



**EU-RISK MANAGEMENT PLAN FOR HEXAXIM[®]/HEXACIMA[®]/HEXYON[®]
(DIPHTHERIA, TETANUS, PERTUSSIS [ACELLULAR, COMPONENT],
HEPATITIS B [rDNA], POLIOMYELITIS [INACTIVATED] AND
HAEMOPHILUS INFLUENZAE TYPE B CONJUGATE VACCINE
[ADSORBED])**

Risk Management Plan (RMP) Version number	Version 14.0
Data Lock Point (DLP)	17-APR-2025
Date of final sign-off	25-JUN-2025



Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Reclassification of missing information as per Guideline on Good Pharmacovigilance Practices (GVP) Module V - Risk management systems (EMA/838713/2011 Rev. 2) in which the definition of the missing information has been changed and as per periodic benefit-risk evaluation report (PBRER) (DLP: 17-Apr-2025). Risk Management Plan updated with the new module templates (integrated format) as per RMP European Guideline on GVP. Risk Management Plan updated with clinical data on preterm infants vaccinated with DTaP-IPV-HB-PRP-T hexavalent vaccine.
Summary of significant changes in this RMP	Reclassification of missing information. No missing information will be considered important for inclusion in the list of safety concerns (LSCs) in the current RMP and as per PBRER (DLP: 17-Apr-2025). There are no additional risk minimization measures (aRMMs) in place and it is unlikely that further evaluation or studies as part of the pharmacovigilance plan or additional pharmacovigilance activities will be able to further evaluate or characterize them, as per Guideline on GVP Module V - Risk management systems (Rev. 2); except routine pharmacovigilance activities.

aRMM: Additional Risk Minimization Measure; DLP: Data Lock Point; EMA: European Medicines Agency; GVP: Good Pharmacovigilance Practices; LSC: List of Safety Concern; PBRER: Periodic Benefit Risk Evaluation Report; RMP: Risk Management Plan.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	13.0
Approved with procedure	Labelling variation to include information for human immunodeficiency virus (HIV)-exposed infants (A3L44) and persistence of immune response (A3L52) EMEA/H/C/WS1965/G
Date of approval (opinion date)	18-Feb-2021

EMA: European Medicines Agency; HIV: Human Immunodeficiency Virus; RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	 ^a , 
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

TABLE OF CONTENT

TABLE OF CONTENT	3
LIST OF TABLES	5
ABBREVIATIONS	6
PART I: PRODUCT (S) OVERVIEW	8
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	11
PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION	19
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE	22
PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS	30
SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME	30
SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES	33
SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES	34
PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE	37
SV.1 POST-AUTHORIZATION EXPOSURE	37
SV.1.1. Method used to calculate exposure	37
SV.1.2. Exposure	37
PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION	38
SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES	38
PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS	39
SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION	39
SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP	39
SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP	39
SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP	39

SVII.3	DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION.....	45
SVII.3.1.	Presentation of important identified risks and important potential risks.....	45
SVII.3.2.	Presentation of the missing information.....	45
PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS.....		46
PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)		47
III.1	ROUTINE PHARMACOVIGILANCE ACTIVITIES	47
III.2	ADDITIONAL PHARMACOVIGILANCE ACTIVITIES.....	47
III.3	SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES.....	47
PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES		48
PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES).....		49
V.1	ROUTINE RISK MINIMIZATION MEASURES	49
V.2	ADDITIONAL RISK MINIMIZATION MEASURES	49
V.3	SUMMARY OF RISK MINIMIZATION MEASURES	49
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN		50
I.	THE MEDICINE AND WHAT IT IS USED FOR.....	50
II.	RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS.....	51
II.A	LIST OF IMPORTANT RISKS AND MISSING INFORMATION	51
II.B	SUMMARY OF IMPORTANT RISKS.....	51
II.C	POST-AUTHORIZATION DEVELOPMENT PLAN	52
II.C.1	Studies which are conditions of the marketing authorization.....	52
II.C.2	Other studies in post-authorization development plan.....	52
REFERENCES		53
PART VII: ANNEXES.....		65

LIST OF TABLES

Table 1 - RMP version to be assessed as part of this application	2
Table 2 - Other RMP versions under evaluation	2
Table 3 - Details of the currently approved RMP	2
Table 4 - QPPV name and signature	2
Table 5 - Product Overview	8
Table 6 - Epidemiology of tetanus	11
Table 7 - Epidemiology of diphtheria	12
Table 8 - Epidemiology of pertussis	13
Table 9 - Epidemiology of poliomyelitis	15
Table 10 - Epidemiology of hepatitis B	16
Table 11 - Epidemiology of Invasive <i>Haemophilus influenzae</i> type b (Hib) disease	17
Table 12 - Key safety findings from non-clinical studies and relevance to human usage	19
Table 13 - Clinical Development Program for DTaP-IPV-HB-PRP-T (as of DLP)	23
Table 14 - Cumulative exposure based on actual exposure and enrollment estimates	25
Table 15 - Cumulative subject exposure to investigational product from completed primary series studies by age and sex since development international birth date	26
Table 16 - Cumulative subject exposure to investigational product from completed booster phase studies by age and sex since development international birth date	26
Table 17 - Exposure by ethnicity totals ^a	27
Table 18 - Exposure in special population totals	28
Table 19 - Important exclusion criteria in pivotal studies in the development programme	30
Table 20 - Limitations common to all clinical trials	34
Table 21 - Exposure of special populations included or not in clinical trial development programmes	34
Table 22 - Summary of the safety concerns	46
Table 23 - List of important risks and missing information	51

ABBREVIATIONS

AE:	Adverse Event
AEFI:	Adverse Event of Special Interest
AFP:	Acute Flaccid Paralysis
aP:	Acellular Bordetella Pertusis
aRMM:	Additional Risk Minimization Measure
ATC:	Anatomical Therapeutic Chemical
CCDS:	Company Core Data Sheet
CDC:	Centers for Disease Control and Prevention
CDP:	Clinical Development Program
CHB:	Chronic Hepatitis B
CI:	Confidence Interval
CSR:	Clinical Study Report
cVDPV:	Circulating Vaccine Derived Poliovirus
D:	Diphtheria
DIBD:	Developmental International Birth Date
DLP:	Data Lock Point
DNA:	Deoxyribonucleic Acid
DTaP-IPV:	Diphtheria, Tetanus, Pertussis, Acellular Component-Inactivated Poliomyelitis Virus
EEA:	European Economic Area
EMA/EMA:	European Medicines Agency
EPAR:	European Public Assessment Report
EPI:	Expanded Program on Immunization
ESC:	Externally Sponsored Collaboration
ESPID:	European Society for Pediatric Infectious Disease
EU:	European Union
FHA:	Filamentous Haemagglutinin
FU:	Follow-Up
GPEI:	Global Polio Eradication Initiative
GVP:	Good Pharmacovigilance Practices
HBs:	Hepatitis B Surface
HBsAg:	Hepatitis B Surface Antigen
HBV:	Hepatitis B Virus
HCC:	Hepatocellular Carcinoma
HCV:	Hepatitis C Virus
Hib:	Haemophilus influenzae Type b
HIV:	Human Immunodeficiency Virus
IM:	Intramuscular
INN:	International Nonproprietary Name
IP:	Investigational Product
IPV:	Inactivated Poliomyelitis Virus
IU:	International Unit
LSC:	List of Safety Concern

LT:	Long Term
MAH:	Marketing Authorization Holder
MARCO:	Margin Consolidated
MHC:	Major Histocompatibility Complex
MoA:	Months of Age
N:	Total Number of Patient
NIP:	National Immunization Program
OPV:	Oral Polio Vaccine
PBRER:	Periodic Benefit Risk Evaluation Report
PL:	Package Leaflet
PSUR:	Periodic Safety Update Report
PT:	Pertussis Toxin
PTC:	Product Technical Complaint
QPPV:	Qualified Person Responsible for Pharmacovigilance
rDNA:	Recombinant Deoxyribonucleic Acid
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
T:	Tetanus
US:	United States
USA:	United States of America
WHO:	World Health Organization
WPV 1:	Wild Polio Virus 1

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (International Nonproprietary Name [INN] or common name)	Diphtheria, tetanus, pertussis (acellular, component), hepatitis B recombinant deoxyribonucleic acid (rDNA), poliomyelitis (inactivated) and Haemophilus influenzae type b conjugate vaccine (adsorbed). Referred in this document as DTaP-IPV-HB-PRP-T.
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Bacterial and viral vaccines, combined (ATC code: J07CA09)
Marketing Authorization Holder (MAH)	Sanofi Winthrop Industrie 82 Avenue Raspail 94250 Gentilly, France [REDACTED] [REDACTED]
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Hexacima (EU/1/13/828) Hexyon (EU/1/13/829)
Marketing authorization procedure	European Centralized Procedure
Brief description of the product	<u>Chemical class:</u> The hexavalent pediatric vaccine combines <i>diphtheria and tetanus toxoids, acellular pertussis (2-component), inactivated poliomyelitis virus (IPV), recombinant hepatitis B surface (HBs) antigen, and Haemophilus influenzae type b (Hib) polysaccharide conjugated to tetanus protein.</i> The vaccine is a preservative free suspension and is adjuvanted by aluminum hydroxide.
	<u>Summary of mode action:</u> Immunological prophylaxis.
	<u>Important information about its composition:</u> <i>Suspension for injection.</i> <i>Hexaxim/Hexacima/Hexyon is a whitish, cloudy suspension.</i>
Hyperlink to the product information	See Module 1 - Section 1.3.1. summary of product characteristics (SmPC), Labelling and Package Leaflet (PL). SmPC will be updated as per recent clinical data.
Indication(s) in the EEA	<u>Current:</u> <i>Hexacima (DTaP-IPV-HB-PRP-T) is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).</i>
	<u>Proposed:</u> No change

Dosage in the EEA

Current:

Posology

Primary vaccination:

The primary vaccination consists of two doses (with an interval of at least 8 weeks) or three doses (with an interval of at least 4 weeks) in accordance with official recommendations.

All vaccination schedules including the World Health Organization (WHO) Expanded Program on Immunization (EPI) at 6, 10, 14 weeks of age can be used whether or not a dose of hepatitis B vaccine has been given at birth.

Where a dose of hepatitis B vaccine is given at birth:

Hexacima can be used for supplementary doses of hepatitis B vaccine from the age of six weeks. If a second dose of hepatitis B vaccine is required before this age, monovalent hepatitis B vaccine should be used.

Hexacima can be used for a mixed hexavalent/pentavalent/hexavalent combined vaccine immunization schedule in accordance with official recommendations.

Booster vaccination:

After a 2-dose primary vaccination with Hexacima, a booster dose must be given. After a 3-dose primary vaccination with Hexacima, a booster dose should be given.

Booster doses should be given at least 6 months after the last priming dose and in accordance with the official recommendations. As a minimum, a dose of Hib vaccine must be administered.

In addition:

In the absence of hepatitis B vaccination at birth, it is necessary to give a hepatitis B vaccine booster dose. Hexacima can be considered for the booster.

When a hepatitis B vaccine is given at birth, after a 3-dose primary vaccination, Hexacima or a pentavalent DTaP-IPV/Hib vaccine can be administered for the booster.

Hexacima may be used as a booster in individuals who have previously been vaccinated with another hexavalent vaccine or a pentavalent DTaP-IPV/Hib vaccine associated with a monovalent hepatitis B vaccine.

WHO-EPI schedule (6, 10, 14 weeks):

After a WHO-EPI schedule, a booster dose should be given

- As a minimum, a booster dose of polio vaccine should be given.
- In absence of hepatitis B vaccine at birth, a hepatitis B vaccine booster must be given.
- Hexacima can be considered for the booster.

Other paediatric population:

The safety and efficacy of Hexacima in infants less than 6 weeks of age have not been established. No data are available.

No data are available in older children (see sections 4.8 and 5.1).

Method of administration:

Immunization must be carried out by intramuscular (IM) injection. The recommended injection sites are preferably the antero-lateral area of the upper thigh (preferred site) or the deltoid muscle in older children (possibly from 15 months of age).

	<u>Proposed:</u> No change																								
Pharmaceutical form(s) and strength(s)	<u>Current:</u> Suspension for injection in pre-filled syringe or in single-dose vial. One dose^a (0.5 mL) contains: <table> <tr> <td>Diphtheria Toxoid</td><td>not less than 20 IU (30 Lf)^{b, d}</td></tr> <tr> <td>Tetanus Toxoid</td><td>not less than 40 IU (10 Lf)^{c d}</td></tr> <tr> <td>Bordetella pertussis antigens</td><td></td></tr> <tr> <td>Pertussis Toxoid</td><td>25 micrograms</td></tr> <tr> <td>Filamentous Haemagglutinin</td><td>25 micrograms</td></tr> <tr> <td>Poliovirus (Inactivated^e)</td><td></td></tr> <tr> <td>Type 1 (Mahoney)</td><td>29 D antigen units^f</td></tr> <tr> <td>Type 2 (MEF-1)</td><td>7 D antigen units^f</td></tr> <tr> <td>Type 3 (Saukett)</td><td>26 D antigen units^f</td></tr> <tr> <td>Hepatitis B surface antigen^g</td><td>10 micrograms</td></tr> <tr> <td>Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein</td><td>12 micrograms</td></tr> <tr> <td></td><td>22-36 micrograms</td></tr> </table> ^a Adsorbed on aluminium hydroxide, hydrated (0.6 mg Al³⁺) ^b As lower confidence limit (p = 0.95) and not less than 30 international unit (IU) as mean value ^c As lower confidence limit (p= 0.95) ^d Or equivalent activity determined by an immunogenicity evaluation ^e Cultivated on Vero cells ^f These antigen quantities are strictly the same as those previously expressed as 40-8-32 D-antigen units, for virus type 1, 2 and 3 respectively, when measured by another suitable immunochemical method ^g Produced in yeast Hansenula polymorpha cells by recombinant deoxyribonucleic acid (DNA) technology DNA: Deoxyribonucleic Acid; IU: International Unit. The vaccine may contain traces of glutaraldehyde, formaldehyde, neomycin, streptomycin and polymyxin B which are used during the manufacturing process (see SmPC section 4.3). <u>Proposed:</u> No change	Diphtheria Toxoid	not less than 20 IU (30 Lf) ^{b, d}	Tetanus Toxoid	not less than 40 IU (10 Lf) ^{c d}	Bordetella pertussis antigens		Pertussis Toxoid	25 micrograms	Filamentous Haemagglutinin	25 micrograms	Poliovirus (Inactivated ^e)		Type 1 (Mahoney)	29 D antigen units ^f	Type 2 (MEF-1)	7 D antigen units ^f	Type 3 (Saukett)	26 D antigen units ^f	Hepatitis B surface antigen ^g	10 micrograms	Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms		22-36 micrograms
Diphtheria Toxoid	not less than 20 IU (30 Lf) ^{b, d}																								
Tetanus Toxoid	not less than 40 IU (10 Lf) ^{c d}																								
Bordetella pertussis antigens																									
Pertussis Toxoid	25 micrograms																								
Filamentous Haemagglutinin	25 micrograms																								
Poliovirus (Inactivated ^e)																									
Type 1 (Mahoney)	29 D antigen units ^f																								
Type 2 (MEF-1)	7 D antigen units ^f																								
Type 3 (Saukett)	26 D antigen units ^f																								
Hepatitis B surface antigen ^g	10 micrograms																								
Haemophilus influenzae type b polysaccharide (Polyribosylribitol Phosphate) conjugated to Tetanus protein	12 micrograms																								
	22-36 micrograms																								
Is or will the product (be) subject to additional monitoring in the European Union (EU)?	No																								

ATC: Anatomical Therapeutic Chemical; DNA: Deoxyribonucleic Acid; DTaP-IPV: Diphtheria, Tetanus, Pertussis, Acellular Component-Inactivated Poliomyelitis Virus; EEA: European Economic Area; EPI: Expanded Program on Immunization; EU: European Union; HBs: Hepatitis B Surface; Hib: Haemophilus influenzae Type b; IM: Intramuscular; INN: International Nonproprietary Name; IPV: Inactivated Poliomyelitis Virus; IU: International Unit; MAH: Marketing Authorization Holder; PL: Package Leaflet; rDNA: Recombinant Deoxyribonucleic Acid; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics; WHO: World Health Organization.

