International Units
Hepatitis B surface antigen (rDNA) [2, 3]	10 micrograms
Haemophilus influenzae type b polysaccharide (polyribosylribitol phosphate) [2]	2.5 micrograms
conjugated to tetanus toxoid as a carrier	5-10 micrograms

[1] adsorbed on aluminium hydroxide hydrated — Total: 0.26 milligrams Al^{3+}
[2] adsorbed on aluminium phosphate — Total: 0.40 milligrams Al^{3+}
[3] produced in *Saccharomyces cerevisiae* cells by recombinant DNA technology

The vaccine is presented as monodose, 2-dose and 10-dose preparations in neutral type I glass vials (Ph. Eur) closed by grey butyl rubber stoppers with aluminium caps and flip-off tops.

DTPw-HBV component

As the DTPw-HBV component is identical to the one used in Tritanrix HepB, the details on the manufacturing process and purification, specifications and stability have not been re-assessed and are only briefly summarised below.

Manufacturing process and purification

The D, T and Pw antigens are manufactured by Chiron-Behring, Marburg, Germany and are supplied as aluminium-adsorbed DTPw concentrate to GSK Bio.
Diphtheria and tetanus toxoids are obtained by formaldehyde treatment of purified *Corynebacterium diphtheriae* and *Clostridium tetani* toxins.
The whole cell pertussis (Pw) component is obtained from a *Bordetella pertussis* suspension, and inactivated with thiomersal and heat.
The surface antigen of the hepatitis B virus (HBV) is produced by culture of genetically engineered yeast cells (*Saccharomyces cerevisiae*) which carry the gene coding for the major surface antigen of the hepatitis B virus.

Manufacturing process development

In accordance with the CHMP points to consider on the reduction, elimination or substitution of thiomersal in vaccines (CPMP/BWP/2517/00, April 2001), the thiomersal content in the DTPw-HBV vaccine was reduced from 25 µg/0.5 ml to 6 µg/0.5 ml by omitting thiomersal from the formulation process of DTPw and DTPw-HBV bulks. This thiomersal reduction has been approved previously for Tritanrix HepB.
Comparative data demonstrate the equivalence of potencies of bulks formulated with and without thiomersal. This change has no demonstrable impact on the potency, sterility, toxicity and stability of the vaccine.
For the purpose of the multidose presentations, this reduced amount has still antimicrobial activity so as to pass the Ph. Eur. criteria B and C for antimicrobial effectiveness (performed on three lots of DTPw-HBV).

Specifications

The D, T and Pw active ingredients are produced and controlled in accordance with Ph. Eur requirements 0445 for DTP vaccine. D and T are identical to that used for production of GSK Bio's acellular pertussis-based vaccines: Infanrix, Infanrix-polio, Infanrix HepB, Infanrix Penta and Infanrix Hexa.
The HBV is the same as that used for the production of the other HBV-containing vaccines (Engerix, Twinrix, Ambirix, Infanrix HepB, Infanrix Penta and Infanrix Hexa). The product is manufactured and controlled according to approved monographs.
The adsorbed DTPw concentrate is tested as intermediate product by Chiron-Behring for aluminium content, formaldehyde content, sodium chloride content, pH, sterility, specific toxicity, potency in animals and by GSK Bio for pH, sterility, identity and aluminium content.

Stability

The diphtheria and tetanus toxoids, the HBV antigen, the adsorbed HBV concentrate and the adsorbed DTPw concentrate are prepared in advance and a shelf life is claimed for them. The stability data presented in the application support all agreed storage period for the active ingredients.
The initial shelf-life granted for the final DTPw-HBV bulk (Tritanrix HepB monodose and 10-dose presentation) was 24 months at +2°C to +8°C. The shelf-life was extended up to 36 months following approval on 25/09/1997 of variation (EMEA/H/C/093/I/01).
Since then, two modifications to Tritanrix HepB were made:
1) an additional 2-dose presentation was approved. Three lots of the 2-dose presentation are currently being assessed for stability at +2°C to +8°C for up to 36 months.

2) change in vaccine composition (thiomersal reduction). Six lots are currently being assessed for stability at +2°C to +8°C for up to 36 months.
Results after 36 months were submitted to the EMEA and are currently under review. Interim results assessed so far support the maintenance of the 36 months shelf-life for the final DTPw-HBV component.

Hib active substance

The Hib_ads 2.5µg component cannot be administered as a stand-alone preparation but only after reconstitution with the DTPw-HBV suspension.

The active ingredient in Hib_ads 2.5µg consists of the capsular polysaccharide of *Haemophilus influenzae* type b (PRP), purified and covalently bound to purified tetanus toxoid (TT) used as carrier protein. The glycoconjugate is indicated as PRP-T and is adsorbed onto aluminium phosphate.

The same PRP is used in all the other Hib containing vaccines manufactured by GSK Bio: Hiberix (monovalent PRP-T vaccine) and the combined acellular pertussis-based vaccines: Infanrix/Hib, Infanrix-IPV/Hib and Infanrix Hexa (DTPa-HBV-IPV/Hib) vaccines.

As compared to the Hib component of Infanrix Hexa, a number of modifications were made:

- Reduction of the number of pre-culture steps for PRP
- Seed-lot system Hib
- Production process of the tetanus toxoid carrier protein
- Hib polysaccharide content reduced from 10µg/dose to 2.5µg/dose

These changes are described in more detail below (manufacturing process development).

Manufacturing process and purification

Production of the Hib_ads 2.5µg includes the following steps:

1. Production of purified PRP
2. Production of tetanus toxoid concentrate (TT)
3. Purification of the tetanus toxoid concentrate (T)
4. Coupling of PRP to T to obtain the PRP-T conjugate
5. Adsorption of PRP-T on aluminium phosphate
6. Formulation, filling and lyophilisation

Step 1, 3, 4, 5 and 6 are performed by GSK Bio, Rixensart, Belgium. Step 2 is performed by GSK Biologicals Kft, Gödöllö, Hungary. Reprocessing does not occur at any step in the manufacturing process.

The PRP-T conjugated bulk is manufactured in compliance with the Ph. Eur. monograph on *Haemophilus influenzae* type b vaccine and on WHO requirements for the same vaccine.

The PRP-T is then adsorbed on aluminium phosphate. The process used for PRP-T adsorption is that used for the adsorbed Hib component of GSK Bio's Infanrix Hexa vaccine.

A brief description of the manufacturing process and summary of the process, containing the operating parameters and in-process controls of the Hib_ads 2.5µg which includes the TT purification, PRP activation, conjugation and adsorption have been provided.

Control of materials, in process controls and corresponding specifications in use during the manufacture of PRP and TT bulks, PRP-TT are the same as those for the production of Hiberix and Infanrix Hexa. The production process is appropriately monitored.

According to the applicant, the storage of intermediate harvests is not applicable.

Manufacturing process development

The Company has validated a new working seed that will replace the current working seed once the stock is depleted. The production of this new working seed is slightly modified in order to stabilize the antigen productivity. A detailed description of the preparation of the MS and WS and a description of the in-process controls (identity, microbial purity, optical density and control of inactivation) performed on the seeds has been submitted and are considered adequate.

With regard to TT, two sources were used in the clinical lots: one supplied by Chiron-Behring, Marburg, Germany and a second supplied by Human Serum Production and Medicine Manufacturing Co Ltd, Gödöllö, Hungary. This company was acquired by GSK Bio in 2002 and was renamed GSK Biologicals Kft (GSK Bio Kft.). For commercial lots, the TT will be sourced exclusively from the Gödöllö facility.
Since completion of the clinical development of Hib_ads 2.5µg, several changes of the TT production process have been validated and were submitted for approval with the present dossier. The main changes relate to the removal of thiomersal and to the reduction of the use of material of animal origin.

Eight lots of TT were produced with all the changes implemented and QC tested according to the Ph. Eur 0542 requirements. All the lots met the requirements and consistent results were obtained regarding antigen purity and antigen content.

Characterisation and specifications of the active substance

The purified PRP, the TT and the conjugated PRP-T have been characterised. Results have been provided and are considered satisfactory.

Impurities in purified PRP may come from the pathogen itself (components of the bacterial cells), from the culture media used in fermentation, from the buffers and other materials used during polysaccharide purification, activation and derivatization. Various steps contribute during the production to the elimination or reduction to traces of the possible different impurities, which are all properly monitored by suitable methods validated for Infanrix Hexa.
Tetanus toxoid (TT) bulks provided by GSK Biologicals Kft. comply with the Ph. Eur. requirement (monograph 0452) for antigenic purity: i.e. not less than 1,000 Lf/mg protein nitrogen. Before coupling to PRP, TT bulks are purified at GSK Biologicals in order to remove aggregates and the Ph. Eur. purity test is carried out on each lot of purified TT. Results are presented in the dossier and meet the Ph. Eur. specification for antigenic purity of the TT used as carrier protein (≥ 1,500 Lf/mg protein nitrogen –EP monograph 1219)

Specifications have been set for the fermentation product, purified PRP (moisture content, ribose content, phosphorous content, protein content (Lowry), nucleic acid content, endotoxin content, molecular size distribution (HPLC) and identity (ELISA)), purified TT (protein nitrogen content, purity, sterility), activated PRP (molecular size distribution (HPLC)) and bulk conjugate (carbodiimide content, cyanide content, PS content, protein content (Lowry), sterility, free PS (ELISA), free carrier protein (HPLC) and molecular size distribution (HPLC)).

The analytical methods for release testing are the same as those used to release final container lots of the Hib_ads 10µg component pertaining to the combined Infanrix Hexa.
Data on the validation of the analytical methods have been provided and are considered satisfactory.

Results obtained for lots of purified polysaccharide, activated polysaccharide, purified tetanus toxoid and bulk conjugate have been provided. All lots meet the current proposed specifications for all the tests, as well as the specifications in force at the time of the release of the lots when different from the current proposed specifications. Consistent results were obtained.
Results obtained for 10 final bulk lots and 10 final container lots of Hib_ads 2.5µg component (4 monodose, 3 two-dose and three 10-dose) have been provided. The tests and specifications are those that were in force at the time the lots were released. All the 10 Hib_ads 2.5µg component lots comply with the specifications in force at the time of lot release.

Stability

Stability data have been provided regarding the polysaccharide, tetanus toxoid, activated polysaccharide, PRP-T conjugate and adsorbed PRP-T conjugate. The stability data presented in the application support all agreed storage periods for the active ingredient. However, the Applicant has initiated additional stability studies to cover the modified production process.

Other ingredients

The powder component (Hib) contains lactose (stabiliser and bulking agent) and the suspension component (DTPw-HBV) contains thiomersal (preservative), sodium chloride (tonicity) and water for injections as excipients. Both components contain aluminium as an adjuvant (as aluminium oxide hydrated and/or aluminium phosphate). Lactose, sodium chloride and water for injections comply with Ph. Eur. Aluminium and thiomersal comply with the British Ph.

Product development and finished product

The Tritanrix HepB/Hib combination is not licensed as such. However sections 4.5 ("Interaction with Other Medicinal Products and Other Forms of Interactions") and 6.6 ("Instructions for Use and Handling") of the Tritanrix HepB SPC say that the vaccine can be used mixed with Hiberix.
As a matter of fact, this combination is so widely used, particularly in developing countries, that there is a need (mostly the Hib component) to increase availability of the vaccine.
As production capacity of PRP-T is limited, GSK Bio has evaluated the possibility to decrease the dose of PRP and has compared 10, 5 and 2.5 µg of PRP in clinical studies.
It should be noted that the TT used in the clinical studies was produced by Human Co. according to a process that involved blood and meat of bovine origin and thiomersal. Human Co. initiated the development of a meat- and thiomersal-free process which was pursued and validated following acquisition of the Gödöllö facility by GSK Bio. The data provided regarding these changes indicate that the TT produced using the thiomersal- and meat-free process is deemed appropriate for use as protein carrier for the PRP-T conjugate.
The lots of Tritanrix HepB used in the clinical studies contained 25 µg of thiomersal per dose whereas in the current product the thiomersal content is 6 µg/dose. Compatibility studies using both the 25 µg and 6 µg thiomersal-containing vaccines gave satisfactory results, when tested in animal according to Ph. Eur requirements; it is generally accepted that vaccines lots that meet these requirements will elicit an appropriate immune response. Therefore, reduction of thiomersal content in Tritanrix HepB should not impact on the efficacy of the vaccine.

