Assessment report for biological medicinal product

Diphtheria, tetanus, pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Influenza Type B Conjugate Vaccine (Adsorbed) (DTwP-rHepB-Hib) 12 September 2018

Division of Health Product Enterprise Services

Thai Food and Drug Administration

Name of product	Diphtheria, tetanus, pertussis (Whole Cell), Hepatitis B (rDNA) and *Haemophilus Influenzae* Type B Conjugate Vaccine (Adsorbed) (DTwP-rHepB-Hib)
Active Substance(s)	- Diphtheria toxoid (*Corynebacterium diphtheria* Strain (CN2000)) - Tetanus toxoid (*Clostridium tetani Harvard* Strain (49205)) - *Bordetella Pertussis* (whole cell, Strain 134 and Strain 509) - r-HBsAg (Clones of *Pichia pastoris* strain 2S) - Purified Capsular Polysaccharide (PRP) of *Haemophilus Influenzae* tybe b (Strain 760705) covalently linked to 20-36.7 mcg of Tetanus Toxoid
Pharmaceutical form	Suspension for injection
Strength	1 dose (0.5 mL) contains: - Diphtheria toxoid: 25 Lf (≥30 IU) - Tetanus toxoid: 5.5 Lf (≥60 IU*) - *B. Pertussis* (whole cell): 16 IOU (≥4 IU**) - r-HBsAg: 12.5 mcg - Purified Capsular Polysaccharide of Hib (PRP) covalently linked to 20 - 36.7 µg of tetanus toxoid: 11 mcg * ≥ 40 IU when tested in guinea pigs and ≥ 60 IU when tested in mice **The lower fiducial limit (p=0.95) of the estimated potency is not less than 2.0 IU.
Route(s) of administration	Intramuscular Injection

Therapeutic indication(s)	Indication as stated in the SmPC: Active immunization against diphtheria, tetanus, pertussis, hepatitis B (HB) and *Haemophilus influenzae* type b disease in infants from 6 weeks of age. Indications as stated in the patient information leaflet (PIL): กระตุ้นให้เกิดการสร้างภูมิคุ้มกันต่อโรคคอตีบ บาดทะยัก ไอกรน ไวรัสตับอักเสบชนิดบี และเยื่อหุ้มสมองอักเสบชนิดบี ในทารกที่มีอายุตั้งแต่ 6 สัปดาห์ขึ้นไป
Registration number and date of registration	2C 15031/61 (NB) 4 June 2018
E-Identifier Number	e6100038

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Abbreviations

API	Active pharmaceutical ingredients
BE	Biological E.Limited
DT vaccine	Diphtheria toxoid-tetanus toxoid vaccine
DTwP-HepB-Hib	Diphtheria toxoid, tetanus toxoid, Pertissis (whole cell) vaccine, Hepatitis B vaccine and Haemophilus influenza tybe b
EPI	Extended Program for Immunization
GMP	Good Manufacturing Practices
LPV	Liquid Pentavalent vaccine
NRA	The national regulatory authority
PSFd	Product Summary Files
PQVAR	Prequalification Vaccine Annual Report
Td	Tetanus Diphteria vaccine
TT	Tetanus toxoid vaccine
UN	United Nations
UNICEF	United Nations Children's Fund
WHO	World Health Organization

Assessment report for biological product
Diphtheria, tetanus, pertussis (Whole Cell), Hepatitis B (rDNA) and Haemophilus Influenza Type B Conjugate Vaccine (Adsorbed) (DTwP-rHepB-Hib)
2C 15031/61 (NB)
E-identifier: e6100038 (Manufacturing site: Biological E.Limited
04 June 2018

Part 1: Introduction and summary review

Diphtheria is a contagious disease caused by *Corynebacterium diphtheriae*, a facultative anaerobic Gram-positive bacterium and is spread by direct physical contact or breathing the aerosolized secretions of infected individuals. It is characterized by sore throat, low fever and an adherent pseudomembrane on the tonsils, pharynx and/or nasal cavity. A milder form of diphtheria can be restricted to the skin. Less common consequences include about 20% myocarditis and about 10% peripheral neuropathy.