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

DTaP-IPV-HB-PRP-T vaccine is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

The epidemiology of the diseases are summarized in the following tables:

Table 6 - Epidemiology of tetanus

Indication	Tetanus
Incidence	In spite of the availability of highly effective vaccines, tetanus continues to exert a substantial health burden in the world. Tetanus is now considered rare (often 0-1 case per 100 000) in most developed countries due to improved hygiene and childbirth practices, improved wound care, reduction in exposure to <i>Clostridium tetani</i> spores and improved rates of active immunization over many birth cohorts. ¹ Although in high income countries tetanus is now considered as a rare disease it still poses a significant burden in low income countries. By 2015 it was estimated that most of the non-neonatal tetanus deaths were Sub-Saharan Africa and south Asia. ² Tetanus is a sporadic and relatively uncommon infection in EU/EEA countries. In 2017, the total reported tetanus incidence in the EU was 0.02 per 100 000 population with 70% of cases aged ≥65 years. Most cases were reported in Italy and Poland, and 10 countries reported no cases. ^{3, 4} Tetanus affects all age groups and case fatality rates can be high even where modern intensive care is available. Tetanus in infants and children commonly reflects poor coverage of the national childhood immunization program. ³ In general, the current distribution of tetanus in developed nations reflects incomplete tetanus toxoid coverage, especially in adults, with the predominance of cases occurring in the elderly. ¹ Immunization with tetanus toxoid containing vaccines early in and throughout life has remarkably reduced the number of tetanus infections in industrialized countries. While the worldwide elimination of neonatal tetanus by 1995 (one of the targets of the WHO) has not been achieved, the number of countries in which neonatal tetanus occurs is progressively decreasing. As of June-2020, there were still 12 countries where elimination of maternal and neonatal tetanus had not been achieved. ^{5, 6}
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of infants from 6 weeks of age. In United States (US) and the EU, male: female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. Risk factors for the disease: Elimination of environmental exposure to <i>C. tetani</i> is impossible; however, the health burden of tetanus is almost completely preventable through routine immunization. Acute or chronic wounds and any skin lesion are commonly associated with tetanus risk. No vaccination or under vaccination is a risk factor for tetanus, especially among

Indication	Tetanus
	older adults in resource rich countries. Lack of hygiene and unclean practices around childbirth and newborn care are risk factors for neonatal tetanus.
Main existing treatment options	All people seeking treatment for care of skin wounds or infections should be evaluated for tetanus prophylaxis with an attention to the number of prior vaccines doses as well as the interval since the last dose. By the time a patient with tetanus presents for treatment the purposes of the tetanus therapy are to inactivate the circulating toxin (by giving anti tetanus immune globulin), to prevent further toxin production by eliminating the organism and to give supportive care for the duration of the illness. Intravenous antibiotics should be given to kill <i>C. tetani</i> . Benzodiazepines can be used for sedation and to control the spasms. A neuromuscular blocker may be necessary. Intubation and respiratory support may be needed.
Natural history of the indicated condition in the untreated population including mortality and morbidity	Worldwide annual deaths from tetanus reported by WHO, in 2016, 72 600 estimated deaths in <5 years of age population. ⁷ The case fatality rate is 8-20%. Without hospitalization and intensive care, fatality is almost 100% amongst the oldest and youngest patients. Potential health risks include fatality and trismus.
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

EEA: European Economic Area; EU: European Union; US: United States; WHO: World Health Organization.

Table 7 - Epidemiology of diphtheria

Indication	Diphtheria
Incidence	Active immunization in the pediatric population with diphtheria toxoid-containing vaccines has markedly altered the epidemiology of diphtheria, reducing the disease to extremely low levels (often 0-5 cases per 100 000) in developed countries and many developing countries. ^{8, 9} In 2017, 8,819 cases of diphtheria were reported worldwide, but many more cases likely go unreported. ¹⁰ Following mass immunization campaigns and additional control measures, diphtheria is now largely under control in the WHO Europe region, with less than 100 cases reported per year since 2010. In developed countries, endemic diphtheria has disappeared or become extremely rare, and infrequent cases of imported diphtheria are reported. Some countries have achieved control of diphtheria comparable to highly developed countries, some have observed dramatic falls of the disease but still have sporadic outbreaks, and a small number continue to have evidence of widespread circulation of toxigenic strains.
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of infants from 6 weeks of age. In US and the EU, male: female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. Risk factors for the disease: Humans are the only natural host for <i>Corynebacterium diphtheriae</i> and the existing data strongly suggest that direct spread of toxigenic bacteria from one individual to another is a major factor in large epidemics without specific risk factor. ¹¹ No vaccination or being under-vaccinated is a risk factor for disease as a recent publication showed that worldwide 65% of the cases were unvaccinated, 13% partially vaccinated and 22% received 3 or more doses of a diphtheria toxoid-containing vaccine. ¹⁰

Indication	Diphtheria
Main existing treatment options	Although diphtheria antitoxin is the mainstay of diphtheria therapy, penicillin or alternatively erythromycin should be given to hasten clearance of the organism, prevent transmission and cease further production of diphtheria toxin. Although treatment with penicillin or erythromycin has no apparent effect on the clinical course of the disease, in most instances the organism can no longer be retrieved on culture within one week; subsequent convalescent carriage is thus uncommon. ¹¹
Natural history of the indicated condition in the untreated population including mortality and morbidity	Membranous pharyngitis may cause respiratory obstruction; toxin may cause myocardial paralysis and cardiac failure. ⁹ The overall case-fatality rate for diphtheria is 5%-10%, with higher death rates (up to 20%) among persons younger than 5 and older than 40 years of age. ¹²
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

EU: European Union; US: United States; WHO: World Health Organization.

Table 8 - Epidemiology of pertussis

Indication	Pertussis
Incidence	Worldwide, there are an estimated 24.1 million pertussis cases and 160 700 deaths from pertussis in children younger than 5 years in 2014, with the African region contributing the largest proportions (7.8 million [33%] cases and 92 500 [58%] deaths). A 5.1 million (21%) estimated pertussis cases and 85 900 (53%) estimated deaths were in infants younger than 1 year of age. In 2012, the most recent peak year, Centers for Disease Control and Prevention (CDC) reported 48 277 cases of pertussis in the US. Approximately 80% of cases occur in children less than 5 year of age. ^{13, 14} In the United States of America (USA), the overall pertussis incidence rate among infants <12 months of age was 117.7/100 000 person-years; infants 3 months of age had the highest incidence rate (247.7/100 000 person-years). ¹⁵ In EU/EEA (in 2017), there were 42 242 reported cases of pertussis. Age-specific rates were highest in <1-year-olds (53.9 cases per 100 000 population), followed by 10-14- and 5-9-year-olds. ¹⁶ Reported pertussis incidence must be interpreted with caution due to variations in case definitions and surveillance system performance among countries. Case definitions based on clinical confirmation are used in many countries due to limited access to laboratory services. Pertussis diagnosis in the neonate as well as older children and adults is difficult without laboratory confirmation. Despite a huge variability on the reported incidence between countries, the highest age-specific incidence of pertussis cases, hospitalizations and complications is now reported in infants, aged from 0 to 1 year, and mainly before 3 months of age in each country. Most of these young infants acquire infection from adolescents or adults in their own households, mainly parents (20-55%) and siblings (19-53%). ¹⁷ Large outbreaks of pertussis reported from numerous countries in recent years have shed light on a phenomenon that had gone largely undetected but was present for decade. In fact, after decades of decreasing case reports of pertussis, the US have documented a reversal of trend in 1980 followed by a steady upward trend in reported cases since then. A striking increase was first noted in 2005, and subsequent outbreaks in 2012 have called attention to the phenomenon of resurgence of pertussis. ^{14, 18, 19, 20, 21, 22, 23}

Indication	Pertussis
	This phenomenon has been since then documented in numerous countries in Europe, Latin America, Asia, Africa and in Australia. Research efforts have attempted to identify the root cause of this resurgence. Most reviews of the available evidence have concluded that the resurgence is a heterogeneous phenomenon largely affected by local historical and current vaccination programs, vaccination schedules, compliance therewith, improvements in surveillance systems and diagnosis, and possibly genotypic shifts in the circulating pathogens. 24, 25, 26, 27, 28 Mode of action of the vaccines and waning of vaccine-induced and infection-induced immunity have also been suggested to play a role. 29, 30, 31, 32 In particular, recent models have suggested that the latter factors, along with the end of the vaccine “honeymoon” period may be the driving factors behind the phenomenon of resurgence. 33 In summary, pertussis, although largely preventable by vaccination, still affects many countries in the world, even in countries with high vaccine coverage. The youngest age groups remain the most affected by pertussis infection. 34, 35, 36
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of children from 6 weeks of age. In US and the EU, male: female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. Risk factors for the disease: Humans are the only reservoir for <i>Bordetella pertussis</i>, and chronic carriage is not known to occur. There is no consistent seasonal pattern and pertussis is acquired through transmission of large respiratory droplets generated by coughing or sneezing from infected persons. Transmission by the indirect route occurs extremely rarely if ever. 37
Main existing treatment options	Macrolides are recommended for both therapy and post-exposure chemoprophylaxis of household and other closed contacts, regardless of vaccination status, and for health care workers with a high risk of, or known exposure to pertussis. Prophylaxis reduces, but does not eliminate the risk of pertussis. The administration of macrolides early in the course of illness will reduce the duration and severity of symptoms and lessen the infectivity. 37
Natural history of the indicated condition in the untreated population including mortality and morbidity	Worldwide, there are an estimated 160 700 deaths from pertussis in children younger than 5 years in 2014, with the African region contributing the largest proportions (92 500 [58%] deaths). 13 Minor complications of pertussis include subconjunctival hemorrhages and epistaxis secondary to the paroxysms. Major complications, which are sometimes fatal in infants, are of three types: pulmonary, encephalopathic, and nutritional. 37
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

CDC: Centers for Disease Control and Prevention; EEA: European Economic Area; EU: European Union; US: United States; USA: United States of America.

Table 9 - Epidemiology of poliomyelitis

Indication	Poliomyelitis
Incidence	Since the Global Polio Eradication Initiative (GPEI) was launched in 1988, 4 WHO regions have been certified polio-free: the Americas in 1994, the Western Pacific in 2000, the European region in 2002 and the South-East Asia region in 2014. ^{38, 39, 40, 41} At the start of 2020 three countries remain endemic, Afghanistan, Pakistan and Nigeria. In June 2020 Nigeria was declared as Wild Polio Virus (WPV) free. ⁴² In 2019, 176 WPV cases were reported, all of them type 1 restricted to Afghanistan (n = 29, 16%) and Pakistan (n = 147, 84%). Compared to 2018, there was a significant increase in cases for both countries, 38% for Afghanistan and 11-times in Pakistan. Between January 2018 and March 2020, circulating vaccine-derived poliovirus (cVDPV) was confirmed in 26 countries, 5 countries reported cVDPV1, while 23 countries reported cVDPV2 cases causing 547 Acute Flaccid Paralysis (AFP). cVDPV3 was only reported in Somalia between 2018 and 2019, with 7 AFP cases. ⁴³ Data on polio cases worldwide is accessible at the GPEI website. ⁴⁴
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of children from 6 weeks of age. In US and the EU, male:female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. Risk factors for the disease: Poliomyelitis is transmitted by person-to-person spread through fecal-oral and oral-oral routes or, less frequently, by a common vehicle (eg, water, milk). The period of communicability may be 4 to 8 weeks. Young age, inadequate or lacking vaccination, low socio-economic status and altered immune status are the leading risk factors for acquiring infection and developing paralytic disease. In the presence of infection, IM injections, strenuous exercise, injury and pregnancy have been identified as risk factors for the development of paralytic manifestations. ⁴⁵
Main existing treatment options	No specific treatment exists for poliomyelitis. Supportive care may be indicated.
Natural history of the indicated condition in the untreated population including mortality and morbidity	The case-fatality rates among paralytic cases range from 5% to 10% in children, predominantly associated with bulbar involvement. ⁴⁶ Most people infected with poliovirus have no symptoms. Disease severity increases with increasing age of people infected. ⁴⁷ Twenty-five (25) percent of those infected develop minor symptoms (fever, headache, and sore throat). ⁴⁶ Acute flaccid paralysis of the limbs, often the legs, and commonly resulting in persistent paralysis and deformities is a potential health risk and occurs when the poliovirus enters the central nervous system and replicates in the motor neurons of the spinal cord. It is experienced in <1% of poliovirus infections in children <5 years of age, varying with serotype and age. ⁴⁶ The ratio of paralytic cases to infections was estimated per 100 infections at approximately 0.5 for serotype 1, 0.05 for serotype 2, and 0.08 for serotype 3, based on data from 15 countries. ⁴⁸
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

AFP: Acute Flaccid Paralysis; cVDPV: Circulating Vaccine-Derived Poliovirus; EU: European Union; GPEI: Global Polio Eradication Initiative; IM: Intramuscular; US: United States; WHO: World Health Organization; WPV 1: Wild Polio Virus 1.