Manufacture of the Product

Production of the final DTPw-HBV bulk consists in mixing the sterile adsorbed DTPw concentrate with the sterile adsorbed HBV concentrate and a sterile solution of sodium chloride in water for injections. The final bulk is then aseptically distributed in siliconized sterile vials which are closed with sterile rubber closures.

The formulation Hib_ads 2.5µg component is performed by mixing a concentrated sterile solution of lactose with water for injections and subsequently adding the appropriate amount of adsorbed Hib conjugate bulk (adsorbed PRP-T). The proportions of lactose and of adsorbed antigen vary depending

on the final presentation (1-dose and 2-dose presentations vs. 10-dose presentation). The final bulk is then filled into sterile siliconised vials. After filling, the vials are automatically loosely stoppered with sterile siliconised butyl rubber stoppers and transferred aseptically to a freeze-dryer. A detailed description of the formulation, the filling and the lyophilisation of the Hib_ads 2.5 µg has been provided. Appropriate in-process controls during formulation, filling and lyophilisation are in place. Validation data for media fill tests with or without freeze-drying simulations for filling lines are presented in the dossier.

Product Specification

The final DTPw-HBV component is tested for description, identity, pH, volume, aluminium content, thiomersal content, free formaldehyde content, sterility, abnormal toxicity, specific toxicity and potency to approved specifications.

The specifications for the release of the final containers for the adsorbed *Haemophilus influenzae* type b conjugate component (Hib_ads 2.5µg component) include tests for identity, sterility, PRP content, moisture content, endotoxin content, aluminium content, pH and free polysaccharide content after desorption. The specifications are in line with the Ph. Eur. Monograph 1219 and the WHO Monograph TRS 897 (2000) on *Haemophilus influenzae* type b conjugate vaccines. The only difference with the latter being that the test for abnormal toxicity is not proposed for routine lot release. According to the WHO monograph, the test may be omitted for routine lot release once consistency of production has been established and when GMPs are in place. Given the satisfactory results obtained on 6 lots of Hib_ads 2.5µg component the regular inspection of GSK Biologicals by Authorities for GMP, and the four times reduced PRP dosage as compared to Hiberix and Infanrix Hexa, the omission of the test is acceptable.
In line with GSK Bio's other Hib vaccines, a specification limit of NLT 80% of the PRP content stated on the label is applied (tested on the bulk conjugate). Given the importance of this test for consistency of vaccine production, the applicant committed to establish alert limits based on consistency data of NLT 15 batches.

In order to demonstrate the compatibility of the DTPw-HepB and the Hib_ads 2.5µg components, various parameters were monitored just prior to and following reconstitution of different lots of adsorbed Hib component with different lots of DTPw-hepB component. The results obtained support the compatibility of the two components following reconstitution.
However, additional compatibility studies will be performed on 3 additional monodose and 2 multidose batches and results will be provided as a post-approval commitment. In the meantime, the Applicant states that they will perform release tests on the reconstituted DTPw-HepB and Hib_ads 2.5µg vaccine until completion of the commitment. In addition, completeness of adsorption will be tested to demonstrate consistency in completeness of adsorption.

Batch release data for 11 lots of Hib_ads 2.5µg component (5 monodose, 3 two-dose and three 10-dose) have been submitted. All the 11 Hib_ads 2.5µg component lots complied with the specifications in force at the time of lot releaseand with the proposed specifications for commercial lot release. Initially, no batch release data had been submitted for lots of vaccines produced according to the new updated process. Subsequently, data on four batches corresponding to Hib_ads 2.5 µg monodose obtained from the commercial process have been provided. The total polysaccharide content for the four "new process" monodose lots seemed consistently lower than for four out of five monodose lots prepared according to the "old process". Therefore, the applicant committed to submit the results of not less than 15 batches of Hib_ads 2.5µg as soon as they become available and re-discuss the issue of a possible systematic difference between the total polysaccharide content of the two production processes.

TSE and viral safety

TSE and viral safety related issues were taken into account for the DTPw-HBV component; it was concluded that the satisfactory assessment of these issues for Tritanrix HepB was fully relevant for the DTPw-HBV component of Quintanrix.

As no cell substrate is used during the preparation of Hib component of the vaccine, validation studies for virus removal/inactivation were not performed. All biological reagents used are sterilised.

The Hib master and working seeds used in clinical lots were identical to those used in Infanrix Hexa, for which compliance with the TSE Guideline has been demonstrated. In the new Hib master and working seed, the materials of animal origin that have been used are compliant with the TSE Guideline.
The materials of animal origin used in the production process of Hib are identical to the one used in Infanrix Hexa, for which compliance with the TSE Guideline has been demonstrated.

For the tetanus toxoid produced according to the meat containing process and used in clinical lots, a certificate of suitability was granted by EDQM. The tetanus toxoid intended for commercial lots is produced according to a meat-free production process, produced from blood-free and meat-free master and working seeds. All the reagents of animal origin used in the production process of tetanus toxoid are compliant with the TSE guideline.

Stability of the Product

On the basis of a real time, real temperature stability study on six lots of finished product, a shelf life of 36 months at +2°C to +8°C is accepted. The tests performed during the study were the same as those for batch release. In addition the applicant performed other assays like immunogenicity test in mice, aluminium phosphate, identity, completeness of adsorption and osmolality.
The three lots of Hib_ads 2.5µg adsorbed finished product in monodose and multidose presentation complied fully with specifications after 36 months of storage at +2°C to +8°C. Higher moisture content was observed after 36 months but there was no impact of this higher moisture content on the other parameters such as free polysaccharides.
With regard to stability data on finished product produced with the intended commercial process, data on 3 monodose lots stored up to 6 months have been submitted so far. These lots will be further tested according to the stability protocol and the applicant commited to provide stability results after 12, 24 and 36 months of storage as soon as the results are available.

<u>Discussion on chemical, pharmaceutical and biological aspects</u>

The data submitted for the DTPw-HBV part of Quintanrix are identical to the data for Tritanrix-HepB, its variations and follow-up measures, and are considered satisfactory. For the Hib part, a number of modifications as compared to the Hib component of Infanrix Hexa were made. However, the applicant has adequately addressed all concerns raised with regard to modifications via responses and commitments.

3. Non-clinical aspects

Introduction
All antigens of this vaccine have already been registered in the European Union as active ingredients of several of the Company's mono-valent and combined paediatric vaccines. Several of the antigens have also been registered worldwide as part of the Company's paediatric combination vaccines.

The amounts of the active ingredients used do not exceed the amounts used in other combination vaccines used for the target population. More specifically,

- the amount of D, T, Pw and HBsAg is exactly the same as in the licensed Tritanrix HepB vaccine, as it is the Tritanrix HepB vaccine that is used as the liquid component of the combined DTPw-HBV/Hib_ads 2.5 µg vaccine.
- the amount of the Hib component is 1/4th of the amount used in the Company's licensed Infanrix HeXa and Hiberix vaccines.

With respect to the excipients (aluminium phosphate, aluminium hydroxide, sodium chloride, thiomersal and water for injections and lactose), these are not novel, and are used at an amount within the range classically used. Of note, in line with recent concerns on potential too high exposure of infants to thiomersal during childhood vaccination, the Company has reduced the amount of the thiomersal preservative from 25 µg per dose in the past to 6 µg per dose. At this concentration, thiomersal has been shown to be still effective as preservative as per Ph. Eur. requirements, which is important for the multi-dose presentation of this vaccine.

Based on the fact that the DTPw-HBV/Hib_ads 2.5 µg vaccine can be considered as a new formulation of existing and licensed antigens, no specific non-clinical toxicity studies were done, neither was a detailed study on the immune response induced in animals conducted.

Due to the fact that Quintanrix is composed of Tritanrix HepB and the PRP Hib component of Infanrix hexa and Hiberix, vaccines that have been administered in many children, it has been considered acceptable that no additional pre-clinical data were collected.

Of note, at the time the clinical development of the vaccine started, the CHMP "Note for Guidance on non-clinical pharmacological and toxicological testing of vaccines" was not yet adopted. However, data generated during quality control testing of the vaccine allowed to conclude that specific toxicity concerns are not warranted and that the immune response induced by the combined vaccine is similar to the one induced by the two components. The similar immunogenicity and overall acceptable safety profile are further confirmed in clinical studies.

4. Clinical aspects

Introduction

The candidate vaccine Quintanrix, is a combined vaccine DPwT-hepatitis B and Haemophilus influenzae type b (DTPw-HBV/Hib_ads 2.5 µg) vaccine, which contains a quarter of the dose of PRP-T antigen contained in GSK Biologicals' Hiberix™ vaccine. The reformulated Hib_ads 2.5 µg is the only novel component in the candidate vaccine. All antigens of this vaccine have already been registered in the European Union as the active ingredient of several of the Company's monovalent and combined paediatric vaccines and several of the antigens have been registered worldwide as part of the Company's paediatric combination vaccines. The amounts of the active ingredients used do not exceed the amounts used in other combination vaccines used for the target population.

In total nine studies were performed to evaluate the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine. A total of 1497 infants received the vaccine as a primary course, with 435 receiving the vaccine as a booster dose. Of these, 1312 (70%) were tested for immunogenicity and 1865 (96%) were analysed for reactogenicity.

One feasibility study (study Hib-052) was followed by four pivotal phase III studies conducted in Myanmar, Nicaragua, Panama, Turkey, Belgium and the Philippines, evaluating a three-dose primary vaccination course with the candidate vaccine in infants aged 6 to 18 weeks at the time of first dose (studies Hib-078, -079, -080 and -081). Three different schedules were assessed with either a one-month or a two-month interval between doses.

Additionally study Hib-091 was conducted to compare the immunogenicity, safety and reactogenicity of DTPw-HBV/Hib_ads 2.5 µg (reduced thiomersal form of Quintanrix) to Tritanrix™-HepB/Hiberix™ when administered as a three-dose primary vaccination course to healthy infants.

One booster study (study Hib-064) was performed to assess the DTPw-HBV/Hib_ads 2.5 µg vaccine as a fourth dose in the second year of life following priming with the same vaccine in study Hib-052. Subjects primed in the five different vaccine groups in study Hib-052 were invited to receive a fourth consecutive dose of the same vaccine, co-administered with measles-mumps rubella (MMR) vaccine at 15-24 months of age in study Hib-064. Safety data were provided from two additional studies, DTPw-HBV/HibMenAC-TT-002 and DTPw-HBV/HibMenC-TT-003.

An overview of studies evaluating the candidate vaccine is represented in the following **Table 1**.

The study designs took into account the Good Clinical Practice Guidelines in use at the time of initiation of each study and that the Declaration of Helsinki and its amendments were respected.