Tetanus is a neurologic toxin-mediated disease which manifests as trimus, lockjaw and severe muscle spasm. It is caused by *Clostridium tetani* through wound contamination. Tetanus neonatorum is a disease in the newborn that has no passing protective antibody from the mother, mostly resulting from contamination of the umbilical stump wound. Complications include laryngospasm, fracture of the spine or long bone, hyperactivity of the autonomic nervous system, nosocomial infection and aspiration pneumonia. The case fatality rate is as high as 30%.

Pertussis (whooping cough) is an important cause of infant death worldwide and continues to be a public health concern even in countries with high vaccination coverage. Estimates from WHO suggest that in 2008 about 16 million cases of pertussis occurred worldwide, 95% of which were in developing countries; and about 195,000 children died from this disease. Pertussis is caused by *Bordetella pertussis*. Symptoms begin with mild upper respiratory tract symptoms and progress to paroxysm of cough, often with a characteristic inspiratory whoop. Infants < 6 months of age may have atypical illness and often require assisted ventilation. Complications include pneumonia and neurologic complications e.g. seizures and encephalopathy.

Hepatitis B virus (HBV) can cause both acute and chronic hepatitis, cirrhosis and primary hepatocellular carcinoma. The prodromal symptoms are fever, malaise, myalgia and arthralgia for 3-10 days followed by jaundice, light or grey stools and hepatomegaly with tenderness for1-3 weeks. The symptoms occur more often in adults than in children. While most acute

hepatitis B infections result incomplete recovery, fulminant hepatitis can occur in 1-2% of persons with mortality rates of 60-90%. Chronic hepatitis B infection causes chronic hepatitis, cirrhosis, liver failure and hepatocellular carcinoma.

***Haemophilus influenzae* type b (Hib)** was the most common cause of bacterial meningitis and a leading cause of other serious invasive infections in young children before the introduction of Hib vaccines. About 55-65% of affected children have meningitis, the remainder suffer from epiglottitis, bacteremia, cellulitis, pneumonia or septic arthritis. The case-fatality rate of meningitis is about 5%. Severe neurologic sequelae occur in 10% to 15% of survivors and deafness in 15-20%. The widespread use of Hib conjugate vaccines in infancy has led to a dramatic decline in the incidence of invasive Hib disease in children. However, the disease remains common in countries not using the vaccine. Active immunization of young infants is the most important means for prevention of Hib infection.

Reported cases of vaccine preventable diseases, 2011-2016 Thailand

Year	Diphtheria	Pertussis	NT: neonatal tetanus (% of all Tetanus)
2011	28	12	1 (1%)
2012	63	14	4 (4%)
2013	28	24	2 (2%)
2014	19	14	2 (2%)
2015	19	51	0
2016	16	84	0
Source: WHO/UNICEF JRF, (2011-2016)			

Prevention

Thailand Immunization schedule, 2018

ตารางการให้วัคซีนในเด็กไทยปกติ
แนะนำโดย สมาคมโรคติดเชื้อในเด็กแห่งประเทศไทย 2561

วัคซีนจำเป็นที่ต้องให้กับเด็กทุกคน

วัคซีน \ อายุ	แรกเกิด	1 เดือน	2 เดือน	4 เดือน	6 เดือน	9 เดือน	12 เดือน	18 เดือน	2 1/2 ปี	4-6 ปี	11-12 ปี
บีซีจี[1] (BCG)	BCG										
ตับอักเสบบี[2] (HBV)	HBV1	(HBV2)									
คอตีบ-บาดทะยัก-ไอกรนชนิดทั้งเซลล์[3] (DTwP)			DTwP-HB1	DTwP-HB2	DTwP-HB3			DTwP กระตุ้น 1		DTwP กระตุ้น 2	Td และ ทุก 10 ปี
โปลิโอชนิดกิน[4] (OPV)			OPV1	OPV2+IPV	OPV3			OPV กระตุ้น 1		OPV กระตุ้น 2	
หัด-หัดเยอรมัน-คางทูม[5] (MMR)						MMR1			MMR2		
ไข้สมองอักเสบเจอี[6] (Live JE)						JE1			JE2		
ไข้หวัดใหญ่[7] (Influenza)					Influenza ให้ 2 เข็ม ห่างกัน 1 เดือน ในช่วงอายุ 6 เดือนถึง 2 ปี						
เอชพีวี[8] (HPV)											เด็กหญิง ป.5 2 เข็ม ห่างกัน 6-12 เดือน