Table 10 - Epidemiology of hepatitis B

Indication	Hepatitis B
Incidence	Although precise disease prevalence figures are not available globally, hepatitis B virus (HBV) infection the resulting diseases are thought to be highly prevalent. Based on modeling analyses conducted on year 2000 data, it is estimated that 2 billion people around the world have serologic evidence of HBV infection, 360 million live with chronic HBV infection and 600 000 die each year of HBV related diseases including liver cirrhosis and hepatocellular carcinoma (HCC). ⁴⁹ By the year 2014 it was estimated than around 3.5% of the global population were chronic carriers of Hepatitis B infection (257 million) and caused 887 000 deaths mostly from cirrhosis and HCC. ⁵⁰ The world can be divided into 3 distinct patterns for hepatitis B endemicity based on prevalence of hepatitis B surface antigen (HBsAg) in the general population: high endemicity with prevalence of HBsAg >8%, medium endemicity with prevalence of HBsAg 2 to 7% and low endemicity with prevalence of HBsAg <2%. There is high heterogeneity of Hepatitis prevalence among WHO regions but is the highest in the African (6.1%) and Western Pacific regions (6.2%), and the lowest in the Americas (0.7%). ⁵⁰ The highest prevalence for chronic infection was reported in the Gambia with 36%. ⁵¹ In the highly endemic regions, the majority of hepatitis B infections occur in the perinatal period (>20% of all infections) and early childhood (>60% of all infections), placing those infected at increased risk for chronic disease and its sequelae. It is estimated that approximately 75% of the world's 360 million chronic carriers of hepatitis B live in these hyperendemic regions, where HBsAg positivity rates may reach 35%. ⁵¹ In low endemicity areas, while a high proportion of chronic infection may result from perinatal vertical transmission and early childhood exposures, most incident infections occur at older ages (adults) mostly in well-defined risk groups. ⁴⁹ In the absence of vaccinations, 80-90% of infants infected perinatally or within the first year of life develop chronic hepatitis B (CHB) infections. ⁵² The risk for chronic HBV infection decreases to 30-50% among children exposed before the age of 6 years and to less than 5% if they are exposed as adults. ^{52, 53} HBV infection is thought to cause 55% of all HCC, and in medium to high endemicity regions, 89% of all HCC can be attributed to the virus. ^{54, 55} The lifetime risk of HCC in a chronically infected individual is 10-25%, which is 15-20 times higher than in persons with no HBV infection. ⁵⁶ In 1992, the WHO assembly endorsed the universal immunization of infants against Hepatitis B. ⁵⁰ The introduction of universal infant vaccination against HBV has resulted in dramatic reduction in prevalence of HBsAg carriage, mainly measured among infant, children and adolescents. In the US, the prevalence declined from 1.6% to 0.04%, in China from 9-12% to <1%, in Italy from 13.4% to 0.91% and in South Africa from 8-9% to 0.9%. ^{57, 58, 59, 60} Consequently, parallel reductions were observed in the incidence of acute and fulminant hepatitis. In the US, while the nationwide reduction in acute hepatitis was from 3 to 0.3 per 100 000, Alaska, with higher risk population, saw acute hepatitis incidence reduced from 19 to 0 per 100 000. ^{61, 62} Although HCC is a much longer-term outcome which may take decades to show the effect of universal vaccination, some impact was noted in Taiwan and Alaska. In the former, the incidence of HCC among 6-9 year-olds was reduced from 0.52 to 0.13 per 100 000 after the program was implemented. ⁶³ In the latter, the incidence of HCC dropped from 3 to 0 per 100 000 with no case of HCC reported since 1999. ⁶²

Indication	Hepatitis B
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of healthy infants and children from six weeks of age. In US and the EU, male:female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. <u>Risk factors for the disease:</u> Hepatitis B virus is transmitted by percutaneous (ie, puncture through the skin) or mucosal (ie, direct contact with mucous membranes) exposure to infectious blood or body fluids. Although HBsAg has been detected in multiple body fluids, only serum, saliva, semen, and vaginal fluid have been demonstrated to be infectious. Hepatitis B virus remains infectious for at least 7 days outside the body and can be found in very low concentrations on fomites, even in the absence of visible blood. Primary sources of HBV infection are perinatal exposure from infected mothers, nonsexual person-to-person contact, sexual contact, and percutaneous exposure to blood or infectious body fluids. Hepatitis B virus is not transmitted by air, food, or water. Risk factors for acquisition of infection vary between countries, although all include lack of or inadequate vaccination. Time of HBV infection of the mother during pregnancy is correlated with the risk of transmission to the fetus or neonate. Injection drug use, unsafe sexual practices and certain living or working conditions also contribute to the risk of HBV infection acquisition. Early age and altered immune status seem to be the main factors of risk for development of CHB. ⁶⁴
Main existing treatment options	No specific antiviral treatment is recommended for persons with acute hepatitis B, as about 95% of infected immunocompetent adults recover spontaneously with anti-HBs seroconversion. Therefore, supportive care is the mainstay of therapy. Antiviral treatment may, however, be considered in patients with severe acute or fulminant hepatitis B. In contrast, in patients with CHB, long-term antiviral treatment has been demonstrated to reduce the risk for disease progression and HCC by approximately 50%. ⁶⁴
Natural history of the indicated condition in the untreated population including mortality and morbidity	An estimated 887 000 deaths annually are attributable to hepatitis B-associated cirrhosis and HCC. ⁶⁵ Fulminant hepatitis case-fatality rate is 0.5-1% while the case-fatality rate from cirrhosis or liver cancer in cases of chronic liver disease is 15-25%. ⁶⁶ Potential health risks include fulminant hepatitis, chronic infection, cirrhosis, and HCC. ⁶⁴
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

CHB: Chronic Hepatitis B; EU: European Union; HBsAg: Hepatitis B Surface Antigen; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; US: United States; WHO: World Health Organization.

Table 11 - Epidemiology of Invasive *Haemophilus influenzae* type b (Hib) disease

Indication	Invasive <i>Haemophilus influenzae</i> type b (Hib) disease
Incidence	Before widespread adoption of vaccination against Hib it was a very common cause of meningitis in children. In the year 2000 it was estimated that it caused 8.13 million cases of in children under 5 and 371 000 deaths ^{67, 68} when only 60 countries had included the vaccine in its National Immunization Program (NIP). By 2015, when 192 countries had included the vaccine in its immunization schedule, deaths decreased to 29 500 in under 5 which were only in infants under 24 months of age. The same model calculated overall 975 000 cases of the disease with 340 000 being severe. Of these cases the majority caused

Indication	Invasive <i>Haemophilus influenzae</i> type b (Hib) disease
	pneumonia (934 000) and a small proportion meningitis or non-pneumonia, non-meningitis (31 400 and 10 000 respectively). In unvaccinated populations, invasive Hib is the dominant cause of non-epidemic bacterial meningitis during the first year of life. ⁶⁷ Active immunization first of young children with unconjugated Hib polysaccharide vaccines and later of infants of less than 6 months of age with conjugated Hib polysaccharide vaccines has dramatically decreased the incidence of invasive diseases by almost 100%. Within a few years of the inclusion of Hib vaccine in routine childhood immunization programs in more than 90 countries in all regions of the world invasive Hib disease has been practically eliminated in these regions. The reported incidence has been decreased between <1 to 5/100 000 in children less than five years of age, in particular where a complete vaccination schedule is applied. ⁶⁹ The majority of invasive Hib disease occurs in resource limited settings when Hib conjugate vaccine is not in routine use. ⁷⁰
Prevalence	Not applicable for acute infectious diseases.
Demographics of the population in the in the authorized or proposed indication(s), as applicable	This vaccine is targeting the general population of healthy infants and children from six weeks of age. In US and the EU, male:female ratio at birth in current birth cohorts is 1.05:1.00 and 1.06:1.00, respectively. Risk factors for the disease: Hib is an obligate human pathogen that spreads from person to person via respiratory droplets and direct contact with respiratory secretions. It enters the body via the upper respiratory tract and colonizes the pharyngeal mucosa. People may remain colonized with Hib for up to 6 months without clinical symptoms. Extremes of age represent a risk factor for Hib disease, along with health conditions associated with a compromised immune system. Socio-economic status, as a proxy for various living conditions and hygiene factors has also been identified as a risk factor for Hib disease. ⁷¹ Children that are HIV+ are at higher risk of Hib disease than those that are not (5.9 fold higher 95% confidence interval (CI); 2.7-12.6). ⁷²
Main existing treatment options	Treatment of Hib disease requires early assessment and identification of the illness, administration of appropriate antibiotic therapy, and supportive management of sequelae. Therapy should be based on patterns of antibiotic resistance in the community. Chemoprophylaxis of household contacts is recommended in certain cases because of the occurrence of secondary infections. Antibiotics that are usually used for the treatment of meningitis often do not eliminate Hib from the upper airway; therefore, the index case may require a different antibiotic to eliminate carriage. ⁷¹
Natural history of the indicated condition in the untreated population including mortality and morbidity	Even with prompt and adequate antibiotic treatment, the case fatality rate of patients with Hib meningitis can reach 20%. Where medical resources are limited, fatality rates for Hib meningitis are typically higher, and severe neurological sequelae are frequently observed in survivors (in up to 30 to 40%). ⁶⁸ Potential health risks include meningitis, pneumonia, bacteremia, septic arthritis, osteomyelitis, pericarditis, cellulitis, epiglottitis, with fatality potentially resulting from some of the most severe complications of Hib invasive disease. ⁷¹
Important co-morbidities	Not applicable because this is a preventive vaccine meant for the general healthy population according to local immunization recommendations.

CI: Confidence Interval; EU: European Union; Hib: *Haemophilus influenzae* Type b; HIV: Human Immunodeficiency Virus; NIP: National Immunization Program; US: United States.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

During the development of DTaP-IPV-HB-PRP-T vaccine, several non-clinical safety studies have been conducted and their main results are summarized below. The non-clinical safety program for diphtheria, tetanus, pertussis (acellular component), hepatitis B (rDNA), poliomyelitis (inactivated) and Hib conjugate vaccine (adsorbed) was comprised of three repeat dose toxicity or local tolerance studies performed in rabbits. Their key findings are summarized in Table 12 below.

The key non-clinical findings are presented in the following table.

Table 12 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity • Repeat-dose toxicity studies: The vaccine induced persistent local inflammation [REDACTED], associated with transient systemic effects (increase in neutrophils), which is an expected finding following administration of a combined vaccine adjuvanted with aluminum hydroxide. • Local tolerance studies: During Phase II of the clinical development, an investigative (for cause) local tolerance study (AA33910) was conducted in rabbits to follow up some cutaneous lesions (a few ulcerations noted at injection sites) observed during a routine batch release test performed in guinea pigs [REDACTED]. There was no evidence of increased local reactions in rabbits after four IM administrations with the vaccine batches that had previously shown ulceration in the guinea pig. The batches tested in this local tolerance study (AA33910) were used for clinical trials and had a comparable safety profile to previously tested batches. Complementary investigations were conducted in guinea-pigs to explain occurrence of ulcerations, and concluded that the lesions were operator-dependent. No observation of ulceration has ever been reported in human clinical trials to date.	Inflammatory reactions at the injection site were expected in humans following vaccination with DTaP-IPV-HB-PRP-T and this was evaluated in the clinical setting. The results obtained in rabbits and subsequently in humans demonstrated that the lesions observed in guinea pigs were not reproduced in humans after an IM vaccination with DTaP-IPV-HB-PRP-T. The investigations showed that intradermal administration of a small quantity (0.1 mL) of the vaccine resulted in the few ulcerations observed at the injection sites in all guinea pigs and thus suggested that the most plausible explanation for the lesions noted originally were likely to be due to some of/or all the product being administered to some guinea-pigs by the intradermal route, in error. DTaP-IPV-HB-PRP-T is indicated for an IM vaccination. Administering via intradermal route is technically difficult and unlikely to occur in the clinical setting.
Reproductive and developmental toxicity	Not applicable as the target population is infants and toddlers only.
Safety pharmacology Consistent with usual vaccine development programs, no safety pharmacology studies were conducted, and there were no significant findings in the toxicology studies that required further investigation of the safety pharmacology of DTaP-IPV-HB-PRP-T	No specific risk anticipated.
Other toxicity-related information or data	Not applicable

IM: Intramuscular.

CONCLUSIONS ON NON-CLINICAL SAFETY DATA

According to the data reported during clinical studies, injection site reactions are very common for reactions such as erythema, swelling and pain, are common for induration, uncommon for nodule and are rare for large injection site reactions (>50 mm), including extensive limb swelling from the injection site beyond one or both joints. These large injection site reactions start within 24-72 hours after vaccination, may be associated with erythema, warmth, tenderness or pain at the injection site, and resolve spontaneously within 3-5 days. The risk appears to be dependent on the number of prior doses of acellular pertussis containing vaccine, with a greater risk following the 4th and 5th doses.

During Phase II of the clinical development, an investigative local tolerance study was conducted in rabbits (AA33910) to follow up some cutaneous lesions (a few ulcerations observed at injection sites) observed during a routine batch release test [REDACTED] in guinea pigs. There was no evidence of increased local reactions in rabbits after IM administration with the vaccine batches that had previously shown ulceration in the guinea pig. The batches tested in this study (AA33910) were used for clinical trials and had a comparable safety profile to previously tested batches. No observation of ulceration has ever been reported in human clinical trials to date. The results generated in the rabbit and subsequently in humans demonstrated that the lesions observed in guinea pigs were not reproduced in humans after an IM vaccination with DTaP-IPV-HB-PRP-T. Complementary investigations were conducted in guinea-pigs to explain the occurrence of ulcerations, and concluded that the lesions were operator-dependent. The investigations showed that intradermal administration of a small quantity (0.1 mL) of the vaccine resulted in the consecutive ulceration in all guinea pigs, and thus suggest the most plausible explanation for the lesions noted originally were likely to be due to some of/or all the products being administered to some guinea-pigs by the intradermal route, in error. DTaP-IPV-HB-PRP-T is indicated for an IM vaccination. Administering via intradermal route is technically difficult and unlikely to occur in the clinical setting.

[REDACTED]

No safety concerns were raised during the non-clinical safety studies.

Non-clinical safety data are consistent with the clinical safety data and there are no specific concerns identified with DTaP-IPV-HB-PRP-T.

Toxicology evaluation of DTaP-IPV-HB-PRP-T was conducted at different steps of its development and included an evaluation of its local and/or systemic toxicity; no nonclinical safety concerns of unknown significance have been identified.

No additional specific toxicity studies were considered necessary to support the administration of DTaP-IPV-HB-PRP-T in the pediatric population, as the non-clinical safety studies conducted in young adult animals were supportive of the pediatric population.

No safety concerns requiring further non-clinical research have been identified.

[REDACTED]

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

BRIEF OVERVIEW OF DEVELOPMENT

DTaP-IPV-HB-PRP-T is based on a backbone of established diphtheria (D), tetanus (T), acellular *Bordetella pertussis* (aP), IPV, and Hib antigens that are included in the Sanofi AcXim family of vaccines (Tetraxim[®]/Tetravac[®] and Pentaxim[®]/Pentavac[®]).

DTaP-IPV-HB-PRP-T is the latest addition to the AcXim family, adding *Hansenula polymorpha*-derived Hepatitis B virus surface antigen to the established DTap-IPV/PRP-T backbone product (Pentavac/Pentaxim), to produce a fully liquid, ready-to-inject, DTap-IPV-HB-PRP-T vaccine. This vaccine benefits from three decades of experience in the development of complex multivalent pediatric combination vaccines by Sanofi (and its ancestral companies),

Hexaxim is supported by thorough international clinical development initiated in 2004 assessing its safety and immunogenicity in a wide range of settings including:

- Different vaccination schedules commonly used for pediatric combination vaccines.
- Different control vaccines selected according to the standards of care in use in the countries where the studies were conducted.
- Different concomitant vaccines commonly used in pediatric vaccination programs.
- Different countries and populations.

CLINICAL TRIAL EXPOSURE

This section presents estimates of cumulative numbers of subjects, from ongoing or completed trials where DTap-IPV-HB-PRP-T vaccine was the investigational product (IP) under study or development, exposed to the IP, placebo, and/or active comparator(s) since the Developmental International Birth Date (DIBD) of 19 January 2004.

Since the DIBD, a total of 7639 subjects have received at least one dose of DTap-IPV-HB-PRP-T vaccine in the worldwide Clinical Development Program (CDP) including 390 subjects who had at least one dose as part of the ongoing study A3L00057.

The CDP comprised of 21¹ completed studies where DTap-IPV-HB-PRP-T vaccine was the IP, and five completed long-term follow-up studies for the evaluation of the persistence of antibodies:

- Sixteen (16) primary series studies in infant aged >6 weeks at inclusion (A3L02, A3L04, A3L10, A3L11, A3L12, A3L15 [primary series], A3L17, A3L24, A3L31, A3L33, A3L35

¹ The clinical development also included another completed study (A3L16) using a pentavalent vaccine and not the investigational vaccine DTap-IPV-HB-PRP-T (thus not accounted here).

[primary series], A3L38² [primary series], A3L39, A3L43-EXT [primary series] [HXM01C-PS], A3L44 [primary series] and A3L45³).