Table 1: Overview of studies evaluating the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine

Study	Country	Study groups	Vaccination Schedule	Number of subjects Enrolled Total	Enrolled Per group	Analysed Safety	Analysed Immuno
Hib-052	Myanmar	**DTPw-HBV/Hib_ads 2.5 µg** DTPw-HBV/Hib_ads 5 µg DTPw-HBV/Hib_ads 10 µg Tritanrix™-HepB/Hiberix™ Tritanrix™-HepB + Hib_ads 10 µg	**6-10-14 weeks**	**694***	**136** 136 136 136 136	**135** 136 135 136 136	**128** 129 130 127 129
Hib-078	Nicaragua Panama	**DTPw-HBV/Hib_ads 2.5 µg** Tritanrix™-HepB + Hiberix™	**2-4-6 months**	**848**	**636** 212	**626** 209	**552** 183
Hib-079	Turkey	**DTPw-HBV/Hib_ads 2.5 µg** Tritanrix™-HepB/Hiberix™	**2-4-6 months**	**360**	**180** 180	**173** 174	**133** 146
Hib-080	Belgium	**DTPw-HBV/Hib_ads 2.5 µg** Tritanrix™-HepB/Hiberix™	**3-4-5 months**	**294**	**148** 146	**148** 146	**107** 108
Hib-081	Philippines	**DTPw-HBV/Hib_ads 2.5 µg** **DTPw-HBV/Hib_ads 2.5 µg** (following a dose of HBV at birth)	**6-10-14 weeks**	**318***	**151** **150**	**122** **130**	**100** **102**
Hib-091	Philippines	**Tritanrix™-HepB $_{low\ thio}$/Hib_ads 2.5 µg (6µg thiomersal)** Tritanrix™-HepB/Hiberix™ - (25µg thiomersal)	**6-10-14 weeks**	**192**	**96** 96	**96** 95	**95** 94
Total number of subjects receiving DTPw-HBV/Hib_ads 2.5 µg as a primary vaccination				**-**	***1497***	***1430***	***1217***
Hib-064	Myanmar	**DTPw-HBV/Hib_ads 2.5 µg + MMR** DTPw-HBV/Hib_ads 5 µg + MMR DTPw-HBV/Hib_ads 10 µg + MMR Tritanrix™-HepB/Hiberix™ + MMR Tritanrix™-HepB + Hib_ads 10 µg + MMR	**15-24 months**	**357***	**66** 75 68 74 68	**65** 75 68 72 65	**63** 73 65 69 62
DTPw-HBV/HibMenAC-TT-002	Philippines	**DTPw-HBV/Hib_ads 2.5 µg***	15-18	-	125	-	-
DTPw-HBV/HibMenAC-TT-003		**DTPw-HBV/Hib_ads 2.5 µg** **DTPw- HBV/Hib_ads 2.5 µg + Meningitec**			139 106	139 106	
Total number of subjects receiving DTPw-HBV/Hib_ads 2.5 µg as a booster dose				-	***435***	***435***	***63***

"/" = combined administration in a single injection after extemporaneous mixing; "+" = separate injection

infants born to HBsAg seropositive mothers were enrolled in a separate group: 14 infants in study Hib-052 received DTPw-HBV/Hib_ads 5 µg, 6 infants in study Hib-064 received DTPw-HBV/Hib_ads 5

µg, and 17 infants in study Hib-081 received DTPw-HBV/Hib_ads 2.5 µg
* data from other study groups not provided in the dossier

Immunogenicity

METHODS

Treatments
The candidate DTPw-HBV/Hib_ads 2.5 µg vaccine was compared with the licensed Tritanrix™-HepB and Hiberix™ vaccines, given either as separate concomitant injections (Tritanrix™-HepB +Hiberix™) or extemporaneously mixed in one single injection (Tritanrix™-HepB/Hiberix™).

The compositions of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine and the licensed comparators Tritanrix™-HepB and Hiberix™ vaccines used in the clinical trials are given in the following **Table 2**.

Table 2: Compositions of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine and the licensed comparators

	Vaccines		
Contents	**DTPw-HBV/Hib_ads 2.5 µg**	**Tritanrix™-HepB**	**Hiberix™**
Diphtheria toxoid	≥ 30 IU (7.5 Lf)	≥ 30 IU (7.5 Lf)	-
Tetanus toxoid (TT)	≥ 60 IU (3.25 Lf)	≥ 60 IU (3.25 Lf)	-
Bordetella pertussis, killed	≥ 4 IU (15 OU)	≥ 4 IU (15 OU)	-
r-DNA HbsAg	10 µg	10 µg	-
PRP (conjugated to TT)	2.5 µg (5-10 µg)	-	10 µg (20-40 µg)
Lactose	12.6 mg	-	12.6 mg
Aluminium (Al^{3+}) from:			-
aluminium oxide hydrated	*260 µg*	*260 µg*	-
aluminium phosphate	*400 µg*	*370 µg*	-
Thiomersal	25 µg	25 µg	-

In the feasibility study Hib-052 immunogenicity and reactogenicity of different quantities of the reformulated Hib component were assessed. The following vaccine groups were evaluated:
DTPw-HBV/Hib_ads 2.5 µg, containing 2.5µg of PRP
DTPw-HBV/Hib_ads 5 µg, containing 5µg of PRP
DTPw-HBV/Hib_ads 10 µg, containing 10µg of PRP
Tritanrix™-HepB/Hiberix™, licensed vaccines containing 10µg of PRP
Tritanrix™-HepB + Hib_ads 10 µg, administered as two separate injections

During the development of Quintanrix, the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine, the clinical trials were conducted with the formulation of DTPw-HBV which was licensed at that time (ie full thiomersal; 25 µg). These are the trials that are presented in the Quintanrix Dossier. However, the current application for licensure of Quintanrix is for the DTPw-HBV component that is currently licensed (low thiomersal; 6µg). Therefore study Hib-091 was conducted to compare the immunogenicity, safety and reactogenicity of DTPw-HBV/Hib_ads 2.5 µg (reduced thiomersal form of Quintanrix) to Tritanrix™-HepB/Hiberix™ when administered as a three-dose primary vaccination course to healthy infants.

Objectives

The feasibility study Hib-052 was designed to assess the feasibility of reducing the PRP antigen content of the Hib component to be used in the combined DTPw-HBV/Hib vaccine.

Three trials were conducted to compare the immunogenicity of the candidate vaccine with the Tritanrix™-HepB and Hiberix™ vaccines, either given as separate concomitant injections (Hib-078) or as a mix (Hib-079 and Hib-080). Vaccines were administered at either 2, 4 and 6 months of age (Hib-078 and Hib-079) or at 3, 4 and 5 months of age (Hib-080).

A fourth trial (Hib-081) compared the immunogenicity of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine when administered at 6, 10 and 14 weeks of age, between infants who received hepatitis B vaccine at birth and infants who did not receive.

Study Hib-091 was conducted to compare the immunogenicity, safety and reactogenicity of DTPw-HBV/Hib_ads 2.5 µg (reduced thiomersal form of Quintanrix) to Tritanrix™-HepB/Hiberix™ when administered as a three-dose primary vaccination course to healthy infants at 6, 10 and 14 weeks of age.

Study Hib-064 was conducted to document the persistence of antibodies up to booster age and to document the booster effect among infants seen in study Hib-052 (see Persistence of antibodies following primary vacination). Subjects who had completed the primary vaccination course in study Hib-052 were invited to receive a booster dose of the same vaccine they received for primary vaccination, co-administered with MMR vaccine at 15-24 months of age.

In all studies, except Hib-064, non-inferiority testing was used to evaluate the anti-PRP response to the reformulated Hib component of the DTPw-HBV/Hib_ads 2.5 µg vaccinecompared to the control groups in terms of the percentage of subjects with anti-PRP antibody titre ≥0.15 µg/ml post-vaccination (primary endpoint) and anti-PRP GMT ratio.

In studies Hib-078 and Hib-080, non-inferiority testing was also used to evaluate antibody response to all other vaccine antigens (seropositivity/seroprotection rates, vaccine response rates and GMT ratios) in the experimental DTPw-HBV/Hib regimens as compared to the control regimen.

In the uncontrolled study Hib-081, the objective was to demonstrate non-inferiority in terms of antibody response to the PRP antigen elicited by the DTPw-HBV/Hib_ads 2.5 µg regimen following a birth dose of hepatitis B vaccine (HBV) as compared to the DTPw-HBV/Hib_ads 2.5 µg regimen without previous priming with HBV.

In study Hib-079, a non-inferiority approach was used to evaluate antibody response to the PRP and the rDNA hepatitis B surface antigens elicited by the candidate DTPw-HBV/Hib_ads 2.5 µg regimen versus the control (DTPw-HBV/Hiberix™). Assays for antibody response to other vaccine antigens were not performed in this study.

Consistency of vaccine manufacturing was evaluated in study Hib-078 using an equivalence approach in terms of seropositivity/seroprotection rates for anti-PRP, anti-diphtheria, anti-tetanus, anti-HBsAg, vaccine response for anti-BPT and GMT ratios for all vaccine antibodies.

The primary objective of study Hib-091 was to demonstrate non-inferiority of Tritanrix™-HepB $_{\text{low thio}}$ /Hib $_{2.5}$ vaccine (reduced thiomersal form of Quintanrix) as compared to Tritanrix™-HepB/Hiberix™ with respect to the immunogenicity of the PRP antigen after the first three vaccine doses.

Outcomes/endpoints
The primary endpoint in all studies was the percentage of subjects with anti-PRP antibody titre ≥ 0.15 µg/ml one month after completion of the three-dose primary vaccination course/administration of the booster, with the exception of Hib-064 in which post-booster blood sample was taken 42 days after vaccination.

In each study report the descriptive analysis included for each treatment group the calculation of the following variables with their corresponding 95% CI:

- seroprotection rates, i.e. the percentages of subjects with antibody titre (anti-PRP, anti-diphtheria, anti-tetanus, anti-HBs) ≥ the defined protective level. In addition, for anti-PRP antibodies, this also included the percentage of subjects with titres ≥1.0 µg/ml.
- vaccine response rates for the *Bordetella pertussis* (BPT) antigen since no protective antibody level has been defined.

Antibody titres against all vaccine antigens were summarized using geometric mean titres (GMT), calculated by taking the anti-log of the mean of the log transformed titres, with their 95% CI. For GMT calculation, titres below the assay cut-off were given the arbitrary value of one-half the assay cut-off.

Several criteria have been proposed as immunological surrogates of efficacy for registration of new Hib conjugate vaccines, in the absence of efficacy data. These criteria include adequate priming in infants similar to that with licensed vaccines, antibody persistence up to the age of booster vaccination, demonstration of immune memory and the functional capacity of the antibodies (i.e. opsonic or bactericidal activity). Antibody avidity increases over time following primary vaccination. Memory responses are also characterised by the production of high-avidity antibodies. Therefore, avidity has been considered by the applicant as a surrogate marker for successful priming, and has been investigated in the booster study Hib-064.

Methods used to evaluate the immunogenicity

Serum samples were collected immediately before the first vaccine dose and one month after completion of the primary vaccination course. To evaluate the persistence of antibodies and the response to a booster dose, samples were also collected before and after booster vaccination.

All assays were performed blinded to vaccine treatment, using validated procedures with adequate controls.

Table 3: Overview of serological assays and cut-offs

Marker	Assay method	Test Kit/ Manufacturer	Assay unit	Cut-off
anti-PRP	ELISA	na	µg/ml	0.15
anti-HBsAg	RIA	AUSAB, Abbott	mIU/ml	10
anti-diphtheria	ELISA	na	IU/ml	0.1
anti-diphtheria	Neutralization	na	IU/ml	0.016
anti-tetanus	ELISA	na	IU/ml	0.1
anti-BPT	ELISA	Labsystems	EL.U/ml	15
anti-mumps	ELISA	Behring	U/ml	231
anti-measles	ELISA	Behring	mIU/ml	150
anti-rubella	ELISA	Behring	IU/ml	4

na = not applicable as commercial kit was not available or not used.

Anti-PRP antibodies were measured by ELISA and expressed in µg/ml (assay cut-off 0.15 µg/ml). For anti-PRP, titres ≥0.15 were considered indicative of protection; however titres ≥ 0.15 and ≥ 1.0 µg/ml were taken into consideration. These cut-offs have been estimated from age specific data among unvaccinated populations and children vaccinated with the polysaccharide vaccine, as well as from antibody measurements in children receiving hyperimmune globulin. On this basis, 0.15µg/ml was regarded as protective on the individual level at the time of the assay, whereas 1.0µg/ml measured at the peak response to vaccination was regarded in the past as 'predictive of protection', allowing for antibody decay in the next few years. However, these values may be less relevant to Hib conjugate vaccines, which also elicit immunologic memory and thus prime for a rapid response upon an encounter with Hib. Therefore Hib conjugate vaccines are likely to protect even when the subject's anti-PRP titres fall below 0.15µg/ml. In order to further evaluate the quality of the Hib response induced by the candidate vaccine with reduced PRP content, the maturation of the Hib response from post-primary to post-booster was also documented. Seropositivity/seroprotection rates were calculated per group with 95%CIs, for antibodies against all vaccine antigen components at each blood sampling time point. Geometric mean antibody titres (GMTs) with 95%CI were calculated by taking the anti-log of the mean of the log titre transformations. Antibody titres below cut-off level were given an arbitrary value of half the cut-off value for the purpose of GMT calculation.