วัคซีนอื่นๆ ที่อาจให้เสริม หรือทดแทน

วัคซีน \ อายุ	2 เดือน	4 เดือน	6 เดือน	9 เดือน	12 เดือน	18 เดือน	2 ปี	2 1/2 ปี	4 ปี	6 ปี	9 ปี	11-12 ปี
คอตีบ-บาดทะยัก-ไอกรนชนิดไร้เซลล์[3] (DTaP, Tdap หรือ TdaP)	DTaP1	DTaP2	DTaP3			DTaP กระตุ้น 1			Tdap หรือ DTaP กระตุ้น 2			Tdap หรือ TdaP ต่อไป Td ทุก 10 ปี
โปลิโอชนิดฉีด[4] (IPV)	IPV1	IPV2	IPV3			(IPV4)			IPV5			
ฮิบ[9] (Hib)	Hib1	Hib2	Hib3			(Hib4)						
ไข้สมองอักเสบเจอี[6] (Inactivated JE)			JE1, JE2 ห่างกัน 4 สัปดาห์ และ JE3 อีก 1 ปี									
ตับอักเสบเอ[10] (HAV)					HAV ชนิดเชื้อไม่มีชีวิต ให้ 2 ครั้ง ห่างกัน 6-12 เดือน ชนิดเชื้อมีชีวิต ฉีดครั้งเดียวเมื่ออายุ 18 เดือนขึ้นไป							
อีสุกอีใส[11] (VZV) หรือวัคซีนรวม หัด-หัดเยอรมัน-คางทูม-อีสุกอีใส (MMRV)					VZV1 (หรือ MMRV1)			VZV2 (หรือ MMRV2)				
ไข้หวัดใหญ่[7] (Influenza)			Influenza ให้ปีละครั้งช่วงอายุ 6 เดือน-18 ปี (เน้นในอายุ 6-24 เดือน) ในปีแรกอาจต้องฉีด 2 เข็ม ห่างกัน 4 สัปดาห์									
นิวโมคอคคัสชนิดคอนจูเกต[12] (PCV)	PCV1	PCV2	(PCV3)		PCV4							
โรต้า[13] (Rota)	Rota1	Rota2	Rota3 (เฉพาะ pentavalent)									
เอชพีวี[8] (HPV)											HPV 2 เข็ม ห่างกัน 6-12 เดือน	
ไข้เลือดออก[14] (DEN)											DEN 3 เข็ม 0, 6 และ 12 เดือน	

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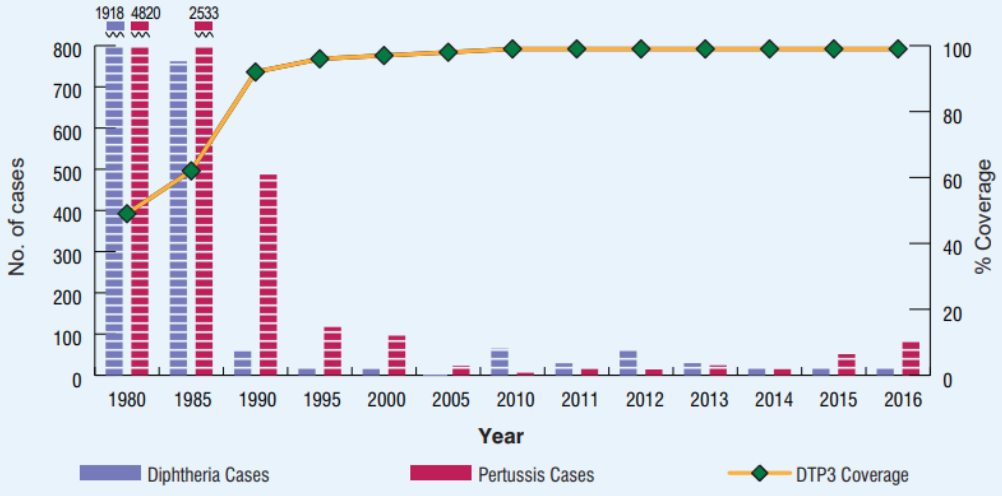
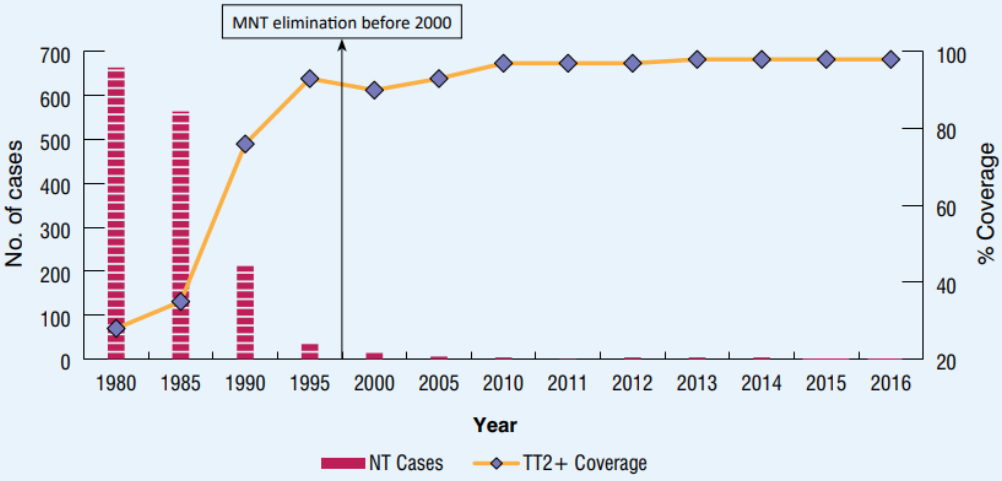
Figure 2: **DTP3 coverage[1], diphtheria and pertussis cases[2], 1980-2016**