- Ten (10)⁴ booster studies in toddlers in the second year of life (A3L01, A3L15 [booster step], A3L21, A3L27, A3L22, A3L35 [booster step], A3L38 [booster step], A3L40 [booster step of A3L39], A3L43-EXT [booster step] [HXM01C-B] and A3L44 [booster step]).
- Five (5)⁵ long-term persistence studies (A3L26 [long-term persistence in subjects who participated in A3L15], A3L28 [long-term persistence in subjects who participated in A3L27], A3L47⁶ [persistence in subjects who participated in the study A3L12], A3L49⁷ [long-term persistence in subjects who participated in A3L12], and A3L00052 [long-term persistence in subjects who participated in A3L38]).

Since the last version of the RMP (Version 13.0 dated April 2020), one company sponsored trial is ongoing (A3L00057).

As DTaP-IPV-HB-PRP-T is licensed in more than 110 countries and has been launched in more than 90 countries since 2013, the total number of subjects exposed to the commercially available product (between 63 117 851 to 252 471 403 subjects) far exceeds the total number of subjects exposed during the CDP of this product. Therefore, data from subject exposure to DTaP-IPV-HB-PRP-T vaccine during clinical trials are now largely outnumbered by data from real-world use.

These trials are listed in the table below.

Table 13 - Clinical Development Program for DTaP-IPV-HB-PRP-T (as of DLP)

Trial ID	Phase	Country (ies)	Ethnicity (main)	Vaccination regimen (in months) and Nb of subjects planned to be included (DTaP-IPV-HB-PRP-T arm / Total enrolled)			Trial status (as of DLP)
				Primary series	Booster	LT FU ^a	
A3L01	I	Argentina	Hispanic ^b		16-19 (30/60)		Completed

² A3L38 had a 2 + 1 schedule: The first two doses corresponding to the primary doses (Two-dose primary series schedule at three, five months of age [MoA]) and a booster dose at 11-12 MoA.

³ For A3L45, only third dose received with DTaP-IPV-HB-PRP-T at six MoA in Russia, three-dose primary series with DTaP-IPV-HB-PRP-T vaccine in Poland.

⁴ Studies A3L15, A3L35, A3L38, A3L43-EXT (HXM01C-B) and A3L44 are counted as one study but they had two parts (one assessing primary series and one assessing booster dose).

⁵ In long-term persistence studies, no dose of DTaP-IPV-HB-PRP-T vaccine was administered to the subjects, so they are not accounted in the cumulative subject exposure in [Table 14](#).

⁶ A3L47 describes the persistence of anti-HB antibodies at 12-18 MoA in subjects who previously participated in the study A3L12.

⁷ A3L49 describes the persistence of anti-HB antibodies at nine to ten years of age in subjects who previously participated in the study A3L12.

Trial ID	Phase	Country (ies)	Ethnicity (main)	Vaccination regimen (in months) and Nb of subjects planned to be included (DTaP-IPV-HB-PRP-T arm / Total enrolled)			Trial status (as of DLP)
				Primary series	Booster	LT FU ^a	
A3L02	II	Argentina	Hispanic ^b	2 – 4 – 6 (312/624)			Completed
A3L16 ^c (post A3L02)	II	Argentina	Hispanic ^b		18 (458)		Completed
A3L04	III	Mexico, Peru	Hispanic	2 – 4 – 6 (1422/2133)			Completed
A3L10	III	Turkey	Caucasian	2 – 3 – 4 (155/310)			Completed
A3L22 (post A3L10)	III	Turkey	Caucasian		15 - 18 (252/254)		Completed
A3L11	III	Mexico	Hispanic	2 – 4 – 6 (1022/1189)			Completed
A3L21 (post A3L11)	III	Mexico	Hispanic		15 - 18 (881/881)		Completed
A3L12	III	Thailand	Asian	2 – 4 – 6 (206/412)			Completed
A3L15	III	Republic of South Africa	African	6 – 10 – 14 (380/715)	15 - 18 (348/567)		Completed
A3L26 ^a (post A3L15)	III	Republic of South Africa	African			3.5 years	Completed
A3L17	III	Peru	Hispanic	2 – 4 – 6 (132/266)			Completed
A3L24	III	Colombia, Costa Rica	Hispanic	2 – 4 – 6 (1031/1376)			Completed
A3L27 (post A3L24)	III	Colombia, Costa Rica	Hispanic		12 - 24 (691/1107)		Completed
A3L28 ^a (post A3L27)	III	Colombia, Costa Rica	Hispanic			4.5 years	Completed
A3L31	III	South Korea	Asian	2 – 4 – 6 (155/310)			Completed
A3L33	III	India	Asian	6 – 10 – 14 (177/177)			Completed
A3L35	III	Vietnam	Asian	2 – 3 - 4 (354/354)	16 - 17 (354/354)		Completed
A3L38	III	Finland, Sweden	Caucasian	3 – 5 (277/554)	11 - 12 (277/554)		Completed

Trial ID	Phase	Country (ies)	Ethnicity (main)	Vaccination regimen (in months) and Nb of subjects planned to be included (DTaP-IPV-HB-PRP-T arm / Total enrolled)			Trial status (as of DLP)
				Primary series	Booster	LT FU ^a	
A3L39	III	Ger., Cz Rep., Spain	Caucasian	2 – 3 – 4 (530/795)			Completed
A3L40 (post A3L39)	III	Ger., Cz. Rep., Spain	Caucasian		12 - 18 (530/795)		Completed
A3L43-EXT (HXM01C-PS)	III	Finland	Caucasian	2 – 3 – 4 (350/350)			Completed
A3L43-EXT (HXM01C-B)	III	Finland	Caucasian		12 (312/312)		Completed
A3L44	III	Republic of South Africa	African	6 – 10 – 14 (64/64)	15 - 18 (64/64)		Completed
A3L45	III	Russia, Poland	Caucasian	3 -4 -5 (50/50) 6 (100/100)			Completed
A3L47 ^a (on A3L12 cohort)	III	Thailand	Asian			18 months	Completed
A3L49 ^a (on A3L12 cohort)	III	Thailand	Asian			9 years	Completed
A3L00052 (on A3L38 cohort)	IV	Finland	Caucasian			6 years	Completed
A3L00057	IV	Italy Finland		3-5	12		Ongoing

^a Long term follow-up for antibody persistence. No vaccine administration.

^b Ethnicity information was not collected.

^c Pentaxim used in this trial as a booster on Hexaxim-primed subjects.

DLP: Data Lock Point; FU: Follow-Up; LT: Long Term; RMP: Risk Management Plan.

Based on the fact that DTaP-IPV-HB-PRP-T is only indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Hib, the following table provides the total exposure to DTaP-IPV-HB-PRP-T by dose of the Primary series (and for all doses of the Primary series) or for the booster and for the complete Primary series and Booster series when evaluated.

Table 14 - Cumulative exposure based on actual exposure and enrollment estimates

Vaccine	Number of subjects ^a
Investigational drug DTaP-IPV-HB-PRP-T	

Vaccine	Number of subjects ^a
At least one primary vaccine injection received	7097
At least one booster dose received	3790
Received at least one dose in primary series or booster	7639
Other comparators	
Hexavac®	30
Pentaxim®/Pentavac® + Engerix B® OR Pentaxim/Pentavac + Euvax B® or Pentaxim/Pentavac ^b	887
Tritanrix®-HB/Hib + OPV	710
Infanrix Hexa®	1802
Combact-Hib® + Engerix B + OPV	242
Received at least one dose of comparator vaccine in primary series or booster	3671

Included in this table are subjects who had at least one injection between 19-Jan-2004 and 17-Apr-2025.

a Number of subjects who received at least one dose in the primary series or booster phase. When treatment assignment is blinded, numbers of subjects can be estimated based on the randomization scheme. Therefore, number of subjects would be actual number of subjects from completed and open-label studies, and estimated numbers based on actual enrollment and allocation ratio from ongoing blinded studies.

b Included in the count 265 subjects from A3L39 study who belong to the Hexa/Penta/Hexa group. Those subjects are also included in the count of subjects who received at least one dose of DTaP-IPV-HB-PRP-T vaccine.

HB: Hepatitis B; Hib: *Haemophilus influenza* Type b; OPV: Oral Polio Vaccine.

The characteristics (gender) of clinical trial population exposed to DTaP-IPV-HB-PRP-T according to age considered here as infants (primary series) and toddlers (booster) is presented below.

Table 15 - Cumulative subject exposure to investigational product from completed primary series studies by age and sex since development international birth date

Treatment Group	Age Range	Number of subjects ^a		
		Male	Female	Total
DTaP-IPV-HB-PRP-T Combined Vaccine	Dose 1 = 1.3 to 7.0 months	3380	3100	6480
	Dose 2 = 2.2 to 6.5 months	3142	2897	6039
	Dose 3 = 3.1 to 9.3 months	3158	2910	6068

a Included in this table are subjects who had at least one injection of DTaP-IPV-HB-PRP-T combined vaccine between 19-Jan-2004 and 17-Apr-2025.

A3L39: For subjects from Germany, the birth date was not collected.

A3L45: For subjects included in Russia, the first dose received as part of the study is considered as Dose 3.

Table 16 - Cumulative subject exposure to investigational product from completed booster phase studies by age and sex since development international birth date

Treatment Group	Age Range	Number of subjects ^a		
		Male	Female	Total

[REDACTED]

		Number of subjects ^a		
DTaP-IPV-HB-PRP-T Combined Vaccine	Booster dose = 10.5 to 23.7 months	1702	1612	3314

a Included in this table are subjects who had at least one injection of DTaP-IPV-HB-PRP-T combined vaccine between 19-Jan-2004 and 17-Apr-2025.

A3L40: For subjects from Germany, the birthdate was not collected.

Ethnicity origin was collected on subjects in all clinical trials, with exception of the studies A3L01, A3L02, A3L16, A3L31, A3L33, A3L35 and A3L45. Three of the trials, A3L01, A3L02 and A3L16, were performed in Argentina where the population was expected to be mainly of Hispanic ethnicity. Overall ethnicity data were obtained from 6012 subjects which represent 83.7% of the vaccine exposed population.

The ethnic origin of subjects included in the integrated safety analysis of the completed clinical trials is shown below.

Table 17 - Exposure by ethnicity totals^a

Ethnic origin	Person n (%)	Person time
American Indian or Alaska native	4 (0.1%)	Not applicable
Asian	210 (2.9%)	
Black	515 (7.1%)	
Black / African American	4 (0.1%)	
Caucasian	1379 (19.0%)	
Hispanic	3857 (53.2%)	
Other	43 (0.5%)	
Unknown	1237 (17.1%)	
Total	7249	

a Ethnicity origin was collected on subjects in all clinical trials, with exception of the studies A3L01, A3L02, A3L16, A3L31, A3L33, A3L35 (Primary), and A3L45.

n: Number of Patient.

DTaP-IPV-HB-PRP-T has not been studied in infants under 6 weeks or over 23.7 months of age (maximum age documented during clinical trials). DTaP-IPV-HB-PRP-T has not been administered in children older than 24 months, adolescents, adults, elderly subjects, pregnant or lactating women.

In addition, DTaP-IPV-HB-PRP-T has not been studied in infants or toddlers with renal and cardiac impairment (exclusion criteria for all studies).

In addition, the MAH has been aware of one retrospective observational study designed to obtain safety data from a preterm population vaccinated with DTaP-IPV-HB-PRP-T. This Investigator-sponsored observational study assessed the occurrence of cardio-respiratory events following the first vaccination with DTaP-IPV-HB-PRP-T in extreme preterm infants hospitalized in the neonatology department [REDACTED].

[REDACTED]

The data obtained from the [REDACTED] cohort (unpublished) are provided in [Appendix 9] of the RMP [Part VII]. The MAH does not have any additional and new information regarding this study. The study has not been communicated in the public domain according to MAH knowledge.

The MAH has supported data generation related to the use of Hexaxim in premature infants through two independent clinical studies.

- Study A3L00053: An Externally Sponsored Collaboration (ESC) [REDACTED] to obtain data from preterm and term infants population vaccinated with DTaP-IPV-HB-PRP-T (primary series at 2-3-4 months and booster dose at 13 months for preterm infants or 15 months for term infants).

The study primary objective was to evaluate immune response to the hexavalent vaccine in preterm or term infants born to women vaccinated or not with Tdap vaccine during pregnancy. There are no safety endpoints in this study. The initial part of the study has been completed; the study report is provided in [Appendix 10] and the study has been published ⁷³. In this study, the immune response to primary vaccination was similar in preterm and term infants for all antigens except hepatitis B and PRP, for which the response was similar post-booster in term and preterm infants, suggesting adequate priming after the 3-dose primary schedule. These data support the use of Hexaxim as primary and booster vaccination in preterm infants.

This study has been extended to evaluate the persistence of the humoral immune response (at three years and five years of age) in both term and preterm born infants after primary vaccination with DTaP-IPV-HB-PRP-T vaccine. This long-term follow-up part of the study is still ongoing; the study report is planned for June 2025. Results of this study were presented as e-poster discussion at European Society for Pediatric Infectious Disease (ESPID) (26 May to 30 May, Abstract 2344).

- Study A3L00056: An ESC sponsored by Fundacion Instituto Hispalense de Pediatria (EudraCT: 2018-004581-34) entitled “An open-label Phase IV trial to evaluate the immunogenicity and safety of diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and Hib (DTaP-IPV-HB-PRP-T) conjugate vaccine (adsorbed) in preterm infants”. There were no significant safety findings from this study, the vaccine was well tolerated, no related serious adverse events nor cases of apnoea were reported. The study is still ongoing at the time of the DLP of this report; the clinical study report (CSR) is planned for June 2025. Results of this study were presented as e-Poster discussion at ESPID (26 May 2025 to 30 May 2025, Abstract 335).

Table 18 - Exposure in special population totals

Populations	Person n (%)	Person time
Pregnant women	0	Not applicable
Lactating women	0	
Renal impairment	0	
Hepatic impairment	0	
Cardiac impairment	0	
Immuno-compromised	0	

Populations	Person n (%)	Person time
Sup populations with genetic polymorphism	0	
Totals	0	

n: Number of Patient.

In addition, there were 3 MAH-sponsored clinical trials where DTaP-IPV-HB-PRP-T vaccine was concomitantly administered with IP of the study.

- MET57 ⁷⁴:** Immunogenicity and safety of an investigational quadrivalent meningococcal conjugate vaccine administered concomitantly with other pediatric vaccines in healthy toddlers.
 - Hexaxim immunogenicity profile was comparable when administered alone or concomitantly with MenACYW conjugate vaccine.
 - MenACYW conjugate vaccine immunogenicity profile was comparable when administered alone or concomitantly with Hexaxim.
 - The safety profile of MenACYW conjugate vaccine when administered alone or concomitantly with licensed pediatric vaccine (s) (MMR +V, DTaP-IPV-HB-Hib, or PCV13), and that of these licensed pediatric vaccines when administered alone or concomitantly with MenACYW conjugate vaccine were generally comparable. No safety concern has been observed during this study
- MET33:** Safety and immunogenicity of a 3-dose schedule of an investigational quadrivalent meningococcal conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers. The CSR was completed on 29 August 2023.
 - Hexaxim immunogenicity profile was comparable when administered alone or concomitantly with MenACYW conjugate vaccine or Menveo following primary series and booster.
 - The safety profile of Hexaxim, whether co-administered with MenACYW conjugate vaccine (MenQuadfi[®]) or with Menveo was similar.
- MET58:** Immunogenicity and safety study of an investigational quadrivalent meningococcal conjugate vaccine when administered concomitantly with routine pediatric vaccines in healthy infants and toddlers in Europe (Czech Republic, Romania, Sweden, Finland, Italy and Spain). The CSR was completed on 07 February 2025.
 - High immune responses were observed for the hexavalent vaccine whether co-administered with MenACYW conjugate vaccine (MenQuadfi) or with Nimenrix[®], and whether given with PCV13 or PCV10.
 - The safety profile of the hexavalent vaccine whether co-administered with MenACYW conjugate vaccine (MenQuadfi) or with Nimenrix was similar.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

A number of exclusion criteria have been used across all clinical trials during clinical development.