Randomisation and Blinding (masking)

Studies were performed in an open fashion if the number of injections differed between groups (open randomised, Hib-052, Hib-081; open, Hib-064). All other studies were conducted in a blinded fashion (randomised double-blinded, Hib-079, Hib-080) as well as the lot-to-lot consistency (Hib-078, randomised, controlled, blinded)

Statistical methods

In all studies, two cohorts were defined for analyses: the total cohort which included all enrolled subjects for whom data were available and the according-to-protocol (ATP), i.e., protocol defined, cohorts. The ATP cohort included vaccinees who complied with all eligibility criteria and all procedures defined in the protocol. Primary analyses of safety and immunogenicity were performed on the ATP cohorts. The purpose of the analyses of the Total cohorts was to ensure that deviations from the protocol were not treatment-related. Unless otherwise specified, all the data presented within this summary are analyses performed on ATP cohorts.

Subjects excluded from the ATP cohorts were identified before data analyses after a review of the individual subject data blinded to treatment group allocation.

As defined in the study protocol, non-inferiority was demonstrated when the upper/lower limit of the 90% CI for the difference between groups was below the pre-specified clinical limit of non-inferiority (one-sided equivalence test; alpha=5%).

Likewise lot-to-lot consistency was demonstrated in study Hib-078 when the 90% CI for the difference between lots was included in the pre-specified limit of clinical equivalence (two-sided equivalence test; alpha = 5%).

RESULTS

Feasibility study (Hib-052)

The feasibility Study Hib-052 demonstrated that the immunogenicity of all components of the DTPw-HBV/Hib_ads 2.5 µg vaccine was not inferior to the reference vaccines. Since the reactogenicity of the candidate vaccine showed a similar profile, further testing of DTPw-HBV/Hib_ads 2.5 µg was justified.

Main studies (Hib-078, 079, 080, 081, 064)

When compared to the licensed vaccines, the candidate vaccine was not inferior with respect to the percentage of subjects showing anti-PRP antibody titres of ≥0.15µg/ml one month after completion of the primary vaccination schedule. One month after completing the primary vaccination course, virtually all subjects (>99.4%) had anti-PRP antibody titres ≥0.15 µg/ml and the majority of subjects (>94.8%) had anti-PRP antibody titres ≥1.0 µg/ml.

Comparison of post vaccination GMTs showed no differences between groups, except for the anti-PRP antibody GMTs. Statistically significantly higher anti-PRP antibody titres were observed following Tritanrix™-HepB and Hiberix™ vaccination in study Hib-078, whereas the candidate vaccine induced significantly higher titres in study Hib-079 and titres similar to those in the control group in study Hib-080. Conflicting results were observed in trials Hib-078 and Hib079 with respect to the titre of anti-PRP antibodies following immunization with the candidate and reference vaccines. However no differences were observed between the candidate and control vaccines in studies Hib-080 and Hib-081 and the seroprotection rates were comparable among all studies. The applicant argues that the anti-PRP response after primary vaccination is known to be highly variable and that the cause appears to be complex and multifactorial. The anti-PRP response observed following priming with 2.5µg of PRP as presented in the Quintanrix dossier is claimed to be within the range previously observed and accepted for 10µg PRP vaccines. Furthermore there appears to be no evidence to suggest that this variability is due to instability of the laboratory assays used during the studies or is there any consistent evidence to show that this was due to differences in pre-vaccination anti-PRP concentrations. Although the applicant did not address the lot-to-lot fluctuations to speculate on their findings, it is acknowledged that the range of variation found for the anti-PRP antibodies in the Quintanrix file remains within the limits already accepted for other combinations from the same manufacturer using the same conjugate.

The immune response of subjects who received the candidate vaccine after having received a monovalent hepatitis B vaccine at birth was comparable with the response of subjects who received the candidate vaccine without a prior dose of hepatitis B, except for hepatitis B. This illustrates that hepatitis B vaccination at birth did not have a negative impact on the subsequent immune responses induced by the candidate vaccine.

Immune responses are presented in the following **Tables 4 & 5**.

Table 4: Seroprotection and pertussis vaccine response rates one month after the third primary vaccination dose of the candidate DTPw-HBV/Hib_ads 2.5 µg and comparator vaccines (ATP cohort)

Schedule	Study (country)	Vaccine	N	Seroprotection and pertussis vaccine response rates (%, [95%CI])					
				PRP ≥0.15 µg/ml	PRP ≥1.0 µg/ml	D ≥0.1 IU/ml	T ≥0.1 IU/ml	BPT VR*	HBs ≥10 mIU/ml
2-4-6 Months	Hib-078‡ (Nicaragua) (Panama)	DTPw-HBV/Hib_ads 2.5 µg (pooled lots)	543	99.4 [98.4 , 99.9]	98.2 [96.6 , 99.1]	96.3 [94.4 , 97.7]	100.0 [99.3 , 100.0]	99.4 [98.4 , 99.9]	98.9 [97.6 , 99.6]
		Tritanrix™-HepB + Hiberix™	178	98.9 [96.0 , 99.9]	97.2 [93.6 , 99.1]	93.8 [89.2 , 96.9]	97.2 [93.6 , 99.1]	99.4 [96.9 , 100.0]	96.5 [92.5 , 98.7]
2-4-6 Months	Hib-079 (Turkey)	DTPw-HBV/Hib_ads 2.5 µg	129	100.0 [97.2 , 100.0]	98.4 [94.5 , 99.8]	-	-	-	100.0 [97.2 , 100.0]
		Tritanrix™-HepB/Hiberix™	145	99.3 [96.2 , 100.0]	95.2 [90.3 , 98.0]	-	-	-	99.3 [96.9 , 100.0]
3-4-5 Months	Hib-080 (Belgium)	DTPw-HBV/Hib_ads 2.5 µg	107	100.0 [96.6 , 100.0]	95.3 [89.4 , 98.5]	99.1 [94.9 , 100.0]	99.1 [94.9 , 100.0]	98.0 [93.1 , 99.8]	95.3 [89.4 , 98.5]
		Tritanrix™-HepB/Hiberix™	108	100.0 [96.6 , 100.0]	94.4 [88.3 , 97.9]	98.1 [93.5 , 99.8]	98.1 [93.5 , 99.8]	94.2 [87.9 , 97.9]	97.2 [92.1 , 99.4]
6-10-14 Weeks	Hib-081 (Philippines)	DTPw-HBV/Hib_ads 2.5 µg	97	100.0 [96.3 , 100.0]	97.9 [92.7 , 99.7]	94.8 [88.4 , 98.3]	100.0 [96.3 , 100.0]	100.0 [96.2 , 100.0]	92.8 [85.7 , 97.0]
		DTPw-HBV/Hib_ads 2.5 µg following a dose of HBV at birth	97	100.0 [96.3 , 100.0]	94.8 [88.4 , 98.3]	94.8 [88.4 , 98.3]	100.0 [96.3 , 100.0]	99.0 [94.3 , 100.0]	99.0 [94.4 , 100.0]

N = Number of subjects included in the ATP cohort for immunogenicity analysis (the actual number analysed may be different for each antigen, depending on whether serological results were available for all subjects)

VR: Pertussis vaccine response defined as appearance of antibodies (≥15 El.U/ml) in initially seronegative subjects or at least maintenance of pre-vaccination antibody titres in initially seropositive subjects

‡ In study Hib-078 all anti-HBs responses were calculated on initially seronegative subjects only.

Table 5: Antibody GMTs one month after the third primary vaccination dose of the candidate DTPw-HBV/Hib_ads 2.5 µg and comparator vaccines (ATP cohort)

Schedule	Study (country)	Vaccine	N	Anti-PRP (µg/ml)	Anti-D (IU/ml)	Anti-T (IU/ml)	Anti-BPT (El.U/ml)	Anti-HBs (mIU/ml)
2-4-6 months	Hib-078‡ (Nicaragua) (Panama)	DTPw-HBV/Hib_ads 2.5 µg (pooled lots)	543	32.843 [29.662 , 36.366]	1.515 [1.363 , 1.684]	3.716 [3.413 , 4.046]	115.2 [108.5 , 122.3]	1717.1 [1537.8 , 1917.3]
		Tritanrix™-HepB + Hiberix™	178	47.686 [38.126 , 59.641]	1.392 [1.132 , 1.712]	2.092 [1.746 , 2.507]	120.9 [109.1 , 134.0]	1549.3 [1206.8 , 1989.1]
2-4-6 months	Hib-079 (Turkey)	DTPw-HBV/Hib_ads 2.5 µg	129	18.805 [15.480 , 22.845]	-	-	-	2109.0 [1715.7 , 2592.5]
		Tritanrix™-HepB/Hiberix™	145	11.219 [9.000 , 13.986]	-	-	-	2158.7 [1739.3 , 2679.3]
3-4-5 months	Hib-080 (Belgium)	DTPw-HBV/Hib_ads 2.5 µg	107	11.065 [8.790 , 13.930]	1.535 [1.303 , 1.808]	2.246 [1.858 , 2.716]	66.4 [57.6 , 76.5]	455.6 [335.7 , 618.3]
		Tritanrix™-HepB/Hiberix™	108	12.573 [9.563 , 16.532]	1.200 [1.007 , 1.429]	1.821 [1.463 , 2.267]	62.7 [52.9 , 74.3]	470.9 [352.3 , 629.3]
6-10-14 weeks	Hib-081 (Philippines)	DTPw-HBV/Hib_ads 2.5 µg	97	9.274 [7.539 , 11.409]	0.699 [0.562 , 0.870]	6.261 [5.185 , 7.561]	111.2 [99.3 , 124.6]	128.8 [94.0 , 176.6]
		DTPw-HBV/Hib_ads 2.5 µg following a dose of HBV at birth	97	8.770 [6.883 , 11.175]	0.626 [0.514 , 0.762]	5.867 [4.695 , 7.332]	112.4 [98.8 , 127.8]	257.5 [196.8 , 337.0]

N = Number of subjects included in the ATP cohort for immunogenicity analysis (the actual number analysed may be different for each antigen, depending on whether serological results were available for all subjects). ‡ In study Hib-078 all anti-HBs responses were calculated on initially seronegative subjects only.

Table 6: Hib-091: Anti-PRP seroprotection rates and antibody GMCs (ATP cohort for immunogenicity)

Group	Timing	N	≥0.15 µg/ml				≥1.0 µg/ml				GMC		
					95% CI		n	%	95% CI		Value	95% CI	
			n	%	LL	UL			LL	UL		LL	UL
1	**PRE**	95	62	**65.3**	54.8	74.7	18	**18.9**	11.6	28.3	**0.285**	0.219	0.371
	PIII(M3)	95	95	**100.0**	96.2	100.0	89	**93.7**	86.8	97.6	**15.285**	11.624	20.100
2	**PRE**	93	60	**64.5**	53.9	74.2	19	**20.4**	12.8	30.1	**0.318**	0.240	0.420
	PIII(M3)	94	94	**100.0**	96.2	100.0	89	**94.7**	88.0	98.3	**13.868**	10.816	17.780

Group.1: Tritanrix™-HepB low thio/Hib_ads 2.5 µg (reduced thiomersal form of Quintanrix);
Group.2: Tritanrix™-HepB/Hiberix™
N = number of subjects with available results
n/% = number/percentage of subjects with Anti-PRP concentration greater than 0.15 & greater than 1mcg/ml
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
PRE =Blood sampling time point prior to vaccination (visit 1)
PIII(M3) = blood sampling time point one month after the third dose (visit 4)

Study Hib-091
100% of subjects in both groups showed seroprotective anti-PRP antibodies. There was no difference between groups in terms of post-vaccination GMC, or in the proportion of subjects reaching the higher cut-off of 1.0 µg/ml (>93% in both groups) (See **Table 6** above).