[1]WHO/UNICEF estimates of national immunization coverage, July 2017 revision
[2]WHO vaccine-preventable diseases: monitoring system 2016

Figure 4: **TT2+ coverage[1] and NT cases[2], 1980-2016**



[1] WHO/UNICEF JRF, Country official estimates, 1980-2016
[2]WHO vaccine-preventable diseases: monitoring system 2016

Diphtheria, Tetanus, Pertussis (Whole Cell), Hepatitis-B (r-DNA) and *Haemophilus influenzae* Type b Conjugate Vaccine (Adsorbed) is a sterile suspension for injection which contains diphtheria (D), tetanus (T) toxoids, whole cell inactivated pertussis bacteria (wP), purified major surface antigen of the hepatitis B virus (HBV), adsorbed on aluminium salts and conjugated *Haemophilus influenzae* type b polysaccharide. It is a whitish turbid liquid in which the mineral carriers, upon keeping, tends to settle down slowly on keeping and disperse uniformity upon shaking. The vaccine meets WHO requirements.

The Diphtheria and Tetanus toxoids are prepared from the toxins of cultures of *Corynebacterium diphtheriae* and *Clostridium tetani* by formalin inactivation using established

technology. The Pw component is obtained by heat inactivation of phase I culture of *Bordetella pertussis* bacteria.

The surface antigen of HBV (HBsAg) is produced from genetically-engineered yeast cells (*Pichia pastoris*) which carry the gene coding for the major surface antigen of the HBV. This HBsAg expressed in yeast cells is purified by several physico-chemical steps.

The capsular polysaccharide is produced from cultures of *Haemophilus influenzae* type b and purified. Purified polysaccharide (PRP) is covalently bound to tetanus toxoid (T) to produce PRP-T conjugate.

Mechanism of action

Active immunization against diphtheria, tetanus, pertussis, hepatitis B (HB) and *Haemophilus influenzae* type b disease

Part 2: Summary of the dossier

2.1 Type of marketing authorization application

- **Product type:** New biological product
- **Application type:** Stand alone application
- **Review method:** Abbreviated review through Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines (WHO/IVB/07.08). WHO supported prequalification summary assessment report and WHO public inspection report of the vaccine manufacturer. The assessment also conduced by review team together with Thai experts panel meeting on 12nd September 2018. CMC part also sent to Institute of Biological Products, Department of Medical Science.