By definition, and by design, all routine pre-licensure Phase I to Phase III clinical trials for vaccines targeted to be used routinely in infants and toddlers are done in healthy subjects. Therefore, the clinical trials considered in this document have all consisted of populations where several exclusion criteria have been applied.

In addition, all medical conditions having a potential impact on the performance of the product, particularly its Benefit/Risk ratio, have been used to define exclusion criteria. They were mainly aiming at excluding all subjects susceptible to develop sub-optimal immune responses to the vaccine.

As with any vaccines, some of the exclusion criteria were considered as temporary or as definitive contraindications for trial enrollment. They are listed in [Table 19](#) below.

Table 19 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Known systemic hypersensitivity to any of the vaccine components or any comparator/co-administered vaccine component, or history of a life-threatening reaction to the trial vaccine or a vaccine containing the same substances	DTaP-IPV-HB-PRP-T should not be administered to anyone with a history of severe allergic reaction to any component of the vaccine or to any pertussis-containing vaccine, or to a vaccine containing the same components or constituents. 75,76 Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following administration of the vaccine.	No	Severe allergic reaction (eg, anaphylaxis) to any component of the vaccine has been and will remain a contraindication for the vaccine.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
History of severe reaction after administration of pertussis containing vaccine, such as encephalopathy	DTaP-IPV-HB-PRP-T vaccine should not be administered to anyone having an evolving encephalopathy. Development of encephalopathy of unknown aetiology within 7 days of administration of a dose of any vaccine containing pertussis antigens (whole cell or acellular pertussis vaccines) has been and will remain a contraindication for the vaccine. 75,76 In these circumstances pertussis vaccination should be discontinued and the vaccination course should be continued with diphtheria, tetanus, hepatitis B, poliomyelitis and Hib vaccines.	No	Evolving encephalopathy is a contraindication to vaccination. Encephalopathy within 7 days of a previous dose of pertussis containing vaccine not attributable to another identifiable cause is a contraindication to vaccination.
History of seizures	Pertussis vaccine should not be administered to individuals with progressive neurologic disorder, uncontrolled epilepsy, or progressive encephalopathy conditions until the treatment regimen has been established, the condition has stabilized and the benefit clearly outweighs the risk. 75	No	Convulsions with or without fever, occurring within 3 days of vaccination will remain a precaution for the vaccine.
For primary series trials, infant born premature (<37 weeks) and with a birth weight <2.5 kg	Standard criterion for investigational clinical trials of new vaccines and drugs.	No	Although it was considered missing information up to RMP v13.0, based on the overall data generated from most recent trials and postmarketing experience, this population is no longer included as missing information.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	Lower immune response may be observed in premature infants in relation with immaturity of the immune system. The risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. 77		
Congenital or acquired immunodeficiency; or immunosuppressive therapy such as long-term systemic corticosteroid therapy	Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.	No	Although it was considered missing information up to RMP v13.0, based on the overall data generated from most recent trials and postmarketing experience, this population is no longer included as missing information.
History of severe reaction after administration of pertussis containing vaccine, such as high fever, inconsolable crying, hypotonic hyporesponsive episode or seizures with or without fever	Antipyretic may prevent fever, thereby preventing febrile convulsions; however, the preventive administration of antipyretic is not routinely recommended in the clinical trials.	No	If any of the following events are known to have occurred in temporal relation to receipt of pertussis-containing vaccine, the decision to give further doses of pertussis-containing vaccine should be carefully considered: 75,76 • Temperature of $\geq 40^{\circ}\text{C}$ within 48 hours not due to another identifiable cause. • Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours of vaccination. • Persistent, inconsolable crying lasting ≥ 3 hours, occurring within 48 hours of vaccination. • Convulsions with or without fever, occurring within 3 days of vaccination. Antipyretic may prevent fever, thereby preventing febrile convulsions. Hypotonic hyporesponsive episode has no long-term sequelae.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Known thrombocytopenia, coagulopathy or bleeding disorder contraindicating IM vaccination	Applies to risks associated with any IM injections: bleeding may occur following an IM administration in such subjects.	No	Generic criterion which should be considered and assessed on a case-by-case basis, per country-specific recommendations for medical practice.
Acute disease or chronic illness at a stage that could interfere with trial conduct or completion, including cardiac or renal disorders, congenital defects	In the opinion of the investigator, is at a stage where it might interfere with trial conduct or completion. In chronic renal failure subjects, an impaired hepatitis B response might be observed.	No	Exclusion criterion associated with the operational aspects of inclusion and follow-up as part of a prospective clinical trial. Benefit of vaccination should be evaluated on a case by case basis. Administration of additional doses of hepatitis B vaccine should be considered according to the antibody level against hepatitis B virus surface antigen (anti-HBsAg).
Febrile illness at the time of inclusion	Temporary exclusion criterion to collect the most accurate safety data.	No	Immunization should be postponed in individuals suffering from moderate to severe acute febrile illness or infection. The presence of a minor infection and/or low grade fever should not result in the deferral of vaccination. 75

HBsAg: Hepatitis B Surface Antigen; IM: Intramuscular; RMP: Risk Management Plan.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Vaccine clinical trial development programs are likely to detect the classical expected adverse reactions due to this class of vaccines, with the caveat that due to the limited number of subjects enrolled, the sensitivity of these programs will be restricted to a certain level of adverse event (AE) incidence. In that context, the classical “*rule of three*” [78](#) is of interest to estimate the expected maximal incidence of any given adverse event of special interest (AEFI) in the absence of its occurrence during the clinical trial development program.

Based on the number of subjects exposed to DTaP-IPV-HB-PRP-T (7249 for completed studies), the duration of subject exposure, and the total number of product doses administered (22 380), no particular limitation of adverse drug reaction detection can be proposed for the DTaP-IPV-HB-PRP-T CDP. This CDP has accumulated enough subjects to predict that the incidence for any AE has 95% probability to occur with a maximum level of 3 per 7249 subjects (or 0.041% or 41 for 100 000 vaccinated subjects) or 3 per 22 380 injections (or 0.013% or 13 for 100 000 injections).

Table 20 - Limitations common to all clinical trials

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	Not evaluable during the clinical program: only 7249 subjects received DTaP-IPV-HB-PRP-T.	The overall exposed group (N = 7249) provides a probability of 95% that any unobserved AEs has a maximum true incidence of 0.041%.
Due to prolonged exposure	Not applicable	Not applicable
Due to cumulative effects	Not applicable	Not applicable
Which have a long latency	Not expected with an inactivated vaccine of this class	Not applicable

AE: Adverse Event; N: Total Number of Patient.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The current database accumulated with DTaP-IPV-HB-PRP-T and presented in this document does not raise any concern about major limitations in terms of populations not studied, which may in turn constitute an important risk to the general target population.

The key clinically-relevant missing information is listed in [Table 21](#) below.

Table 21 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Infants/ Toddlers/ Children/ Adolescents	By design, the clinical trials for DTaP-IPV-HB-PRP-T were carried out in infants and toddlers. Since DTaP-IPV-HB-PRP-T is a vaccine targeting exclusively infants and toddlers, it has not been evaluated in subjects older than 24 months and in neonates (birth to 27 days). However, the limited postmarketing experience in children >2 years of age up to 6 years of age did not evidence any safety issues. The most frequently reported adverse events in this population were fever and injection site reactions, consistent with those reported in infants <2 years old. 79
Premature infants	Several immunization guidelines and recommendations specifically state that all pre-term infants, regardless of their gestational ages, should be vaccinated with routine paediatric vaccines following the same schedule as that used for term infants and in accordance with their chronological ages. 75, 80, 81, 82, 83, 84 On-time vaccination is particularly important for pre-term infants as they do present an increased risk for several vaccine preventable diseases, including pertussis and invasive diseases caused by Hib. 85, 86, 87, 88 Many studies with tetravalent, pentavalent and hexavalent combination vaccines against diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B and invasive diseases caused by Hib have documented the safety and immunogenicity of these vaccines when administered to pre-term infants during their first year of life. 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102 It is known that extreme preterm infants (born at less than 28 weeks of gestation) may be at risk for cardio-respiratory apnoea given the presence of respiratory

Type of special population	Exposure
	immaturity. This concern has led in many countries to recommend cardio-respiratory monitoring for 48-72 hours following the first dose of the primary immunization series. 80, 83, 84, 93, 97 Clinical trial data published to date show that when such vaccines are given to pre-term infants they are safe with no particular increase of incidence of cardio-respiratory events. 93, 97 In addition, these trials also show that the immune responses to the antigens contained in these vaccines are generally similar to those of the overall study population, with occasional lower immune responses observed for some antigens 89, 90, 91, 92, 96 for which the clinical interpretation is unknown. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed. In particular, a study of DTaP-IPV vaccine (Tetravac/Tetraxim), the predecessor of DTaP-IPV-HB-PRP-T, administered to prematurely born infants using the three dose primary schedule, showed good immunogenicity profile for the pertussis antigens (Pertussis Toxin [PT] and Filamentous Haemagglutinin [FHA]), and persistence of immunity 1 year after vaccination. 94, 95 In recently completed prospective study in Belgium most of 105 preterm infants vaccinated with DTaP-IPV-HB-PRP-T were seroprotected against diphtheria, tetanus, poliomyelitis types 1, 2 and 3, Hib invasive diseases and hepatitis B after primary and booster vaccinations. Preterm infants included into the study responded as well as term infants in terms of anti-PT and anti-FHA antibody concentrations. Study report is provided in [Appendix 10]. An ESC phase IV study with the aim to evaluate the immunogenicity and safety of DTaP-IPV-HB-PRP-T vaccine in preterm infants (including extremely preterm infants) in Spain demonstrated that DTaP-IPV-HB PRP-T vaccine is immunogenic and well tolerated in preterm infants. 103 No cases of apnoea were reported as related in this clinical study, conducted in pre-term infants. For DTaP-IPV-HB-PRP-T, the recommendation for cardio-respiratory monitoring is already included in its Summary of Products Characteristics (Section 4.4). In addition, "Apnoea in very premature infants" is also listed as a potential risk and, as such, is specifically monitored by the MAH through the routine pharmacovigilance activities, with no safety concern observed since the first launch of the product (Jun-2013).
Elderly	By design, since DTaP-IPV-HB-PRP-T vaccine is a vaccine targeting exclusively infants and toddlers, it has not been evaluated in subjects older than 24 months.
Pregnant or breast feeding women	By design, since DTaP-IPV-HB-PRP-T vaccine is a vaccine targeting exclusively infants and toddlers, it has not been evaluated in pregnant women.
Patients with hepatic impairment	DTaP-IPV-HB-PRP-T has not been evaluated in infants and toddlers with hepatic impairment. Considering our knowledge of vaccines to date, no safety concerns are expected in this population.
Patients with renal impairment	DTaP-IPV-HB-PRP-T has not been evaluated in infants and toddlers with renal impairment. Considering our knowledge of vaccines to date, no safety concerns are expected in this population.
Special groups/ Patients with relevant comorbidity	DTaP-IPV-HB-PRP-T has not been evaluated in infants and toddlers with other morbidities. By design, and similar to all vaccines intended to be administered intra-muscularly, DTaP-IPV-HB-PRP-T has not been studied in

Type of special population	Exposure
	immunocompromised individuals (secondary to underlying pathologies or iatrogenic immuno-suppression), in subjects with bleeding disorders contra-indicating IM administration, in subjects with severe chronic illness, including cardiac and renal impairments, in subjects with a history of seizures, or severe neurological disorder after pertussis containing vaccine, in subjects having a personal history, or born from mothers with HBV or hepatitis C virus (HCV) seropositivity, as they do constitute classical temporary or definitive contraindication in vaccine trials.
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Not applicable as every vaccine trial for a preventative vaccine is done on healthy subjects.
Sub-population carrying known and relevant polymorphisms	Immune responses to vaccines are under the control of a multitude of genes, and very few studies have started to decipher the role of certain gene variants within the major histocompatibility complex (MHC) region, or of certain variants within the genes encoding for cytokines and cytokines receptors. 104, 105 In that context, no particular genetic profile has been so far identified fully explaining the variability of the responses against the antigens contained in DTaP-IPV-HB-PRP-T. No clinically-relevant and more importantly no practically-usable pharmacogenetic polymorphism marker has been identified so far for the DTaP-IPV-HB-PRP-T vaccine.
Populations with relevant different ethnic origin	Clinical trials with DTaP-IPV-HB-PRP-T have been conducted in infants and toddlers representing a large number of ethnicities (see Part II SIII). The results observed across ethnicities do not provide evidence of clinically-relevant differences across ethnicities both in terms of the safety and immunogenicity of the product.

FHA: Filamentous Haemagglutinin; HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; Hib: Haemophilus influenzae Type b; IM: Intramuscular; MAH: Marketing Authorization Holder; MHC: Major Histocompatibility Complex; PT: Pertussis Toxin.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1. Method used to calculate exposure

The MAH is currently utilizing the Margin Consolidated (MARCO) application for reporting of sales data from postmarketing experience. Vaccine distribution data are retrieved from MARCO for periods from January 2021. For older products, the data for period 1993-2020 is taken from historical database Sales and Margin and consolidated with data from MARCO into a single table.

As compared to historical extractions run before January 2025 using Sales and Margin, the data for period 2021-2024 is now taken from MARCO, which may result in variations of doses distributed due to differences across both systems.

In addition, intermediate products (not corresponding to finished goods and therefore not reflecting patient exposure) have now been excluded from the methodology of extractions.

Sales data is collected monthly, as a result, the data may not correspond precisely to the current reporting interval.

Sales figures for the interval period were received for the period. Exposure from the cumulative experience is available from 01 June 2013⁸ through 30 April 2025.

SV.1.2. Exposure

Assuming that vaccines received three doses in primary vaccination at an interval of 1-2 months and one booster dose within the second year of life, in accordance with the recommended schedule in the company core data sheet (CCDS)⁹, the estimated number of patients who received DTaP-IPV-HB-PRP-T from 01 June 2013 (first distribution of doses on the market) through 30 April 2025 is between 63 117 851 (considering 4 doses maximum per subject during one year period) and 252 471 403 (considering 1 dose per subject).

Post-authorization use in populations not studied in clinical trials

No relevant safety information regarding post-authorization use in special populations has become available since the initial market authorization.

⁸ No data retrieved prior to 01 June 2013.

⁹ Local schedules may vary from one country to another.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

The potential for misuse for illegal purposes is very low given the nature of the product. The vaccine is used by healthcare professionals only; this limits the risk of illegal use.

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Risk Management Plan version 2.0 included no additional pharmacovigilance activities and no aRMMs. Therefore, in line with GVP Module V Rev. 2 and PBRER (DLP 17 April 2025), no safety concerns are included in the present RMP version 14.0 submission.

The missing information are reclassified based on:

- Good Pharmacovigilance Practices Module V Rev. 2 guideline (2017), the MAH has applied the principle that a safety concern should be presented within the RMP when it warrants further evaluation as part of the pharmacovigilance plan or additional risk minimization activities.
- Concepts previously classified as “missing information” for which the gap in knowledge is not considered clinically significant (no suspicion of safety concern, with no plans for additional pharmacovigilance activities), were removed from missing information in LSC (“Premature infants”; “Immunocompromised individuals (from disease or treatment)”; and “Duration of protection with acellular pertussis vaccines”).
- Based on definition of GVP Module V Rev. 2 guideline, missing information is not considered as important for inclusion in the LSCs in current EU-RMP.
- The risks do not impact the benefit-risk balance of the product. There are no aRMMs and it is unlikely that further studies or additional pharmacovigilance activities will be able to further evaluate or characterize the risks.