Non-inferiority of the reduced thiomersal form of Quintanrix was demonstrated since, in terms of the anti-PRP response, the upper limit of the 95% CI for the difference in the proportion of subjects with anti-PRP antibody concentration ≥ 0.15 µg/ml was below the pre-defined limit of 10%.

Consistency of the immune response of the DTPw-HBV/Hib_ads 2.5 µg vaccine (Study Hib-078)
With respect to the primary endpoint, pairwise comparison of the percentage of subjects with anti-PRP antibody titres ≥0.15µg/ml for the three Hib_ads 2.5 µg vaccine lots, met the pre-defined criteria for clinical equivalence. Study Hib-078 therefore demonstrated lot-to-lot consistency in terms of antibody response to the PRP antigen.

Persistence of antibodies following primary vaccination with the DTPw-HBV/Hib_ads 2.5 µg vaccine and immunogenicity of a booster dose in the second year of life (Study Hib-064)
In study Hib-052 subjects received a booster dose of the same vaccine they received for primary vaccination, co-administered with MMR vaccine at 15-24 months of age. Only the groups boosted with the DTPw-HBV/Hib_ads 2.5 µg vaccine or the licensed Tritanrix™-HepB/Hiberix™ are discussed here.

Prior to booster vaccination, seroprotection rates and antibody GMTs were similar in both groups, as shown by the overlapping 95%CIs. All subjects primed with the DTPw-HBV/Hib_ads 2.5 µg vaccine had anti-PRP antibodies ≥0.15µg/ml.

Forty-two days after booster vaccination, similar responses were seen among subjects receiving a fourth dose of the DTPw-HBV/Hib_ads 2.5 µg vaccine and those receiving a fourth dose of Tritanrix™-HepB/Hiberix™. All subjects had anti-PRP antibody titres ≥1.0µg/ml (See **Table 7**).

When the DTPw-HBV/Hib_ads 2.5 µg vaccine was given as a fourth consecutive dose at 14 to 19 months of age, substantial increases in anti-PRP antibody titres were induced (post vaccination antibody GMT was 25-fold higher compared to the pre-booster titre). This substantial increase in anti-PRP antibodies (similar to that induced by a fourth consecutive dose of Tritanrix™-HepB/Hiberix™ and resulting in similar post booster vaccination antibody GMTs) is suggestive of effective priming and induction of immune memory, regardless of the quantity of PRP and the formulation of the Hib component used for priming.

The avidity and bactericidal activity was measured one month post primary and again one month after booster vaccination in sera from 25 subjects who received the candidate vaccine and 25 who had

received the Tritanrix™-HepB/Hiberix™ control vaccines in studies Hib-052 and Hib-064. A subset representative of the range of titres observed after primary vaccination was selected. The antibody avidity and bactericidal activity was similar between groups and showed also similar increases from post primary to post booster, in both groups. These data are evidence of the existence of anti-PRP memory and demonstrate the functional capacity of the anti-PRP antibodies in subjects who have received the candidate vaccine as a primary vaccination course.

The available data demonstrate immunogenicity and antibody persistence following primary immunisation with the candidate vaccine, the induction of immune memory as evidenced by the booster response and the maturation of the antibodies induced, similar to that observed with the licensed Tritanrix™-HepB/Hiberix™ vaccine. However, when comparing the seroprotection rates of the different groups in studies Hib064, Hib085 and Hib008, the number of children receiving the 2.5 µg vaccine was very small (n=63; Group 4 of study Hib 064) when compared to the number of children receiving the 5 µg or 10 µg vaccines. As a consequence, the need for booster vaccination has not been established as the total number of infants seen during follow-up was too small to assess the persistence of antibodies following primary vaccination and to evaluate the protective effect of booster vaccination. The applicant has committed to provide additional data as soon as they are available.

Table 7: Seroprotection/seropositivity/pertussis vaccine response rates and antibody GMTs prior to and one month after booster vaccination in study Hib-064 (ATP Cohort)

	DTPw-HBV/Hib_ads 2.5 µg (N = 63)				Tritanrix™-HepB/Hiberix™ (N = 69)			
	Pre-booster		Post booster		Pre-booster		Post booster	
Antibody	% [95%CI]	GMT [95%CI]	% [95%CI]	GMT [95%CI]	% [95%CI]	GMT [95%CI]	% [95%CI]	GMT [95%CI]
Anti-PRP ≥ 0.15 †	100.0 [94.3 , 100.0]	2.095 [1.472 , 2.983]	100.0 [94.3 , 100.0]	52.459 [38.463 , 71.549]	97.1 [89.9 , 99.6]	3.414 [2.278 , 5.117]	100.0 [94.8 , 100.0]	57.898 [43.991 , 76.200]
Anti-PRP ≥ 1.0 ‡	66.7 [53.7 , 78.0]	-	100.0 [94.3 , 100.0]	-	76.8 [65.1 , 86.1]	-	100.0 [94.8 , 100.0]	-
Anti-D *ELISA*	49.2 [36.4 , 62.1]	0.101 [0.081 , 0.126]	98.4 [91.5 , 100.0]	2.821 [2.065 , 3.854]	37.7 [26.3 , 50.2]	0.087 [0.071 , 0.107]	97.1 [89.9 , 99.6]	1.942 [1.413 , 2.669]
Vero-cell assay	*90.5 [80.4 , 96.4]*	-	-	-	*89.9 [80.2 , 95.8]*	-	-	-
Anti-T	88.9 [78.4 , 95.4]	0.331 [0.260 , 0.423]	100.0 [94.3 , 100.0]	6.930 [5.936 , 8.092]	95.7 [87.8 , 99.1]	0.364 [0.297 , 0.445]	100.0 [94.8 , 100.0]	7.561 [6.420 , 8.905]
Anti-BPT	41.3 [29.0 , 54.4]	12.6 [10.6 , 14.9]	100.0 [94.1 , 100.0]	142.06 [120.9 , 168.2]	36.2 [25.0 , 48.7]	12.3 [10.2 , 14.7]	100.0 [94.8 , 100.0]	113.0 [98.1 , 130.1]
*Vaccine response**	-	-	*98.4 [91.2 ; 100.0]*	-	-	-	*97.1 [89.9 ; 99.6]*	-
Anti-HBs	82.5 [70.9 , 90.9]	48.4 [33.3 , 70.4]	98.4 [91.5 , 100.0]	2695.3 [1701.3 , 4270.1]	71.0 [58.8 , 81.3]	27.9 [19.7 , 39.5]	92.8 [83.9 , 97.6]	1215.1 [708.1 , 2085.3]

% percentage of subjects with titres ≥ assay cut-off (≥0.15 µg/ml (†) and ≥1.0 µg/ml (‡) for anti-PRP, ≥0.1 IU/ml for anti-diphtheria by ELISA and ≥0.016 IU/ml for Vero-cell assay pre-booster, ≥0.1 IU/ml for anti-tetanus, ≥15 El.U/ml for anti-BPT and ≥10 mIU/ml for anti-HBs); Units for GMTs: µg/ml for anti-PRP, IU/ml for anti-D and anti-T, El.U/ml for anti-BPT and mIU/ml for anti-HBs

*Pertussis vaccine response defined as appearance of antibodies (≥15 El.U/ml) in initially seronegative subjects or at least 2-fold increase of pre-booster antibody titres in initially seropositive subjects

Protective efficacy of the remaining vaccine components; immunogenicity following primary vaccination

The immune response to diphtheria, tetanus, pertussis (BPT), and Hepatitis B components were evaluated in studies Hib-052, -078, -080 and –081, following the Methods section. In study Hib-079, only the immune response to Hepatitis B component was evaluated.

Vaccine response rates and seroprotection rates for pertussis, diphtheria, tetanus and hepatitis B measured one month after completion of the three-dose primary vaccination course were similar between the candidate vaccine and the licensed control groups.

Table 8 Hib-091: Seroprotection/vaccine response rates and antibody GMCs for anti-tetanus, diphtheria, pertussis and hepatitis B antibodies
(ATP cohort for immunogenicity)

Group	Timing	N	% seroprotected/VR				GMC		
					95% CI		Value	95% CI	
			n	%	LL	UL		LL	UL
Diphtheria				**%≥0.1 IU/ml**			**IU/ml**		
1	PRE	94	27	**28.7**	19.9	39.0	**0.075**	0.064	0.087
	PIII(M3)	94	84	**89.4**	81.3	94.8	**0.767**	0.588	1.001
2	PRE	94	29	**30.9**	21.7	41.2	**0.081**	0.068	0.096
	PIII(M3)	94	82	**87.2**	78.8	93.2	**0.576**	0.439	0.757
Tetanus				**%≥0.1 IU/ml**			**IU/ml**		
1	PRE	95	85	**89.5**	81.5	94.8	**2.136**	1.509	3.024
	PIII(M3)	95	95	**100.0**	96.2	100.0	**3.198**	2.636	3.880
2	PRE	94	84	**89.4**	81.3	94.8	**1.740**	1.216	2.490
	PIII(M3)	94	94	**100.0**	96.2	100.0	**3.565**	2.977	4.268
Pertussis				**%VR**			**EL.U/ml**		
1	PRE	95		**NA**			**8.4**	7.8	9.1
	PIII(M3)	94	94	**100**	96.2	100	**118.2**	105.0	133.0
2	PRE	94		**NA**			**7.8**	7.5	8.2
	PIII(M3)	92	91	**98.9**	94.1	100	**79.5**	68.8	91.9
Hepatitis B				**%≥10mIU/ml**			**mIU/ml**		
1	PRE	93	25	**26.9**	18.2	37.1	**12.8**	9.0	18.0
	PIII(M3)	93	83	**89.2**	81.1	94.7	**108.9**	77.9	152.2
2	PRE	93	21	**22.6**	14.6	32.4	**11.4**	8.1	16.2
	PIII(M3)	93	73	**78.5**	68.8	86.3	**67.1**	47.0	96.0

Group.1: Tritanrix™-HepB $_{low\ thio}$/Hib_ads 2.5 µg (reduced thiomersal form of Quintanrix); Group.2: Tritanrix™-HepB/Hiberix™
N = number of subjects with available results
n/%seroprotected/VR = number/percentage of subjects with antibody concentration above the level specified/vaccine response for pertussis
NA: not applicable
95% CI = 95% confidence interval; LL = Lower Limit; UL = Upper Limit
VR: appearance of antibodies in initially seronegative subjects, or post-vaccination concentrations ≥pre-vaccination concentration in initially seropositive subjects
PRE =Blood sampling time point prior to vaccination (visit 1)
PIII(M3) = blood sampling time point one month after the third dose (visit 4)

- Pertussis

The anti-BPT antibody titres and vaccine response rates following vaccination with Tritanrix™-HepB

were previously shown to be similar to those of Tritanrix™. The data provided here show that the response to the candidate vaccine was not different from that obtained following vaccination with Tritanrix™-HepB, either injected as such or mixed with Hiberix™.

The Pw component of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine is identical to the Pw component of the licensed Tritanrix™ and Tritanrix™-HepB vaccines. The same Pw component (in combination with D and T) was used as a comparator group in a household contact study in Germany to determine the vaccine-efficacy against pertussis (*Schmitt et al. J Am Med Assoc. 1996; 275: 37-41*). The DTPw vaccine was administered at 3, 4 and 5 months of age and the cohort was followed for a median period of 250 days after completion of the primary vaccination course. Schmitt et al. (J Am Med Assoc. 1996; 275: 37-41) reported that the vaccine efficacy of the acellular vaccine was estimated at 88.7%. However since the DTPw receiving subjects were more frequently in contact with patients treated with erythromycin than the DTPw receiving subjects, the authors concluded that the efficacy of the DTPw vaccine may have been overestimated.

- Diphtheria

Overall, 96.3% of subjects receiving the candidate vaccine had anti-diphtheria antibody titres of ≥ 0.1 IU/ml one month after completion of the primary vaccination course. One month after the booster dose virtually all subjects had protective antibody titres.