2.2 Administrative data

2.2.1 Product

Name of Product: Invented name	Diphtheria, tetanus, pertussis (Whole Cell), Hepatitis B (rDNA) and *Haemophilus Influenzae* Type B Conjugate Vaccine (Adsorbed) (DTwP-rHepB-Hib)
Active Substance(s)	- Diphtheria toxoid (Corynebacterium diphtheria Strain (CN2000)) - Tetanus toxoid (Clostridium tetani Harvard Strain (49205)) - *Bordetella Pertussis* (whole cell, Strain 134 and Strain 509)

	- r-HBsAg (Clones of Pichia pastoris strain 2S) - Purified Capsular Polysaccharide (PRP) of *Haemophilus Influenzae* tybe b (Strain 760705) covalently linked to 20-36.7 mcg of Tetanus Toxoid
Strength	1 dose (0.5 mL) contains: - Diphtheria toxoid: 25 Lf (≥30 IU) - Tetanus toxoid: 5.5 Lf (≥60 IU*) - B. Pertussis (whole cell): 16 IOU (≥4 IU**) - r-HBsAg: 12.5 mcg - Purified Capsular Polysaccharide of Hib (PRP) covalently linked to 20 - 36.7 µg of tetanus toxoid: 11 mcg * ≥ 40 IU when tested in guinea pigs and ≥ 60 IU when tested in mice **The lower fiducial limit (p=0.95) of the estimated potency is not less than 2.0 IU.
Pharmaco-therapeutic group (EMA)/Therapeutic class (USFDA)	Bacterial vaccines ATC code: J07CA11
Pharmaceutical form	Suspension for injection
Route of administration	Intramuscular Injection
Drug Characteristics	Whitish turbid liquid in which the mineral carriers, tends to settle down slowly on keeping and disperse uniformly upon shaking.
Packaging	Vial, glass type I
Package size(s)	0.5 ml (1 dose vial), 1.0 ml (2 doses vial), 2.5 ml (5 doses vial), 5.0 ml (10 doses vial), packed in paper box

2.2.2 Source

1. Name and address of the applicant for importation

Biogenetech Thailand

18 Soi Udomsuk 37, Sukhumvit 103 Rd. Bangjak, Prakanong, Bangkok 10260 Thailand.

Tel.: 027489333

2. Name and address of the manufacturer(s) for drug product

Biological E. Limited

Plot No.1, S.P. Biotech Park, Phase II, Ranga Reddy District, Shameerpet Mandal, Telangana, Replublic of India.

According to WHO public inspection report of the vaccine manufacturer conducted by prequalification team inspection services indicated that Biological E. Limited was considered to be operating at an acceptable level for compliance with WHO GMP guidelines. This report will remain valid for 3 years (3-7 October 2016 to October 2018) , provided that the outcome of any inspection conducted during this period is positive.

Reviewer's assessment

Biological E. Limited was licensed as manufacturer for human medicinal product with WHO GMP compliance inspected by WHO prequalified team and Drug Control Administration Government of Telangana. Therefore, the manufacturer has acceptable GMP standard.

Part 3: Analytical Physico-Chemical, Biological and Microbiological Documentation

Drug substance

Drug substance 1: Bulk Purified Diphtheria Toxoid.

Manufacturing process and testing are performed at Biological E. Limited located at Plot NO.1, Phase II, S.P. Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), Telangana, India.

Stability test:

Type of Study	Real Time
Storage condition	2-8 °C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 1, 2, 3, 6, 9, 12, 18, 24, 30, 36 and 42
Result	All 3 batches of BPDT comply with the specifications up to 36 months.

Type of Study	Accelerated
Storage condition	25±2°C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 1, 2, 3 and 6 months
Result	All 3 batches of BPDT comply with the specifications up to 6 months.

The results of the stability studies revealed that Bulk Purified Diphtheria Toxoid is stable up to 6 months, when stored at Accelerated storage conditions (25±2°C) and stable up to 36 months, when stored at Real time storage conditions (2-8°C). The real time stability study is ongoing.

Note: The shelf-life is assigned as 36 months based on the completed stability studies on initial batches of Bulk Purified Diphtheria Toxoid manufactured in Year 2007.

Container closure system

USP monograph <660> CONTAINERS—GLASS: Type I glass containers are suitable for most products for parenteral and nonparenteral uses.

Bulk Purified Diphtheria Toxoid is stored in 10 L or 20 L borosilicate glass bottles (Type-I) with blue color polypropylene (PP) screw cap closures and the stability data can prove the compatibility of BPDT with the container closure system.