- Clinical study (study A3L00056) providing immunogenicity and safety data with DTaP-IPV-HB-PRP-T vaccine in preterm infants: the vaccine is immunogenic and well tolerated in preterm infants. No cases of apnoea were reported as related in this ESC.
- Large clinical trial experience with DTaP-IPV-HB-PRP-T vaccine since 2004 with at least 21 clinical trials with approximately 7639 subjects in different countries.
- Large post-marketing experience with 12 years (from 01 June 2013 through 30 April 2025) since DTaP-IPV-HB-PRP-T vaccine was first introduced on the market, and with at least 252 471 403 doses distributed worldwide.
- In addition, as per the Preliminary Variation Assessment Reports (2019 and over) for other Sanofi's products (ie, Pentavac, Tetravac, Repevax[®], Covaxis[®], Acthib[®] and others), assessors have requested re-classification/removal of important risks and missing information based on GVP Module V Revision 2; and to remove all identified and potential risks and missing information, from the LSCs in the EU-RMP.
- Thus, based GVP Module V Rev. 2 guideline, following the regulatory authorities requests, and with the aim to harmonize the Sanofi's products, all identified and potential risks for DTaP-IPV-HB-PRP-T vaccine have been re-classified by MAH and removed from the LSCs, including category of missing information.

Rationale for each risk is provided below.

The following is MAH's rationale for the above-mentioned decision.

REMOVAL OF MISSING INFORMATION:

Missing information refers to gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant. ¹⁰⁶

The absence of data itself (eg, exclusion of a population from clinical studies) does not automatically constitute a safety concern. Instead, the risk management planning should focus on situations that might differ from the known safety profile.

If the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information. Excluded populations from the clinical trial development program should be included as missing information only when they are relevant for the approved and proposed indications, ie, "on-label", and if the use in such populations might be associated with risks of clinical significance.

It is expected that as the product matures, the classification as missing information might not be appropriate anymore once new data become available, or when there is no reasonable expectation that the existing or future feasible pharmacovigilance activities could further characterize the safety profile of the product with respect to the areas of missing information. ¹⁰⁷

[REDACTED]

The following categories of missing information were routinely monitored through PBRER (as of DLP 17 April 2025) and signal detection activities for DTaP-IPV-HB-PRP-T vaccine:

- Premature infants
- Immunocompromised individuals (from disease or treatment)
- Duration of protection with acellular pertussis vaccines

The above-mentioned categories were initially included in DTaP-IPV-HB-PRP-T vaccine LSC, since these populations were not included in clinical trials, with exception of “Duration of protection with acellular pertussis vaccine”.

This section includes evidence to support removal of all missing information mentioned above from DTaP-IPV-HB-PRP-T vaccine LSC.

For all missing information, there is no identified or anticipate safety concern, there is no plan to further study these populations, and does not impact the benefit-risk balance of the product. There are no aRMMs or additional pharmacovigilance activities to further evaluate or characterize the risk.

Therefore, the MAH considers removing *all missing information from the LSC. There is no need for maintain* all missing information in the list of missing information *through PBRER, routine pharmacovigilance is sufficient.*

PREMATURE INFANTS

While absolute primary antibody responses may be lower in preterm compared to term infants vaccinated according to chronological age, the majority achieve antibody concentrations higher than levels generally accepted to correlate with protection. Preterm infants should be vaccinated using the same schedule as term infants. ^{108. 109}

Early active immunity is particularly important in preterm infants because they are among the most vulnerable populations to pediatric infectious diseases. ^{108. 109} As a priority, vaccinations for diphtheria, tetanus, pertussis, polio and *Hemophilus influenzae* can be offered in the absence of documented evidence of prior vaccination. ¹¹⁰

Therefore, use of DTaP-IPV/Hib vaccine in premature infants is no longer considered a safety concern and missing information.

In addition, Safety clinical data with DTaP-IPV-HB-PRP-T vaccine are now available regarding the use of the vaccine in premature infants:

- Safety data in this population was evaluated in the study A3L00056 (Spain) and no safety concern was identified. *This study warrants the safety data in this population.* There is no plan to further study these populations.

The use of DTaP-IPV-HB-PRP-T vaccine in Premature infants is appropriately managed in the product information (CCDS Section 5.1 Warning/Special Population). This routine risk

[REDACTED]

minimization activity with warning message and guidance for preventing or treating immediate risk has become integrated into standard vaccination practices.

The potential risk of apnoea and the need for respiratory monitoring for 48-72 hours should be considered when administering the primary immunization series to very premature infants (born ≤ 28 weeks of gestation) and particularly for those with a previous history of respiratory immaturity. As the benefit of vaccination is high in this group of infants, vaccination should not be withheld or delayed.

Study A3L00056 demonstrated that DTaP-IPV-HB-PRP-T vaccine is immunogenic and well tolerated in preterm infants. ¹⁰³ No cases of apnoea were reported as related in this ESC.

Immunogenicity data, supporting the use of Hexaxim in preterm infants, are available from two studies (study A3L00053 (Belgium, n = 105) and study A3L00056 (Spain, n = 143). As expected in preterm infants, lower immune response has been observed for some antigens, when indirectly compared to term infants, although seroprotective levels have been achieved.

Overall, based on available information, there is no identified or anticipated safety concern for use in premature infants. Thus, the use of Hexaxim vaccine in premature infants is no longer considered a safety concern and missing information and can be removed from the LSC.

IMMUNOCOMPROMISED INDIVIDUALS (FROM DISEASE OR TREATMENT)

Use in immunocompromised patient population (HIV-exposed infants) was assessed in a company sponsored clinical study (A3L44 South Africa, n = 64).

Although, limited clinical data are available with DTaP-IPV-HB-PRP-T vaccine in immunocompromised individuals are available; there is no anticipated concern. In addition, due to their nature and that immunocompromised patients have increased susceptibility to vaccine-preventable infections, inactivated vaccines are recommended in these special groups:

- DTaP-IPV-HB-PRP-T vaccine is including the same IPV vaccine antigens for immunocompromised subjects even in countries that still recommend OPV ^{111, 112, 113, 114} or using same vaccine antigens. ¹¹⁵
- Other special groups. ^{116, 117, 118, 119}

An immunosuppressive treatment or an immunodeficient condition may induce a decrease in the immune response to the vaccine. It is therefore recommended to wait for the end of the treatment for the vaccination or to make sure that the subject is well protected. However, the vaccination of subjects with chronic immunodepression, such as HIV infection, asplenia ^{120, 121, 122, 123, 124} or sickle cell disease ^{120, 124, 125, 126, 127} is recommended even though there is a risk of suboptimal immune response.

Several trials with HIB (PRP/T) vaccine (same HIB[PRP/T] used for reconstitution with DTaP-IPV/Hib Pentavac) in immunocompromised subjects have been conducted. ^{128, 129, 130, 131, 132, 133, 134, 135, 136, 137} No specific safety concern was observed in this population.

“The immunogenicity of the vaccine may be reduced by immunosuppressive treatment or immunodeficiency. It is recommended to postpone vaccination until the end of such treatment or disease. Nevertheless, vaccination of subjects with chronic immunodeficiency such as HIV infection is recommended even if the antibody response may be limited”.

Overall, based on available information, there is no identified or anticipated safety concern, there is no plan to further study these populations, and no impact on the benefit-risk balance of the product.

DURATION OF PROTECTION WITH ACELLULAR PERTUSSIS VACCINES

Thus, “Duration of protection with pertussis antigens” was added as “missing information” to these two products, and as per “harmonization” this missing information was adopted as well for all other pertussis containing vaccines produced by Sanofi, including DTaP-IPV-HB-PRP-T vaccine (Hexyon/Hexaxim or DTaP-IPV/PRP-T vaccine (Pentavac/Pentaxim).

- Since the first launch/ market use of Hexaxim (2013), or Pentavac/Pentaxim (1998), Tdap5 (ADACEL, 1999), there was sufficient exposure to these vaccines (Hexaxim/ Hexyon, Pentavac/Pentaxim, Covaxis and Repevax) to ascertain that they are safe to use and offer protection that prevents disease in recipients, similarly to what is seen after whole-cell pertussis priming.
- However, as pertussis requires a lifelong approach to vaccination, one cannot expect either acellular or whole-cell pertussis vaccines to provide long (>10 years) durations of protection. Moreover, whole-cell pertussis vaccines cannot be given after 7 years of age, so boosting with acellular pertussis vaccines is the only option for providing lifelong protection.
- There is no way to determine a single, simple correlate of protection for any pertussis vaccine. As such, it becomes difficult to assess the duration of protection without such

correlate of protection. The best proxy measure available for protection is long-term antibody persistence, which has been demonstrated for both Covaxis and Repevax.

In addition, paediatric vaccines using acellular pertussis components, including Hexyon or Pentavac, are indicated and used in infants and children during the 1st and 2nd year of life; usually followed by additional pertussis booster vaccination as vaccination in toddlers/ pre-school and/or adolescents are recommended and applied in the majority of countries.

All EU/EEA Member States include pertussis vaccination in their routine childhood immunization schedules and all except Poland are using acellular pertussis-containing vaccines for primary immunization.

Indeed, the current schedules in EU/EEA Member States for vaccination below 24 months of age with acellular pertussis-containing vaccines can be, for the majority, divided into the following groups: ¹³⁸

- A so-called “2p + 1” schedule, corresponding to two doses of primary vaccination and a booster dose, with the vaccine given at three, five and 12 months;
- A so-called “3p + 1” schedule, corresponding to three doses given in the first year of life, starting as early as two months, with a booster in the second year of life.

Further doses (ie, Tdap containing vaccines) are given at the time of school entry (4-7 years of age), adolescence and adulthood, and this varies across countries; thus, booster vaccinations provide lifelong protection. ^{139, 140, 141, 142}

For “Duration of protection with pertussis antigens (waning immunity/protection)” there is no anticipated safety concern. Therefore, it is not eligible for classification as missing information for DTaP-IPV-HB-PRP-T vaccine.

As a result:

Considering the above, “Duration of protection with pertussis antigens” is no longer considered missing information, as defined by the GVP Module V Revision 2 (EMA 2017), for Hexyon/Hexaxim, and is removed from the LSCs for the PBRER (DLP 17 April 2025).

Overall, based on available information, there is no identified or anticipated safety concern, there is no plan for further studies, and no impact the benefit-risk balance of the product. There are no additional RMMs or additional pharmacovigilance activities to further evaluate or characterize the duration of protection.

The MAH considers removing “Duration of protection with pertussis antigens” from the LSC. There is no anticipated public health concern. *There is no need for maintain* “Duration of protection with pertussis antigens” in the list of missing information *through PBRER, routine pharmacovigilance is sufficient.*

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risks have been identified for DTaP-IPV-HB-PRP-T:

- Important identified risk:
 - None
- Important potential risk:
 - None
- Missing information:
 - None

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable

SVII.3.2. Presentation of the missing information

Not applicable

[REDACTED]

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 22 - Summary of the safety concerns

Important identified risk	None
Important potential risk	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The applicant maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepares reports for regulatory authorities (eg, individual case safety reports, PBRERs, etc), and maintains continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains further details of these systems and standard practices.

No routine pharmacovigilance activities beyond adverse reactions reporting and signal detection are deemed necessary to monitor the risks of DTaP-IPV-HB-PRP-T vaccine.

The safety profile of DTaP-IPV-HB-PRP-T vaccine will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports, product technical complaints (PTCs) relating to AEs, and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities planned for this product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable since there are no additional pharmacovigilance activities ongoing or planned for DTaP-IPV-HB-PRP-T vaccine.

No effectiveness evaluation is set up since there are no risk minimization activities beyond routine in place.

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for DTaP-IPV-HB-PRP-T vaccine.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

Routine risk minimization measures are in place for the safety risks of this medicinal product as conveyed in the labeling information. Because none of the safety risks and missing information are relevant for the RMP of DTaP-IPV-HB-PRP-T vaccine and in line with the GVP Module V (Rev 2.0), RMP Section [V.1](#) is left empty.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

Routine risk minimization activities as described in Section [V.1](#) are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

The routine risk minimization measure with warning message and guidance for preventing or treating immediate risk has been integrated into standard vaccination practices. There are no aRMMs in place.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Hexaxim/Hexacima/Hexyon (DTaP-IPV-HB-PRP-T)

This is a summary of the RMP for Hexaxim, Hexacima and Hexyon. The RMP details important risks of Hexaxim, Hexacima and Hexyon how these risks can be minimized, and how more information will be obtained about Hexaxim, Hexacima and Hexyon's risks and uncertainties (missing information).

Hexaxim, Hexacima and Hexyon's SmPC and its PL give essential information to healthcare professionals and patients on how Hexaxim, Hexacima and Hexyon should be used.

This summary of the RMP for Hexaxim, Hexacima and Hexyon should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Hexaxim, Hexacima and Hexyon's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Hexacima is indicated for primary and booster vaccination of infants and toddlers from six weeks of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Haemophilus influenzae type b (Hib).

Suspension for injection in pre-filled syringe or in single-dose vial.

The hexavalent pediatric vaccine combines diphtheria and tetanus toxoids, acellular pertussis (2-component), inactivated poliomyelitis virus, recombinant hepatitis B surface antigen and Hib polysaccharide conjugated to tetanus protein.

The vaccine is a preservative free suspension and is adjuvanted by aluminum hydroxide.

Immunization must be carried out by intramuscular injection.

Further information about the evaluation of Hexaxim, Hexacima and Hexyon's benefits can be found in Hexaxim, Hexacima and Hexyon's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

Refer to EPAR ref. EMEA/H/C/002796 and EMEA/H/C/002702 dated 01 July 2020 available on the EMA website at the following links:

<https://www.ema.europa.eu/en/medicines/human/EPAR/hexyon>

<https://www.ema.europa.eu/en/medicines/human/EPAR/hexacima>

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Hexaxim, Hexacima and Hexyon, together with measures to minimize such risks and the proposed studies for learning more about Hexaxim, Hexacima and Hexyon's risks, are outlined below:

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A LIST OF IMPORTANT RISKS AND MISSING INFORMATION

Important risks of Hexaxim, Hexacima and Hexyon are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hexaxim, Hexacima and Hexyon. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine); thus, the identified and potential risks and missing information are reclassified as follows:

Table 23 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

II.B SUMMARY OF IMPORTANT RISKS

Not applicable

II.C POST-AUTHORIZATION DEVELOPMENT PLAN

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Hexaxim, Hexacima and Hexyon.

II.C.2 Other studies in post-authorization development plan

There are no studies required for Hexaxim, Hexacima and Hexyon.