In study Hib-091, subjects who were seronegative by ELISA testing after vaccination were tested with the more sensitive in vitro neutralisation assay on Vero cells. 96.2% of subjects in both groups had seroprotective antibody concentrations by either method (ELISA or Vero).

- Tetanus

One month after completion of the primary vaccination course the candidate vaccine induced anti-tetanus antibody titres of ≥ 0.1 IU/ml in virtually all subjects, no difference being observed among the different vaccines.

In study Hib-078, the reference vaccine generated lower tetanus antibody titres than the candidate vaccine. Only 97.2% of subjects in the reference group showed seroprotection to tetanus and the confidence limits of the GMTs were not overlapping although the same lot of the DTPw-HBV vaccine was used. Since consistency of lot production was demonstrated in terms of anti-tetanus antibody response and given the high rates of seroprotective antibody concentrations achieved by subjects in all studies, it is unlikely that these differences are of clinical relevance.

- Hepatitis B

Compiled data from studies with the DTPw-HBV/Hib_ads 2.5 µg vaccine confirm that the majority (>95%) of subjects reached anti-HBsAg antibody titres ≥10mIU/ml one month after completing the primary vaccination. The candidate vaccine therefore meets the WHO recommendation for hepatitis B vaccination. As shown in study Hib-081, the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine can be safely administered according to the EPI schedule at 6, 10 and 14 weeks of age, after a birth dose of HBV vaccine. In these circumstances, the candidate vaccine elicited a high hepatitis B seroprotection rate of 99.0%, without interference on the immune responses to the other vaccine antigens.

Although the same lot of the DTPw-HBV (15762A2) vaccine was used in studies Hib-78 and Hib-80 the confidence intervals of the mean antibody titres against HBsAg were not overlapping (e.g. in the Philippines the GMT's were significantly lower). The data presented suggest that the variability in the response to hepatitis B after vaccination with the same lot may be explained by the schedule in which the vaccine was used. Although the magnitude of the post-vaccination response differed, Quintanrix was shown to be immunogenic and to induce seroprotective anti-HBs antibody concentrations in the majority of subjects studied, including when administered in the most immunologically challenging schedule.

In study Hib091, the seroconversion rate for antibodies to HBsAg was higher in the group receiving the reduced thiomersal form of Quintanrix when compared to the group receiving the full thiomersal vaccine (89.2% versus 78.5%), with a comparable GMC titre (157.8 vs. 136.8mIU/ml) among

seroconverting subjects among both groups. This finding indicates that the reduced thiomersal content did not interfere with the immunogenicity of the hepatitis B antigen. Although the post-vaccination anti-HBs GMC was significantly higher in the group receiving the reduced thiomeral form of Quintanrix vaccine, when only subjects seropositive after vaccination are considered, this difference is no longer observed. Since the hepatitis B seroconversion rates in studies Hib078, Hib079, Hib080 and Hib081 were strictly comparable (all children received the full thiomersal vaccine) the lower seroconversion rate observed in study Hib091 with the full thiomersal vaccine is not considered as relevant.

Subjects enrolled into study Hib-091 were born of HBsAg negative mothers as established by prior screening. Even so, approximately 25% of subjects enrolled had detectable anti-HBs antibodies prior to vaccination, reflecting prior maternal vaccination or previous maternal infection with viral clearance. There is no evidence that the presence of maternal antibody had an impact on the response to primary vaccination.

The anti-HBs antibody GMC and the proportion of subjects who developed seroprotective antibodies after vaccination with the reduced thiomersal form of Quintanrix is comparable to that observed in previous studies with Quintanrix in the same population, when no birth dose of hepatitis B was administered. Anti-HBs responses were at least as good as the responses observed with the licensed vaccine without reduced thiomersal content.

Protective efficacy of the remaining vaccine components; consistency of the immune response of the DTPw-HBV/Hib_ads 2.5 µg vaccine (Study Hib-078)
The 90% CI of the differences in seroprotection rates (diphtheria, tetanus, hepatitis B) and vaccine response rate (pertussis) for all pairwise comparisons were within the preset limits defining clinical equivalence (-10%, 10%). Similarity of post vaccination anti-diphtheria and anti-HBs antibody titres could not formally be concluded since the 90% CIs of the GMT ratios were marginally outside the pre-set limit and one group was not consistently below the others. These differences in antibody titres did not result in different seroprotection rates between groups. The consistency of the candidate vaccine can thus be concluded.

Protective efficacy of the remaining vaccine components; Persistence of antibodies following primary vaccination with the DTPw-HBV/Hib_ads 2.5 µg vaccine and immunogenicity of a booster dose in the second year of life (Study Hib-064)
Before booster vaccination, 82.5% of infants primed with the DTPw-HBV/Hib_ads 2.5 µg vaccine still had protective antibody titres against hepatitis B and 88.9% against tetanus. *Bordetella pertussis* antibodies had declined significantly, but were not different from those in the control group. Using an *in vitro* neutralisation assay on Vero cells with a cut-off of 0.016 IU/ml to retest seronegative serum samples, it was concluded that the majority of subjects (90%) remained protected against diphtheria at the time of booster vaccination.

Forty-two days after booster vaccination, similar responses were seen among subjects receiving a fourth dose of the DTPw-HBV/Hib_ads 2.5 µg vaccine and those receiving a fourth dose of Tritanrix™-HepB/Hiberix™. All subjects had seroprotective antibody titres against tetanus. More than 98% of the subjects had seroprotective antibody titres against diphtheria or hepatitis B, or showed a booster response for anti-BPT antibodies following the booster dose of the DTPw-HBV/Hib_ads 2.5 µg vaccine. In both groups, the booster dose induced a 10 to 55-fold increase in mean antibody titres compared to the pre-booster levels for all vaccine components.

Co-administration of other vaccines
- Co-administration of oral polio vaccine (OPV) and Bacille-Calmette-Guérin (BCG) vaccine

Both OPV and BCG vaccines are routinely administered during the first months of life in Latin America and Asia where the majority of clinical trials were conducted. Therefore, the administration of these vaccines according to local practices was not considered to be an exclusion or elimination criterion in the clinical trials conducted with the candidate vaccine.

In trial Hib-052, OPV was provided by GSK and was co-administered to all subjects during the study.

In the other trials, approximately 85% of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine doses were co-administered with OPV, with similar rates of OPV co-administration in the control groups.

In order to provide data on the immune response to OPV following co-administration with DTPw-HepB/Hib_ads 2.5 µg, the following studies were selected for additional testing of Polio antibodies: Hib-079 Hib-081 and Hib-091. The data presented above indicate that co-administration of OPV and Quintanrix results in anti-polio seroconversion rates and GMTs similar to those observed after co-administration of OPV and the licensed Tritanrix™-HepB/Hiberix™. In a developing country, co-administration of OPV and Quintanrix produces seroconversion rates at least as high as those previously reported in the literature.

With regard to BCG vaccine, 25% of the subjects in study Hib-052 and 45% of the subjects in study Hib-079 received one dose of BCG concomitantly with one of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine doses, with similar rates of BCG co-administration in the control groups. The Mantoux or Tuberculin test remains the most frequently used test to measure the delayed-type hypersensitivity reaction to tuberculin as an indication of immunity induced by BCG vaccination. However the tuberculin test was not performed during clinical trials of DTPw-HepB/Hib_ads 2.5 µg. Currently there is no in-vitro test available to assess the immunogenicity of BCG. Therefore no serological testing of the response to BCG when co-administered with DTPw-HepB/Hib_ads 2.5 µg could be performed.

As this co-administration did not lead to any obvious impact on the overall immunogenicity and reactogenicity profiles of the vaccine, it can be concluded that when needed, the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine can be co-administered with BCG vaccine, according to medical practices in place.

- Co-administration of measles-mumps-rubella (MMR) vaccines in the second year of life

In the booster study Hib-064 the candidate vaccine was co-administered with GSK's licensed MMR vaccine (Priorix™) at 15-24 months of age. The specific MMR reactogenicity and immunogenicity data observed in this study was similar to GSK's previous clinical experience with Priorix™. Therefore MMR vaccine can safely and effectively be co-administered with DTPw-HBV/Hib_ads 2.5 µg in the second year of life when appropriate.

Discussion on clinical efficacy

The 3-5-12 month schedule that is used in some European countries was not evaluated in clinical studies and is reflected in section 4.2 of the SPC.

The immune response to the Hib component elicited by the candidate vaccine following primary and booster vaccination was statistically not inferior to the reference vaccines.

The variability in anti-PRP antibody concentrations observed during the clinical development of Quintanrix is consistent with that reported in the literature with Hib vaccines from other manufacturers, and with previous experience in clinical trials performed by GSK. The exact causes of the variation in the magnitude of the anti-PRP response are likely to be complex and multi-factorial. Despite the differences in the magnitude of the response, the proportion of subjects with seroprotective anti-PRP antibody concentrations was high, and there is evidence to show that immune memory was induced. These observations emphasise that the anti-PRP response following priming with 2.5µg of PRP is similar to that elicited by currently licensed 10µg PRP vaccines. Therefore, this variability is likely to be of no clinical significance.

In study Hib-078, the reference vaccine elicited a smaller immune response to tetanus one month following primary vaccination than the candidate vaccine. Since neither the persistence of tetanus antibodies following primary vaccination, nor the effect of booster vaccination was studied in Hib-078, the significance of these findings remains unknown.

Although the same lot of the DTPw-HBV (15762A2) vaccine was used in studies Hib-78 and Hib-80, the confidence intervals of the mean antibody titres against the Pw as well as the HBsAg component were not overlapping in the two studies. The applicant claims that notwithstanding the variability of the response, the infants were satisfactorily sero-protected when referring to the validated markers and cut off levels for protection. This was indeed the case. However, since the validated surrogate markers demonstrate a high level of sero-protection, the point can be considered as solved.

The consistency of the immune response of the different lots of the candidate vaccine was demonstrated for all vaccine components.

Study Hib-091 confirms the satisfactory immunogenicity of DTPw-HepB/Hib_ads 2.5 µg vaccine containing reduced thiomersal. Non-inferiority of the vaccine was demonstrated in terms of the anti-PRP response after vaccination. Seroprotection rates and vaccine response rates for the other vaccine antigens were at least as high as those achieved after vaccination with Tritanrix™-HepB/Hiberix™ without reduced thiomersal content.

The small number of children seen during follow-up in study Hib-064 precludes a reliable conclusion about the persistence of protective antibodies after primary vaccination and about the immunogenic effect of booster vaccination. As a consequence, the need for booster vaccination has not been established. The candidate DTPw-HBV/Hib 2.5 vaccine when used as a booster has been evaluated by the applicant in other clinical studies, namely DTPw-HBV/Hib-MenAC-TT-002 and DTPw-HBV/Hib-MenC-TT-003. The applicant has committed to provide the full study reports of studies DTPw-HBV/Hib-MenAC-002 and DTPw-HBV/Hib-MenC-003, including the booster data, as soon as they are available.

In the studies performed with the Quintanrix, no HIV screening took place. Therefore, the applicant commits to perform a clinical trial in an HIV seropositive infant study population. In this exploratory study, infants will be screened for HIV before study entry and approximately 50 infants will receive the study vaccine. The objective of this study will be to assess both clinical protection and reactogenicity following primary vaccination with the Quintanrix vaccine containing 2.5 µg PRP, compared to the reference vaccine, Tritanrix™-HepB/Hiberix™ containing 10 µg PRP. The results of this study will be submitted when they become available.

Clinical safety

Patient exposure
The overall reactogenic profile of the candidate vaccine was based upon data collected from 1334 infants receiving the vaccine as a primary vaccination during 4 clinical studies (Hib-078, Hib-079, Hib-080 and Hib-081) and from 435 infants who received a booster dose. The incidence per dose of solicited and unsolicited local and general symptoms is presented for each study.