Drug substance 2: Bulk Purified Tetanus Toxoid

Manufacturing process and testing are performed at M/s. Biological E. Limited located at 7-4-114, Gaganpahad, Rajendra Nagar Mandal, Ranga Reddy (District), Telangana, India.

Stability test

Type of Study	**Real Time**
Storage condition	2-8 °C
Container	Polypropylene Bottles with screw caps
Time frequency (Months)	3, 6, 9, 12, 18, 24, 30, 36 and 42
Result	All 3 batches of BPTT comply with the specifications up to 42 months.

Type of Study	**Accelerated**
Storage condition	21-25°C
Container	Polypropylene Bottles with screw caps
Time frequency (Months)	1, 2, 3 and 6
Result	All 3 batches of BPTT comply with the specifications up to 6 months.

Three Bulk Purified Tetanus Toxoid (BPTT) batches, which are manufactured at commercial scale were placed on stability at 2-8°C (real time) for 42 months and 21-25°C (accelerated) for 6 months.

From the results of the stability studies, it can be concluded that the product is stable up to 6 months, when stored at Accelerated storage conditions (21-25°C) and up to 42 months, when stored at Real time storage conditions (2-8°C).

Container closure system

USP monograph <661> PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION: Plastic components used for products of high risk, such as those intended for inhalation, parenteral preparation, and ophthalmics.

Bulk Purified Tetanus Toxoid is stored in 10 or 20 L white Polypropylene bottles, graduated with two handles, Polypropylene screw closure, TPE gasket. The stability data can prove the compatibility of BPTT with the container closure system.

Drug substance 3: Whole cell pertussis antigen bulk.

Manufacturing process and testing are performed at Biological E. Limited located at Plot NO.1, Phase II, S.P. Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), Telangana, India.

Stability test

Type of Study	**Real Time**
Storage condition	2-8°C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 3, 6, 9, 12, 15, 18, 24, 30 and 36
Result	All 3 batches of wPAB comply with the specifications up to 18 months.

Type of Study	**Accelerated**
Storage condition	25±2°C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 1, 2, 3 and 6
Result	All 3 batches of wPAB comply with the specifications up to 3 months.

Three Whole cell Pertussis Antigen bulk batches, which are manufactured at commercial scale have been placed on stability at 2-8°C (real time) for and 25±2°C (accelerated).

From the results of stability studies, it can be concluded that, the bulk antigen is stable up to 18 months when stored at 2-8°C and up to 3 months when stored at accelerated conditions.

Container closure system

USP monograph <660> CONTAINERS—GLASS: Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Type I glass containers are suitable for most products for parenteral and nonparenteral uses.

Whole cell Pertussis Antigen Bulk is stored in 10/20 L borosilicate glass bottles with blue color polypropylene (PP) screw cap closures and the stability data can prove the compatibility of wPAB with the container closure system.

Drug substance 4: Hepatitis B Purified Bulk.

Manufacturing process and testing are performed at Biological E. Limited located at Plot NO.1, Phase II, S.P. Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), Telangana, India.

Stability test

Type of Study	**Real Time**
Storage condition	2-8°C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 3, 6, 9, 12, 15, 18, 24, 30, 36 and 42
	All 3 batches of HBPB comply with the specifications up to 42 months.

Type of Study	**Accelerated**
Storage condition	21-25°C
Container	USP type 1 Schott Duran Glass bottle with Schott Duran Blue color screw caps
Time frequency (Months)	0, 1, 2, 3 and 6
Result	All 3 batches of HBPB comply with the specifications up to 6 months.

Three batches which are manufactured at commercial scale were placed on stability at 2-8°C (real time) for 36 months and at 21-25°C (accelerated) for 6 months.

From the results of the stability studies, it can be concluded that the product is stable up to 6 months, when stored at Accelerated storage conditions (21-25°C) and up to 42 months, when stored at Real time storage conditions (2-8°C).

Container closure system

USP monograph <660> CONTAINERS—GLASS: Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Type I glass containers are suitable for most products for parenteral and nonparenteral uses.

Hepatitis-B purified bulk is stored in 10 L or 20 L borosilicate glass bottles with blue color polypropylene (PP) screw cap closures and the stability data can prove the compatibility of HBPB with the container closure system.