REFERENCES

1. Roper MH, Wassilak SGF, Tiwari TSP. Tetanus Toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Plotkin's Vaccines* (Seventh Edition). Philadelphia, PA: W.B. Saunders; 2018. p. 1052-79.
2. Kyu HH, Mumford JE, Stanaway JD, Barber RM, Hancock JR, Vos T, et al. Mortality from tetanus between 1990 and 2015: findings from the global burden of disease study 2015. *BMC Public Health*. 2017 Feb 8;17(1):179.
3. WHO Weekly epidemiological record: Tetanus vaccines: WHO position paper – 2017 February: 2017 February 10, 92th YEAR. [cited 2019 Apr 08]. Available from: <http://apps.who.int/iris/bitstream/handle/10665/254582/WER9206.pdf;jsessionid=04C71A1B221A0ED39ACA7A7977DD3FEE?sequence=1>
4. European Centre for Disease Prevention and Control_Tetanus - Annual Epidemiological Report 2017. [cited 2020 Jan 02]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/tetanus-annual-epidemiological-report-2017_0.pdf
5. World Health Organization. Maternal and Neonatal Tetanus Elimination (MNTE) [Internet]. Geneva: World Health Organization; [cited 2019 Nov 21]. Available from: https://www.who.int/immunization/diseases/MNTE_initiative/en/
6. Available from: https://www.who.int/immunization/diseases/MNTE_initiative/en/index4.html [cited 2019 Nov 21].
7. WHO_Immunization, Vaccines and Biologicals_Tetanus. Accessed on 2019 Apr 08. Available from: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/passive/tetanus/en/
8. WHO Vaccine-preventable diseases: monitoring system - Global Summary 2006. [cited 2019 Apr 08]. Available from: http://www.who.int/immunization_monitoring/data/en/
9. WHO Position Paper on Diphtheria Vaccine. *Weekly Epidemiological Record*. 2017. 92 (31): 417-436. [cited 2019 April 08]. Available from: <http://www.who.int/wer/en/>
10. Clarke KEN, MacNeil A, Hadler S, Scott C, Tiwari TSP, Cherian T. Global Epidemiology of Diphtheria, 2000-2017(1). *Emerg Infect Dis*. 2019 Oct;25(10):1834-42.
11. Tiwari TSP, Wharton M. Diphtheria toxoid. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. Philadelphia, PA: WB Saunders Company; 2013. p.153-66.
12. CDC. Diphtheria. [cited 2019 Apr 08]. Available from: <https://www.cdc.gov/diphtheria/clinicians.html>
13. Yeung KHT, Duclos P, Nelson EAS, Hutubessy RCW. An update of the global burden of pertussis in children younger than 5 years: a modelling study. *Lancet Infect Dis*. 2017 Sep;17(9):974-80.

14. WHO Position Paper on Pertussis Vaccine. WER. 90(35). [cited 2019 Apr 08]. Available from: <http://www.who.int/wer/2015/wer9035.pdf?ua=1>
15. Masseria C, Martin CK, Krishnarajah G, Becker LK, Buikema A, Tan TQ. Incidence and Burden of Pertussis Among Infants Less Than 1 Year of Age. *Pediatr Infect Dis J*. 2017 Mar;36(3):e54-e61.
16. European Centre for Disease Prevention and Control_Pertussis - Annual Epidemiological Report 2017. [cited 2019 Oct 14]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2017-pertussis.pdf
17. Wendelboe AM, Njamkepo E, Bourillon A, Floret DD, Gaudelus J, Gerber M, et al. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J*. 2007 Apr;26(4):293-9.
18. Winter K, Harriman K, Zipprich J, Schechter R, Talarico J, Watt J, et al. California pertussis epidemic, 2010. *J Pediatr*. 2012 Dec;161(6):1091-6.
19. Rodgers L, Martin SW, Cohn A, Budd J, Marcon M, Terranella A, et al. Epidemiologic and laboratory features of a large outbreak of pertussis-like illnesses associated with cocirculating *Bordetella holmesii* and *Bordetella pertussis*--Ohio, 2010-2011. *Clin Infect Dis*. 2013 Feb;56(3):322-31.
20. Mandal S, Tatti KM, Woods-Stout D, Cassiday PK, Faulkner AE, Griffith MM, et al. Pertussis Pseudo-outbreak linked to specimens contaminated by *Bordetella pertussis* DNA From clinic surfaces. *Pediatrics*. 2012 Feb;129(2):e424-30.
21. Centers for Disease Control and Prevention. Summary of Notifiable Diseases-United States, 2010. *MMWR* 2012;59(53):1-111.
22. Centers for Disease Control and Prevention. Summary of Notifiable Diseases-United States, 2011. *MMWR* 2013;60(53):1-117.
23. Centers for Disease Control and Prevention. Final 2012 reports of nationally notifiable infectious diseases. *MMWR* 2013;62(33):669-82.
24. Glanz JM, Narwaney KJ, Newcomer SR, Daley MF, Hambidge SJ, Rowhani-Rahbar A, et al. Association between undervaccination with diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine and risk of pertussis infection in children 3 to 36 months of age. *JAMA Pediatr*. 2013 Nov;167(11):1060-4.
25. Imdad A, Tserenpuntsag B, Blog DS, Halsey NA, Easton DE, Shaw J. Religious exemptions for immunization and risk of pertussis in New York State, 2000-2011. *Pediatrics*. 2013 Jul;132(1):37-43.
26. Nilsson L. Pertussis surveillance in Sweden - Fifteen year report. The Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet) 2013. [cited on 2019 Apr 08]. Available from: [http://www.folkhalsomyndigheten.se/pagefiles/17379/pertussis-surveillance%20in-sweden-fifteen-year-report\(2\).pdf](http://www.folkhalsomyndigheten.se/pagefiles/17379/pertussis-surveillance%20in-sweden-fifteen-year-report(2).pdf)
27. Tarr GA, Eickhoff JC, Koepke R, Hopfensperger DJ, Davis JP, Conway JH. Using a bayesian latent class model to evaluate the utility of investigating persons with negative

- polymerase chain reaction results for pertussis. *Am J Epidemiol*. 2013 Jul 15;178(2):309-18.
28. Kaczmarek MC, Valenti L, Kelly HA, Ware RS, Britt HC, Lambert SB. Sevenfold rise in likelihood of pertussis test requests in a stable set of Australian general practice encounters, 2000-2011. *Med J Aust*. 2013 Jun 17;198(11):624-8.
 29. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A*. 2014 Jan 14;111(2):787-92.
 30. Domenech de Celles M, Riolo MA, Magpantay FM, Rohani P, King AA. Epidemiological evidence for herd immunity induced by acellular pertussis vaccines. *Proc Natl Acad Sci U S A*. 2014 Feb 18;111(7):E716-7.
 31. Magpantay FM, Domenech DE Celles M, Rohani P, King AA. Pertussis immunity and epidemiology: mode and duration of vaccine-induced immunity. *Parasitology*. 2016 Jun;143(7):835-49.
 32. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. *Pediatrics*. 2014 Mar;133(3):e513-9.
 33. Domenech de Celles M, Magpantay FMG, King AA, Rohani P. The impact of past vaccination coverage and immunity on pertussis resurgence. *Sci Transl Med*. 2018 Mar 28;10(434).
 34. Celentano LP, Massari M, Paramatti D, Salmaso S, Tozzi AE; EUVAC-NET Group. Resurgence of pertussis in Europe. *Pediatr Infect Dis J*. 2005 Sep;24(9):761-5.
 35. Ulloa-Gutierrez R, Avila-Aguero ML. Pertussis in Latin America: current situation and future vaccination challenges. *Expert Rev Vaccines*. 2008 Dec;7(10):1569-80.
 36. Hozbor D, Mooi F, Flores D, Weltman G, Bottero D, Fossati S, et al. Pertussis epidemiology in Argentina: trends over 2004-2007. *J Infect*. 2009 Oct;59(4):225-31.
 37. Edwards KM, Decker MD. Pertussis vaccines. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. Philadelphia, PA: WB Saunders; 2013. p. 447-92.
 38. Centers for Disease Control and Prevention (CDC). International Notes Certification of Poliomyelitis Eradication -- the Americas, 1994. *MMWR* 1994;43(49):720-2.
 39. Centers for Disease Control and Prevention (CDC). Public Health Dispatch: Certification of Poliomyelitis Eradication - Western Pacific Region, 2000 October. *MMWR* 2001;50(01):1-3.
 40. Hoile E. WHO declares European Region polio-free. *Euro Surveill* 2002; 6(27): 1932. [cited 2019 Apr 08]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=1932>
 41. Eurosurveillance Europe's journal on infectious disease surveillance, epidemiology, prevention and control. [cited 2019 Apr 08]. Available from: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=1932>
 42. World Health Organization Regional Office for Africa. Africa's wild polio-free status to be determined in August [Internet]. Brazzaville: WHO Regional Office for Africa; [cited

2020 June 19]. Available from: <https://www.afro.who.int/news/africas-wild-polio-free-status-be-determined-august>

43. Centers for Disease Control and Prevention. Progress Toward Maternal and Neonatal Tetanus Elimination — Worldwide, 2000–2018. *MMWR Morb Mortal Wkly Rep* [Internet]. 2020 Jun 26 [cited 2023 May 24];69(25):784-789. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a4.htm?s_cid=mm6925a4_w
44. Global Polio Eradication Initiative. [cited 2019 Oct 14]. Available from: <http://polioeradication.org/wp-content/uploads/2016/08/Weekly-GPEI-Polio-Analyses-WPV.pdf>
45. Sutter RW, Kew OM, Cochi SL, Aylward RB. 2012, "Poliovirus vaccine - live". In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. Philadelphia, PA: W.B. Saunders; 2013, p. 598-647.
46. WHO Position Paper - Polio Vaccines. *Weekly Epidemiological Record*, 2014;89(9):73-92. [cited 2019 Apr 08]. Available from: <http://www.who.int/wer/2014/wer8909.pdf>
47. Centers for Disease Control and Prevention. Updated recommendations of the Advisory Committee on Immunization Practices regarding routine polio-virus vaccination, 2009. *MMWR* 2009;58(30):829-30.
48. Bernier RH. Some observations on poliomyelitis lameness surveys. *Rev Infect Dis*. 1984 May-Jun;6 (Suppl 2):S371-5.
49. Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *Int J Epidemiol*. 2005 Dec;34(6):1329-39.
50. WHO (2017). Hepatitis B vaccines: WHO position paper - 2017 July. *Weekly epidemiological record*, 92(27), 369-92. [cited 2020 Jan 23]. Available from: <https://www.who.int/wer/2017/wer9227/en/>
51. Shepard CW, Simard EP, Finelli L, Flore AE, Bell BP. Hepatitis B virus Infection: Epidemiology and Vaccination. *Epidemiol Rev*. 2006;28:112-25.
52. WHO 2013d. Hepatitis B Fact Sheet. [cited 2014 Aug 27]. Available from: <http://www.who.int/mediacentre/factsheets/fs204/en/>
53. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine*. 2012 Mar 9;30(12):2212-9.
54. Bosch FX, Ribes J, Diaz M, Cleries R. Primary liver cancer: worldwide incidence and trends. *Gastroenterology*. 2004 Nov;127(5 Suppl 1):S5-S16.
55. Kew MC. Epidemiology of chronic hepatitis B virus infection, hepatocellular carcinoma, and hepatitis B virus-induced hepatocellular carcinoma. *Pathol Biol (Paris)*. 2010 Aug;58(4):273-7.
56. Schafer DF, Sorrell MF. Hepatocellular carcinoma. *Lancet*. 1999 Apr 10;353(9160):1253-7.

57. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. *J Infect Dis*. 2009 Jul 1;200(1):39-47.
58. Perz JF, Elm JL Jr, Flore AE, Huggler JI, Kuhnert WL, Effler PV. Near elimination of hepatitis B virus infections among Hawaii elementary school children after universal infant hepatitis B vaccination. *Pediatrics*. 2006 Oct;118(4):1403-8.
59. Da Villa G, Romano L, Sepe A, Iorio R, Paribello N, Zappa A, et al. Impact of hepatitis B vaccination in a highly endemic area of south Italy and long-term duration of anti-HBs antibody in two cohorts of vaccinated individuals. *Vaccine*. 2007 Apr 20;25(16):3133-6.
60. Simani OE, Leroux-Roels G, Francois G, Burnett RJ, Meheus A, Mphahlele MJ. Reduced detection and levels of protective antibodies to hepatitis B vaccine in under 2-year-old HIV positive South African children at a paediatric outpatient clinic. *Vaccine*. 2009 Jan 1;27(1):146-51.
61. Shepard CW, Finelli L, Fiore AE, Bell BP. Epidemiology of hepatitis B and hepatitis B virus infection in United States children. *Pediatr Infect Dis J*. 2005 Sep;24(9):755-60.
62. McMahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology*. 2011 Sep 2;54(3):801-7.
63. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*. 1997 Jun;336(26):1855-9.
64. Van Damme P, Ward J, Shouval D, Wiersma S, Zanetti A. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*. 6th ed. Philadelphia: WB. Saunders Company; 2012. p. 205-34.
65. World Health Organization. Hepatitis B [Internet]. Geneva: World Health Organization; [cited 2019 Oct 14]. Available from: <https://www.who.int/news-room/fact-sheets/detail/hepatitis-b>
66. Bosch FX, Ribes J, Borrás J. Epidemiology of primary liver cancer. *Semin Liver Dis*. 1999;19(3):271-85.
67. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Glob Health*. 2018 Jul;6(7):e744-e757.
68. World Health Organisation. *Haemophilus influenzae* type b (Hib) Vaccination Position Paper - September 2013. *Weekly epidemiological record*. 2013 Sep;88(39):413-28.
69. Morris S, Moss W, Halsey N. *Haemophilus influenzae* type b conjugate vaccine use and effectiveness. *Lancet Infect Dis*. 2008 Jul;8(7):435-43.
70. World Health Organisation. WHO Position Paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly Epidemiological Record*. 2006;81(47):445-52.

71. Chandran A, Watt JP, Santosham M. 2012, "Haemophilus influenzae vaccines". In: Plotkin S.A., Orenstein W.A. & Offit P.A. editors, *Vaccines*, 6th ed, Philadelphia, PA: W.B. Saunders; 2012, p. 167-82.
72. Madhi SA, Petersen K, Khoosal M, Huebner RE, Mbelle N, Mothupi R, et al. Reduced effectiveness of Haemophilus influenzae type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J*. 2002 Apr;21(4):315-21.
73. Maertens K, Orije MRP, Huoi C, Boissard F, Lyabis O. Immunogenicity of a liquid hexavalent DTaP-IPV-HB-PRP-T vaccine after primary and booster vaccination of term and preterm infants born to women vaccinated with Tdap during pregnancy. *Vaccine*. 2023;41(3):795-804.
74. Dhingra MS, Namazova-Baranova L, Arredondo-Garcia JL, Kim KH, Limkittikul K, Jantarabenjakul W, et al. Immunogenicity and safety of a quadrivalent meningococcal tetanus toxoid-conjugate vaccine administered concomitantly with other paediatric vaccines in toddlers: a phase III randomised study. *Epidemiol Infect*. 2021;149:e90.
75. Centers for Disease Control and Prevention. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). [consulted on 2017 May 21]. Available from: <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.html>
76. Kroger AT, Atkinson WL, Pickering LK. General immunization practices. In: Plotkin SA, Orenstein WA, Offit PA, editors. *Vaccines*, 6th edition. Philadelphia: Saunders Elsevier; 2013.p.88-112.
77. European Medicines Agency. Procedural steps taken and scientific information after the authorization. [consulted on 2017 Jun 07]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000231/WC500056445.pdf
78. Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? Interpreting zero numerators. *JAMA*. 1983;249(13):1743-5.
79. Florence Boissard, Christine Manson, Laurence Serradell & Denis Macina (2023) DTaP-IPV-HB-Hib vaccine (Hexaxim): an update 10 years after first licensure, *Expert Review of Vaccines*, 22:1, 1196-1213, DOI: 10.1080/14760584.2023.2280236
80. Government of Canada. Page 5: Canadian Immunization Guide: Part 3 - Vaccination of Specific Populations. [consulted on 2017 May 21]. Available from: <https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-5-immunization-infants-born-prematurely.html>
81. Esposito S, Serra D, Gualtieri L, Cesati L, Principi N. Vaccines and preterm neonates: why, when, and with what. *Early Hum Dev*. 2009;85(10 Suppl):S43-5.