Adverse events
All vaccines administered in the feasibility study Hib-052 elicited similar reactogenicity profiles. Grade 3 local and general solicited symptoms occurred infrequently and no vaccine related safety concerns were identified.

Overall, incidences of solicited symptoms were similar among the groups receiving the DTPw-HBV/Hib_ads 2.5 µg vaccine and the control groups receiving Tritanrix™-HepB and Hiberix™ vaccines in each study. Grade 3 symptoms were infrequently reported and were similar between groups in the same trial. In study Hib-078, local reactions observed at the Tritanrix™-HepB injection site were similar to those observed at the DTPw-HBV/Hib_ads 2.5 µg injection site, thus showing that the addition of the Hib_ads 2.5 µg component does not affect the local reactogenicity profile of the DTPw-HBV component.

In order to delineate an "average" reactogenicity profile, the incidences of solicited symptoms following primary vaccination with the candidate vaccine in studies Hib-078, Hib-079, Hib-080 and Hib-081, representing a total of 3509 doses, have been pooled and are presented in **Table 9**. These

have been used to describe in the SPC the symptoms that most likely occur and their respective frequencies.

Table 9: Pooled per dose incidences (%) of solicited local and general symptoms with a suspected or probable causal relationship to vaccination (any and grade 3) over the four-day follow-up period following primary vaccination with the candidate DTPw-HBV/Hib_ads 2.5 µg

Symptom	DTPw-HBV/Hib_ads 2.5 µg (Pooled data on 3509 doses) %	CIOMS frequency categorisation
Pain	49.2	Very common
Redness	37.4	Very common
Swelling	33.4	Very common
Fever*	46.6	Very common
Grade 3 fever*	1.4	Common
Drowsiness	28.3	Very common
Irritability	47.2	Very common
Loss of appetite	21.1	Very common

% = percentage of doses followed by a specified symptom

*Fever defined by a measurement ≥37.5°C (axillary) or ≥38.0°C (rectally)

Grade 3 fever: temperature measurement >39.0°C (axillary) and > 39.5°C (rectally).

Although incidences of symptoms were similar for the different groups in the same trial, some variability of the reactogenicity profile was observed between studies:

⇒ Grade 3 pain varies between 3.0% in Belgium and 10.2 % in Nicaragua and Panama.

⇒ Redness >20 mm is 0.6% in Nicaragua and Panama versus 11.4% in the Philippines

⇒ Swelling >20 mm is observed in 1.3 % in Nicaragua an Panama and 15% in the Philippines.

The applicant's explanation with respect to the impact of cultural factors on symptom reporting such as pain is satisfactory. However, redness and swelling are signs observed by the care provider and should not be affected by cultural factors. Nevertheless the applicant stresses that the incidence of local symptoms were similar among children receiving Quintanrix and the licensed control in each trial, indicating that the reactogenicity profile of Quintanrix was similar to that of the licensed control vaccine. The applicant's response was considered acceptable.

Consistency of reactogenicity of the DTPw-HBV/Hib_ads 2.5 µg vaccine (Study Hib-078)

Incidences of solicited local and general symptoms (any intensity and grade 3) were similar between the three groups in study Hib-078 receiving different lots of the Hib_ads 2.5 µg component, reconstituted with the same lot of Tritanrix™-HepB. Exact 95%CIs computed on the ratio of the incidences of each solicited symptom did not indicate a significant difference between each pair of DTPw-HBV/Hib_ads 2.5 µg vaccine lots in terms of proportion of subjects for whom symptoms were reported. A consistent reactogenicity profile of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine was therefore demonstrated.

Reactogenicity observed in study Hib-091

Overall, the incidence of any general symptom was high in study Hib-091, but similar to that reported in the same population previously (study Hib-081). Similarly, the incidence of grade 3 systemic symptoms including fever >39.0°C reported in study Hib-091 was low (reported after <3.0% of doses), and was comparable with rates reported after vaccination with the high-thiomersal-containing formulation of Tritanrix™-HepB/Hiberix™ in study Hib-081 (Grade 3 symptoms reported after <4% of doses). Temperature and irritability were the most frequently reported general symptoms in both groups in study Hib-091. Exploratory comparisons showed significant differences between groups in terms of Any drowsiness, irritability and temperature ($p<0.05$), with higher rates reported after the reduced thiomersal form of Quintanrix, however there were no significant differences between groups in terms of symptoms of grade 3 intensity.

There were 12 SAEs reported during the study period. None were considered by the investigator to be related to vaccination. One subject experienced two seizure episodes that began 18 days after the

second dose of Tritanrix™-HepB/Hiberix™. A diagnosis of seizure disorder was made and treatment was commenced. At study end therapy was ongoing and the subject had not returned for follow-up investigations. The subject received the third vaccine dose without complications.

Reactogenicity associated with booster dose of DTPw-HBV/Hib $_{2.5}$ in the second year of life
The safety of the candidate DTPw-HBV/Hib 2.5 vaccine when used as a booster has been evaluated by the applicant in several clinical studies, representing 435 vaccine doses administered. Sixty three doses were administered in the Hib-064 study and a total of 370 doses in studies DTPw-HBV/Hib-MenAC-TT-002 and DTPw-HBV/Hib-MenC-TT-003. The applicant has committed to provide the full study reports of studies DTPw-HBV/Hib-MenAC-002 and DTPw-HBV/Hib-MenC-003, including the immunogenic data, as soon as they are available.

Overall, symptoms tended to be reported more frequently following the booster dose as compared to the primary course. This was observed previously for other DTP vaccines. Reports of grade 3 symptoms remained infrequent even after the fourth consecutive dose.

In study Hib-064, the candidate vaccine showed a higher reactogenicity than the licensed control and the other experimental vaccines: pain, fever, irritability/fussiness and loss of appetite were more frequently reported. The rates of symptoms were not statistically different because of the limited number of vaccines in each subgroup. Although these minor side effects should be interpreted with caution since such events may be affected by local beliefs and practices, the phenomenon does not preclude a real difference in reactogenicity between the candidate vaccine and the Hib and reference vaccines.

Data were also available from groups receiving other experimental vaccines with higher amounts of the reformulated PRP-T component (5 or 10 µg of PRP). Despite the fact that these vaccines are identical to the candidate vaccine, except for a 2- respectively 4-fold higher PRP antigen content, the reactogenicity profile observed in these groups is more in line with that of the licensed control. However, it should be stressed that only 10 µg PRP containing vaccines are licensed in the EU, not the 5 µg containing vaccine. Any comparison with the latter vaccine in terms of seroprotection or reactogenicity is strictly spoken not appropriate.

The overall reactogenicity profile of the DTPw-HBV/Hib_ads 2.5 µg vaccine remained acceptable when given as a booster in the second year of life, even when co-administered with the MMR vaccine.

Nevertheless the number of children seen during follow-up is too small to allow any reliable conclusion about the safety of the vaccine at booster vaccination. Especially with respect to the risk of febrile convulsions (children at booster age are especially prone to this particular serious adverse event), the safety data have a very limited value. It should also be stressed that study Hib-064 was an open study, bearing the risk of introducing bias.

Unsolicited symptoms
One hundred-and-twenty-one primary vaccination doses of the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine were followed within 30 days by at least one report of an unsolicited symptom assessed by the investigator to be suspected or probably related (SU/PB) to vaccination. The vast majority of these symptoms were reports of injection site induration that resolved within 2 to 3 weeks. Symptoms were related to childhood diseases commonly reported in this age group.

In the four pivotal studies performed with DTPw-HBV/Hib_ads 2.5 µg there were 37 reports of bronchitis and 21 reports of cough occurring within 30 days of any dose of vaccine (ATP cohort for safety). Of these cases, six subjects (five from study Hib-078 and one from study Hib-081) reported bronchitis and/or cough were initially considered by the investigators to be suspected/probably related to vaccination. In retrospect, after re-assessing the cases, all investigators felt that there was no relationship of the AE with the study vaccination.

No unsolicited symptoms suspected or probably related to vaccination were reported following boosting with the DTPw-HBV/Hib_ads 2.5 µg vaccine. To further assess the safety of the candidate

vaccine, unsolicited symptoms and serious adverse events (SAEs) reported following primary (studies Hib-065 and Hib-071) or booster (study Hib-064), vaccination with the related DTPw-HBV/Hib_ads 5 µg vaccine were also reviewed. This did not reveal any safety concern.

Serious adverse event/deaths/other significant events
A total of 58 SAEs were reported for a total of 11,932 doses of any vaccine administered across all trials included in the dossier. Twenty-four SAEs were reported among subjects vaccinated with the DTPw-HBV/Hib_ads 2.5 µg vaccine (23 during the primary vaccination course and 1 following a booster dose) and 18 were reported among subjects vaccinated with the related DTPw-HBV/Hib_ads 5 µg vaccine (16 during the primary vaccination course and 2 following a booster dose).

Only 9 SAEs were considered by the investigator to be suspected or probably related to vaccination (all occurred during the primary vaccination course, except one following a booster dose of Tritanrix-HepB™ and Hiberix™). Four of these occurred in subjects receiving the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine, two hypotonic-hyporesponsive episodes (HHE) and two cases of convulsions (**Table 10 & 11**). All 4 subjects recovered. Three events occurred following the administration of Tritanrix™-HepB and Hiberix™ vaccines; one following DTPw-HBV/Hib_ads 5 µg and one following separate administration of Tritanrix™-HepB and Hib_ads 10 µg vaccines. Details are given in the following Tables .

Shock or shock-like state, collapse and hypotonic-hyporesponsive episodes (HHE)

Table 10: Cases of Hypotonic-Hyporesponsive Episodes (HHE) reported in trials evaluating DTPw-HBV/Hib_ads 2.5 µg and DTPw-HBV/Hib_ads 5 µg vaccines

Vaccine	Study	PID	SAE	Previous dose	Onset (hours)	Duration (min)	Outcome	Relation-ship
DTPw-HBV/Hib_ads 2.5 µg	Hib-078	519	Shock-like syndrome	1	1.5	15-20	Recovered	PR
	Hib-078	497	Shock-like syndrome	1	3.5	60	Recovered	PR
DTPw-HBV + Hiberix	Hib-078	632	Shock-like syndrome	3	1.5	30	Recovered	PR

PR: probably related
PID: patient identification

Upon review of the unsolicited symptoms reported for the different trials included in the dossier, no other symptoms indicative of HHE could be identified. Therefore the incidence of HHE with the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine can be estimated to be 2/3,601 doses or 1/1,800 doses. When taking into account only the 1,828 doses of DTPw-HBV/Hib_ads 2.5 µg vaccine administered in study Hib-078, the incidence of HHE was still within the range reported in the literature.

HHE was previously considered to be a contraindication to further pertussis immunization. While most parents and physicians withheld pertussis vaccines after HHE, approximately 25% did not, and this did not result in adverse events following subsequent immunisations. Recent studies also indicated that children are unlikely to have recurrent events after further vaccination. Therefore HHE has been maintained in the SPC as a precaution to further vaccination, and not as an absolute contraindication. This is also in line with the SPC of other licensed pertussis containing vaccines.

Convulsions
In addition to the convulsions discussed in connection with the SAEs having a fatal outcome (see further), seizures were reported for 11 other subjects (**Table 11**). Ten of these subjects were hospitalised and therefore the convulsions were reported as SAE.