82. Gaudelus J, Pinquier D, Romain O, Thiebault G, Vie le Sage F, Dommergues MA, et al. Is the new vaccination schedule recommended in France adapted to premature babies?. *Arch Pediatr*. 2014 Sep;21(9):1062-70.
83. The Australian Immunization Handbook. 3.3 Groups with special vaccination requirements. [consulted on 2017 May 21]. Available from: <http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home-handbook10part3-handbook10-3-3#3-3-2>
84. UK. Immunisation of individuals with underlying medical conditions: the green book, chapter 7. [consulted on 2017 May 21]. Available from: <https://www.gov.uk/government/publications/immunisation-of-individuals-with-underlying-medical-conditions-the-green-book-chapter-7>
85. Czajka H, Lauterbach R, Pawlik D. Vaccination of preterm infants by polyvalent vaccines: immunogenicity and safety- review of literature. *Dev Period Med*. 2014 Jul-Sep;18(3):360-6.
86. Bonhoeffer J, Siegrist CA, Heath PT. Immunisation of premature infants. *Arch Dis Child*. 2006 Nov;91(11):929-35.
87. D'Angio CT. Active immunization of premature and low birth-weight infants: a review of immunogenicity, efficacy, and tolerability. *Paediatr Drugs*. 2007;9(1):17-32.
88. Saliou P, Ajjan N, Guerin N. Efficacy and tolerance of vaccinations in premature infants. *Arch Pediatr*. 2002 Jun;9(6):629-37.
89. Slack MH, Schapira D, Thwaites RJ, Burrage M, Southern J, Andrews N, et al. Immune response of premature infants to meningococcal serogroup C and combined diphtheria-tetanus toxoids-acellular pertussis-Haemophilus influenzae type b conjugate vaccines. *J Infect Dis*. 2001 Dec 15;184(12):1617-20.
90. Slack MH, Cade S, Schapira D, Thwaites RJ, Crowley-Luke A, Southern J, et al. DT5aP-Hib-IPV and MCC vaccines: preterm infants' response to accelerated immunisation. *Arch Dis Child*. 2005 Apr;90(4):338-41.
91. Omenaca F, Garcia-Sicilia J, Garcia-Corbeira P, Boceta R, Romero A, Lopez G, et al. Response of preterm newborns to immunization with a hexavalent diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio and Haemophilus influenzae type b vaccine: first experiences and solutions to a serious and sensitive issue. *Pediatrics*. 2005 Dec;116(6):1292-8.
92. Vazquez L, Garcia F, Ruttimann R, Coconier G, Jacquet JM, Schuerman L. Immunogenicity and reactogenicity of DTPa-HBV-IPV/Hib vaccine as primary and booster vaccination in low-birth-weight premature infants. *Acta Paediatr*. 2008 Sep;97(9):1243-9.
93. Schulzke S, Heininger U, Lucking-Famira M, Fahrenstich H. Apnoea and bradycardia in preterm infants following immunisation with pentavalent or hexavalent vaccines. *Eur J Pediatr*. 2005 Jul;164(7):432-5.

94. Vermeulen F, Verscheure V, Damis E, Vermeulen D, Leloux G, Dirix V, et al. Cellular immune responses of preterm infants after vaccination with whole-cell or acellular pertussis vaccines. *Clin Vaccine Immunol*. 2010 Feb;17(2):258-62.
95. Vermeulen F, Dirix V, Verscheure V, Damis E, Vermeulen D, Loch C, et al. Persistence at one year of age of antigen-induced cellular immune responses in preterm infants vaccinated against whooping cough: comparison of three different vaccines and effect of a booster dose. *Vaccine*. 2013 Apr 8;31(15):1981-6.
96. Faldella G, Alessandroni R, Magini GM, Perrone A, Sabatini MR, Vancini A, et al. The preterm infant's antibody response to a combined diphtheria, tetanus, acellular pertussis and hepatitis B vaccine. *Vaccine*. 1998 Oct;16(17):1646-9.
97. Pfister RE, Aeschbach V, Niksic-Stuber V, Martin BC, Siegrist CA. Safety of DTaP-based combined immunization in very-low-birth-weight premature infants: frequent but mostly benign cardiorespiratory events. *J Pediatr*. 2004;145(1):58-66.
98. Baxter D. Premature infants and vaccination. *Hum Vaccin*. 2010;6(6):512-20.
99. EU Clinical Trials Register. [consulted on 2017 May 21]. Available from: <https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-002898-47/results>
100. European Medicines Agency. Assessment Report. [consulted on 2017 May 21]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/003982/WC500202437.pdf
101. Martinelli D, Fortunato F, Del Matto G, Iannelli G, Prato R. Post-marketing surveillance study of the DTaP2-IPV-HB-Hib (Hexyon) vaccine administered in preterm infants in the Apulia region, Italy, in 2017. *Vaccine*. 2020 Jul 14;38(33):5148-53.
102. E Chiappini E, C Petrolini C, C Caffarelli C, M Calvani M, F Cardinale F, M Duse M et al. Hexavalent vaccines in preterm infants: an update by Italian Society of Pediatric Allergy and Immunology jointly with the Italian Society of Neonatology. *Ital J Pediatr*. 2019 Nov 19;45(1):145.
103. Salamanca de la Cueva I, Gonzalez Lopez M, Roldan Lopez R, Ocana Jaramillo S, Baca Cots M, Alvarez Aldean J, et al. Immunogenicity and safety of a 2+1 schedule of a hexavalent combination vaccine in preterm infants: an open-label phase IV trial. Presented at the 43rd Annual Meeting of the European Society for Pediatric Infectious Diseases, 26-30 May 2025. Bucharest, Romania, Abstract 335.
104. Yucesoy B, Talzhanov Y, Johnson VJ, Wilson NW, Biagini RE, Wang W, et al. Genetic variants within the MHC region are associated with immune responsiveness to childhood vaccinations. *Vaccine*. 2013 Nov 4;31(46):5381-91.
105. Yucesoy B, Johnson VJ, Fluharty K, Kashon ML, Slaven JE, Wilson NW, et al. Influence of cytokine gene variations on immunization to childhood vaccines. *Vaccine*. 2009 Nov 23;27(50):6991-7.
106. Guideline on good pharmacovigilance practices (GVP) Annex I - Definitions (Rev 5) at GVP Annex I Definitions (dated 22 July 2024).

107. Guideline on good pharmacovigilance practices (GVP), module v – risk management systems (rev 2), 28 March 2017, ema/838713/2011 rev 2;p1-36. At guideline on good pharmacovigilance practices (GVP) module v – risk management systems (rev 2).
108. Gagneur, Arnaud et al. “Immunization of preterm infants.” Human vaccines & immunotherapeutics vol. 11,11 (2015): 2556-63. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4685684/pdf/khvi-11-11-1074358.pdf> (accessed on 29 March 2022)
109. ACIP USA 2022.- Vaccine Recommendations and Guidelines of the ACIP.- Special Situations.- Vaccination of Preterm Infants.- available at <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/special-situations.html> (accessed on 29 March 2022).
110. CDC Europe.- European Centre for Disease Prevention and Control.- Vaccinations to be offered in the absence of documented evidence of prior vaccination. March 2022.- Available at: <https://www.ecdc.europa.eu/en/publications-data/infographic-vaccinations-offered-absence-documented-prior-vaccination> (accessed on 29 March 2022).
111. Polio vaccines: WHO position paper – March, 2016. Wkly Epidemiol Rec. 2016 Mar 25;91(12):145-68.
112. Duchet Niedziolka P, Launay O, Salmon Ceron D, Consigny PH, Ancelle T, Van der Vliet D, et al. Antiviral immunization of immunocompromised adults, literature review. Rev Med Interne. 2008 Jul;29(7):554-67.
113. Barbi M, Bardare M, Luraschi C, Zehender G, Clerici Schoeller M, Ferraris G. Antibody response to inactivated polio vaccine (E-IPV) in children born to HIV positive mothers. Eur J Epidemiol. 1992 Mar;8(2):211-6.
114. Barbi M, Biffi MR, Binda S, Clerici-Schoeller M, Ferraris G, Luraschi C, et al. Immunization in children with HIV seropositivity at birth: antibody response to polio vaccine and tetanus toxoid. AIDS. 1992 Dec;6(12):1465-9.
115. Koen A, Madhi S, Lyabis O, Vidor E, Cowper B, Marais T, et al. Immunogenicity and safety of a hexavalent pediatric vaccine in HIV-exposed infected and uninfected infants in Republic of South Africa. Hum Vaccin Immunother. 2021 Jun 3;17(6):1770-8.
116. Debat Zoguereh D, Ruiz JM. Immunosuppression and vaccinations. Sante. 2000 May-Jun;10(3):211-9.
117. Mikulska M, Cesaro S, de Lavallade H, Di Blasi R, Einarsdottir S, Gallo G, et al; European Conference on Infections in Leukaemia group. Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019 Jun;19(6):e188-99.
118. Cordonnier C, Einarsdottir S, Cesaro S, Di Blasi R, Mikulska M, Rieger C, et al; European Conference on Infections in Leukaemia group. Vaccination of haemopoietic stem cell transplant recipients: guidelines of the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019 Jun;19(6):e200-12.

119. Principi N, Esposito S. Vaccine use in primary immunodeficiency disorders. *Vaccine*. 2014 Jun 24;32(30):3725-31.
120. Centre for disease control and prevention. General recommendations on Immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physician (AAFP). *MMWR* 2002; 51(N°RR-2): 1-36 (Altered immunocompetence).
121. ACIP CDC USA. General Best Practice Guidelines for Immunization: Introduction: Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). April 20, 2017. [Cited 2020 Jun 5]. Available from: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html>
122. Webber SA, Sandor GGS, Patterson MWH, Mitchell LA, Scheifele D, Ochnio JJ, et al. Immunogenicity of Haemophilus influenzae type b conjugate vaccine in children with congenital asplenia. *J Infect Dis* 1993;167(5):1210-2.
123. Gibb D, Spoulou V, Giacomelli A, Griffiths H, Masters J, Misbah S, et al. Antibody responses to Haemophilus influenzae type b and Streptococcus pneumoniae vaccines in children with human immunodeficiency virus infection. *Pediatr Infect Dis J*. 1995;14(2):129-35.
124. Leroy V, Ladner J, Nsengumuremyi F, Dabis F, Simonon A, Salamon R. Safety of Haemophilus influenzae conjugate vaccine in children born to HIV-1 infected mothers: Kigali (Rwanda), 1992-1994. *Vaccine*. 1996;14(2):177-8.
125. ACIP USA. General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Page last reviewed: August 20, 2019. [Cited 2020 Jun 05]. Available from: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html>
126. CDC. Recommendations and reports of the Advisory Committee on Immunization Practices (ACIP): Use of Vaccines and Immune Globulins in Persons with Altered Immunocompetence. *MMWR* 1993; 42(N°RR-4): 1-19 (Specific considerations for use of vaccines, Haemophilus influenzae b conjugate vaccine).
127. Kaplan SL, Duckett T, Mahoney Jr DH, Kennedy LL, Dukes CM, Schaffer DM, et al. Immunogenicity of Haemophilus influenzae type b polysaccharide-tetanus protein conjugate vaccine in children with sickle hemoglobinopathy or malignancies, and after systemic Haemophilus influenzae type b infection. *J Pediatr*. 1992;120(3):367-70.
128. Goldblatt D, Johnson M, Evans J. Antibody responses to Haemophilus influenzae type b conjugate vaccine in sickle cell disease. *Arch Dis Child*. 1996;75(2):159-61.
129. Neu AM, Lederman HM, Warady BA, Fivush BA. Haemophilus influenzae type b immunization in infants on peritoneal dialysis. Pediatric Peritoneal Dialysis Study Consortium. *Pediatr Nephrol*. 1996;10(1):84-5.
130. Sever MS, Yildiz A, Eraksoy H, Badur S, Yuskel-Onel D, Gorcin B, et al. Immune response to Haemophilus influenzae type B vaccination in renal transplant recipients with well-functioning allografts. *Nephron*. 1999;81(1):55-9.

131. Barra A, Cordonnier C, Preziosi MP, Intrator L, Hessel L, Fritzell B, et al. Immunogenicity of Haemophilus influenzae type b conjugate vaccine in allogeneic bone marrow recipients. *J Infect Dis.* 1992;166(5):1021-8.
132. Shenep JL, Feldman S, Gigliotti F, Roberson PK, Marina N, Foreschle JE, et al. Response of immunocompromised children with solid tumors to a conjugate vaccine for Haemophilus influenzae type b. *J Pediatr.* 1994;125(4):581-4.
133. Sinsalo M, Aittoniemi J, Kayhty H, Vilpo J. Haemophilus influenzae type b (Hib) antibody concentrations and vaccination responses in patients with chronic lymphocytic leukaemia: predicting factors for response. *Leuk Lymphoma.* 2002;43(10):1967-9.
134. Robertson JD, Nagesh K, Jowitt SN, Dougal M, Anderson H, Mutton K, et al. Immunogenicity of vaccination against influenza, Streptococcus pneumonia and Haemophilus influenzae b in patients with multiple myeloma. *Br J Cancer.* 2000;82(7):1261-5.
135. Siber GR, Gorham C, Martin P, Corkery JC, Schiffman G. Antibody response to pretreatment immunization et post-treatment boosting with bacterial polysaccharide vaccines in patients with Hodgkin's disease. *Ann Intern Med.* 1986;104(4):467-75.
136. Ambrosino DM, Lee MY, Chen D, Shamberger RC. Response to Haemophilus influenzae type B conjugate vaccine in children undergoing splenectomy. *J Pediatr Surg.* 1992;27(8):1045-7; discussion 1048.
137. Kristensen K. Antibody response to a Haemophilus influenzae type b polysaccharide tetanus toxoid conjugate vaccine in splenectomized children and adolescents. *Scand J Infect Dis.* 1992;24(5):629-32.
138. European Centre for Disease Prevention and Control- An agency of the European Union- Pertussis - Annual Epidemiological Report for 2018. September 2020. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/AER_for_2018_pertussis.pdf
139. European Centre for Disease Prevention and Control. Vaccine scheduler. [internet]. Stockholm: ECDC; 2020. Available from: <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx>
140. Vaccine Scheduler- Pertussis: Recommended vaccinations. 2020. Available at: <https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=3&SelectedCountryIdByDisease=-1>
141. WHO recommendations for routine immunization - summary tables as of November 2021. Available at: <https://www.who.int/teams/immunization-vaccines-and-biologicals/policies/who-recommendations-for-routine-immunization-summary-tables> and https://cdn.who.int/media/docs/default-source/immunization/immunization_schedules/immunization-routine-table1.pdf?sfvrsn=c7de0e97_9&download=true
142. Centers for Disease Control and Prevention (CDC) Vaccine Information Statement. - Tdap (Tetanus, Diphtheria, Pertussis) Vaccine. 2022. Available at:

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]

<https://www.cdc.gov/vaccines/hcp/vis/vis-statements/tdap.pdf> and
<https://www.cdc.gov/vaccines/>

[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]

PART VII: ANNEXES

[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED]

ANNEX 4

**SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP
FORMS**

NOT APPLICABLE

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

ANNEX 6

**DETAILS OF PROPOSED ADDITIONAL RISK
MINIMIZATION ACTIVITIES**

NOT APPLICABLE

[REDACTED]