Table 11: Convulsions with a favourable outcome reported in clinical trials evaluating DTPw-HBV/Hib_ads 2.5 µg and DTPw-HBV/Hib_ads 5 µg vaccines

Vaccine	Study	PID	SAE	Previous dose	Onset (days)	Outcome	Relation-ship
DTPw-HBV/Hib_ads 2.5 µg	Hib-052	239	Infantile beri beri, malaria febrile convulsions	2	16	Recovered	NR
	Hib-052	404	Febrile convulsions	3	0	Recovered	NR
	Hib-078	480	Viral meningitis, febrile convulsions	1	8	Recovered	NR

	Hib-079	70	Afebrile seizures, cerebral atrophia	2	0	Recovered with sequela	PR
	Hib-079	84	Purulent meningitis	1	7	Recovered	NR
	Hib-079	104	Fever with generalised seizures	2	0	Recovered	PR
DTPw-HBV/Hib_ads 5 µg + MMR	Hib-064	265	Acute gastroenteritis, febrile convulsions	4	54	Recovered	NR
DTPw-HBV + Hib_ads 10 µg	Hib-052	489	Fever, suspected URTI, febrile fits	1	0	Recovered	PR
DTPw-HBV + Hiberix	Hib-078	22	Seizures (reported in the unsolicited symptoms section because subject not hospitalised)	3	0	Recovered	PR
DTPw-HBV/Hiberix + MMR	Hib-064	450	Febrile convulsion, acute viral infection	4	9	Recovered	NR
DTPw-HBV/Hiberix	Hib-080	247	Benign myoclonies, possibly epilepsy	1	25	Recovered	NR

NR - not related; PR - probably related

PID - patient identification

URTI - Upper Respiratory Tract Infection

Four events were considered probably related to vaccination (two of which were in the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine group). All 4 probably-related cases occurred on the day of vaccination, as well as one additional case that occurred the day of administration of the 3rd DTPw-HBV/Hib_ads 2.5 µg dose, but was assessed as not related to study vaccination.

Six SAEs in the DTPw-HBV/Hib_ads 2.5 µg vaccine group involved convulsions, of which three occurred on the day of vaccination. The three other cases of convulsions, reported in the DTPw-HBV/Hib_ads 2.5 µg vaccine group, were considered as not related to vaccination. This is in line with the reported underlying diseases (infantile beri beri and possibly malaria, viral meningitis and purulent meningitis) and the onset of at least 7 days after vaccine administration.

Whole-cell pertussis vaccines have been associated with an increased risk of febrile seizures, on the days of vaccination or the first subsequent days. However, as compared to other children with febrile seizures that were not associated with vaccination, the children who had febrile seizures after vaccination were not found to be at a higher risk for subsequent seizures or neuro-developmental disabilities. With the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine, 3 cases of febrile convulsions without any other concomitant disease were observed on a total of 3,601 doses administered for an incidence of 0.08% (95%CI: 0.02-0.24). This is in line with the incidence of febrile convulsions following DTPw vaccination, as reported previously (9 cases on 15,752 doses. or 0.06% with 95%CI: 0.03-011.

In line with these observations, convulsions within 2 to 3 days following vaccination are listed in the Undesirable Effects section of the proposed SPC for the candidate vaccine. No other neurological safety issues were identified for the candidate DTPw-HBV/Hib_ads 2.5 µg vaccine.

Other SAEs considered as being related to the vaccine

In addition to the events already discussed, 3 SAEs were assessed by the investigator to be probably related to study vaccination. None of these occurred in the candidate vaccine group. Two cases of injection site cellulitis occurred 3-4 days post vaccination, one with the DTPw-HBV/Hib_ads 5 µg vaccine in Argentina (Study Hib-085) the other with the control vaccine in the Philippines. Both resolved, but a scar remained. One subject in study Hib-078 in Nicaragua developed fever on the day of the second dose of study vaccination with Tritanrix™-HepB and Hiberix™. A viral meningo-encephalitis was diagnosed, but the investigator could not exclude a possible causal relationship with study vaccination.

Table 12: Other probably or suspected to be related SAEs or SAEs with onset within 3 days after vaccination reported in clinical trials evaluating DTPw-HBV/Hib_ads 2.5 µg and DTPw-HBV/Hib_ads 5 µg vaccines

Vaccine	*Study*	*PID*	*SAE*	*Previous dose*	*Onset (days)*	*Outcome*	*Relation-ship*
DTPw-HBV/Hib_ads 5 µg	*Hib-071*	*1*	*Cellulitis at injection site*	*2*	*3*	*Recovered with sequelae*	*PR*

DTPw-HBV + Hiberix	*Hib-078*	*148*	*Viral meningoencephalitis*	*2*	*0*	*Recovered*	*PR*
	Hib-085	*102*	*Cellulitis at injection site*	*4*	*4*	*Recovered with sequelae*	*PR*

NR - not related; PR - probably related

PID - patient identification

Deaths

Three SAEs with fatal outcome occurred in the DTPw-HBV/Hib_ads 2.5 µg vaccine group. Two children died following gastro-enteritis with severe dehydration and hypovolemic shock. The third death in the candidate vaccine group was reported in a child who developed a convulsive disorder following asphyxia of unknown etiology. A subdural hematoma was also diagnosed. SAEs with fatal outcome are summarised in the following Table, none were considered to be related to vaccination.

Two additional fatal cases seem to be linked to an infectious etiology: one case of gastro-enteritis in Nicaragua and one case of pneumonia in Mexico. This is not unexpected, as infections are an important cause of infant mortality in these countries. Two other deaths occurred in Myanmar: one was related to aspiration following a convulsive disorder of unclear origin and the other was diagnosed as beri beri (vitamin B deficiency endemic in south-east Asia) with heart failure. No autopsies were performed.

Only limited clinical information is available for the last SAE with fatal outcome that occurred 25 days after a 2nd dose of Tritanrix™-HepB mixed with Hiberix™. The investigator considered the cause of death in this 5 month old boy to be Sudden Infant Death Syndrome (SIDS).

Table 13: Deaths reported in clinical trials evaluating DTPw-HBV/Hib_ads 2.5 µg and DTPw-HBV/Hib_ads 5 µg vaccines

Vaccine	**Study**	**PID**	**SAE**	**Previous dose**	**Onset (days)**	**Outcome**	**Relation-ship**
DTPw-HBV/Hib_ads 2.5 µg	Hib-052	153	Gastro-enteritis, hypovolemic shock	2	12	Death	NR
	Hib-079	48	Diarrhoea, severe dehydration	3	5	Death	NR
	Hib-080	92	Myoclonic seizures and subdural hematoma	2	34	Death	NR
(following HepB at birth)	Hib-081	57	SIDS	-	2	Death	NR
DTPw-HBV/Hib_ads 5 µg	Hib-071	854	Vomiting, diarrhoea, high fever, convulsions	1	52	Death	NR
	Hib-071	914	Pneumonia, septicaemia, septic shock	2	8	Death	NR
(following HepB at birth)	Hib-065	368	Febrile, drowsy, seizures	-	53	Death	NR
DTPw-HBV/Hib_ads 10 µg	Hib-052	42	Convulsions, crying	2	17	Death	NR
DTPw-HBV + Hib_ads 10 µg	Hib-052	467	Beri beri with heart failure	1	25	Death	NR
DTPw-HBV/Hiberix	Hib-080	191	SIDS	2	25	Death	NR

NR - not related

PID - patient identification

SIDS - sudden infant death syndrome

Discussion on clinical safety

Review of the solicited and unsolicited adverse events reported in the different studies did not reveal any specific safety concerns with respect to the candidate vaccine, the incidence of local and general symptoms being comparable in the groups who received the candidate and reference vaccines as a mix or separate injection during primary vaccination.

There was no sign of differences between the low thiomersal form of Quintanrix and Tritanrix™-HepB/Hiberix™ in terms of grade 3 symptoms occurring after vaccination. Overall, the incidence of any general symptoms was high in study Hib-091, but similar to that reported in the same population previously (study Hib-081). Temperature and irritability were the most frequently reported general symptoms in both groups in study Hib-091. Although comparison between studies should be made with caution, the incidence of local and general symptoms following vaccination with the reduced thiomersal form of Quintanrix vaccine was within the range of historical controls.

In the booster study Hib-064, symptoms such as pain, fever and irritability/fussiness and loss of appetite were more frequently reported following a booster dose in the candidate vaccine than in the

other vaccines. This has been reflected in section 4.8 of the SPC. The applicant argues that this phenomenon may be due to chance only and that it must be interpreted with caution since such events may be affected by local believes and practices. However it may reflect a real difference, which was "statistically" not significantly different because the number of children in the 5 subgroups of study Hib-064 was too small.

The safety of the candidate DTPw-HBV/Hib 2.5 vaccine when used as a booster has been evaluated by the applicant in several clinical studies, representing 435 vaccine doses administered. Sixty three doses were administered in the Hib-064 study and a total of 370 doses in studies DTPw-HBV/Hib-MenAC-TT-002 and DTPw-HBV/Hib-MenC-TT-003. The applicant has committed to provide the full study reports of studies DTPw-HBV/Hib-MenAC-002 and DTPw-HBV/Hib-MenC-003, including the immunogenic data, as soon as they are available.

The applicant has committed to perform a robust post-marketing surveillance program in Europe/the countries where the vaccine will be marketed to further elucidate the safety of its vaccine.

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.
Viral safety and batch-to-batch consistency has been documented and the relevant tests will be performed according to the agreed specifications.

Non-clinical pharmacology and toxicology

Based on the fact that the candidate vaccine DTPw-HBV/Hib_ads 2.5 $\mu g_{\mu g}$ Quintanrix, can be considered as a new formulation of existing and licensed antigens, no specific non-clinical toxicity studies were done, neither was a detailed study on the immune response induced in animals conducted.

Furthermore the clinical development of the vaccine started, the CPMP "Note for Guidance on non-clinical pharmacological and toxicological testing of vaccines" was not yet adopted. However, data generated during quality control testing of the vaccine allowed to conclude that specific toxicity concerns are not warranted and that the immune response induced by the combined vaccine is similar to the one induced by the two components. The similar immunogenicity and overall acceptable safety profile were further confirmed in clinical studies. These are indeed the more relevant data to be considered in assessing the acceptability of the new DTPw-HBV/Hib_ads 2.5 µg vaccine.

Due to the fact that Quintanrix is composed of Tritanrix HepB and the PRP Hib component of Infanrix hexa and Hiberix, vaccines that have been administered in many children, the fact that no additional pre-clinical data were collected was accepted.

Immunogenicity and Safety

In conclusion, although the immunogenicity of the vaccine was clearly demonstrated for all components, the very limited number of children for whom immunogenicity data are currently available at booster vaccination hampers a reliable conclusion on the persistence of protective antibody following primary vaccination as well as on the protective effect of booster vaccination. The applicant has committed to provide additional booster data by performing longitudinal trials.

The applicant has committed to provide further immunogenicity and safety data, among which a study investigating the immunogenicity and the reactogenicity of this new combination vaccine in HIV infected infants and children, since the vaccine is mainly intended to be used in industrialized as well as in and developing countries where the burden of HIV infection is very high.

Benefit/risk assessment

The vaccine was immunogenic for all antigens in all study populations when administered according to a variety of schedules. In those populations, it was shown to be clinically not inferior in terms of immunogenicity with respect to the licensed vaccines Tritanrix™-HepB and Hiberix™, when given either as two separate injections or administered mixed in one single injection. The overall rate of protection to *H. influenzae* type b following primary vaccination was 99.7%, whereas the rate for diphtheria, tetanus and hepatitis B was 96.3%, 99.9% and 98% respectively. A response to the pertussis component was observed in 99.4% of vaccinees.

The reactogenicity profile of the combined candidate vaccine Quintanrix was comparable with the profile of the Tritanrix™-HepB and Hiberix™ vaccines during primary vaccination. Pain (49%), redness (37%), swelling (33%), fever ≥ 37.5°C (47%), drowsiness (28%), irritability (47%) and loss of appetite (21%) were very common. The candidate vaccine was administered as a booster dose to 435 infants in the second year of life, although the data submitted and assessed were only from 63 infants (study Hib-064). The booster dose is potentially associated with an increased incidence of adverse events such as fever or local reactions when compared with the primary vaccination. However, at booster vaccination, Quintanrix does not seem to demonstrate a higher reactogenicity than other vaccines having a 5 or 10 µg PRP antigen content: in this contextit should be borne in mind that the candidate vaccine contained only 2.5 µg of PRP.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Quintanrix in the treatment of primary immunisation of infants (during the first year of life) against diphtheria, tetanus, pertussis, hepatitis B and invasive disease caused by *Haemophilus influenzae* type b and for booster immunisation of young children during the second year of life was favourable and therefore recommended the granting of the marketing authorisation.