Drug substance 5: *Haemophilus influenzae* type b Bulk Conjugate, Biological E. Limited.

Manufacturing process and testing are performed at Biological E. Limited located at Plot NO.1, Phase II, S.P. Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), Telangana, India.

Stability test

Type of Study	**Real Time**
Storage condition	2-8°C
Container	Schott Duran Glass bottle with Blue color screw caps
Time frequency (Months)	0, 1, 2, 3, 6, 9 and 12
Result	All initial 3 batches of HITT and new 3 batches of HITT comply with the specifications up to 12 months.

Type of Study	**Accelerated**
Storage condition	25±2°C
Container	Schott Duran Glass bottle with Blue color screw caps
Time frequency (Months)	0, 1, 2, 3 and 6
Result	All initial 3 batches of HITT comply with the specifications up to 6 months.

Three batches of HITT, which are manufactured at commercial scale were placed on stability at 2-8°C (real time) for 12 months and at 25±2°C (accelerated) for 6 months.

From the results of stability studies it can be concluded that the bulk antigen is stable up to 12 months, when stored at Real time storage conditions (2-8°C) and up to 6 months, when stored at accelerated conditions (25±2°C).

Container closure system

USP monograph <660> CONTAINERS—GLASS: Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Type I glass containers are suitable for most products for parenteral and nonparenteral uses.

Hib bulk conjugate is packed in 10 L or 20 L borosilicate glass bottles with polypropylene (PP) screw cap closures and the stability data can prove the compatibility of HITT with the container closure system.

Reviewer's assessment

The drug substance and excipients meet the standard criteria for vaccine. The control of drug substances, the analytical procedures, container closure system and stability tests are acceptable and meet the standard criteria from ICH guidlines.

3.2 Drug product

3.2.1 Manufacture

Manufacturer: Biological E. Limited: Plot No. 1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District. – 500 078, Telangana INDIA.

The information manufacturing process is appropriate and considered acceptable. Biological E. Limited Company was inspected by WHO prequalification team and found compliance to WHO standard.

The quantitative formulations are appropriate. The ingredients have been appropriately controlled.

Control of drug product

Finished product specification and test method is acceptable. According to prequalification summary assessment report from WHO, the manufacturing and control of the ready to use pentavalent vaccine manufactured by Biological E. Ltd. had faced no issues or constraints which may affect its international supply during the reporting period. There are no recalls reported of the ready to use pentavalent vaccine manufacturing by Biological E. Ltd.

Stability test:

Real Time Stability: Three batches of DTwP-rHepB-Hib vaccine Single dose and Ten doses were kept on real time storage conditions (2-8°C) are meeting the specifications after completion of 30 months.

The real time stability studies on Two and Five dose presentations were completed up to 9 months and further studies are ongoing.

Accelerated Stability: Three batches of DTwP-rHepB-Hib vaccine Single dose and Ten dose were kept on accelerated conditions (stored at 25±2°C) are meeting the specifications after completion of 2 months.

Note: The accelerated stability studies for two and five doses presentations are not done due to applied bracketing approach, as the formulations are the same for all presentations.

Stability Conclusion: The results of these stability studies proved that *the vaccine is stable up to 30 months, when stored at real time storage conditions (2-8°C)* & stable up to 2 months, when stored at accelerated storage conditions (25±2°C).

Reviewer's assessment

According to prequalification summary assessment report from WHO, an extensive stability programme is conducted to monitor stability of the vaccine over its shelf life and after the introduction of major changes. The programme includes real time studies / real conditions studies with the vaccine strored at 2-8 C and tested accordingly the protocols.

Drug product stability conforms with ASEAN Guideline. The shelf-life and storage conditions as stated in the SmPC are acceptable.

Container closure system

USP monograph <660> CONTAINERS—GLASS: Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Type I glass containers are suitable for most products for parenteral and nonparenteral uses.

DTwP-rHepB-Hib vaccine (Liquid Pentavalent Vaccine) is filled in USP type I glass vials stoppered with bromobutyl rubber stoppers and sealed using Aluminium flip off seals and the stability data can prove the compatibility of DP with the container closure system.

Reviewer's assessment

Container closure system is acceptable and in compliance with USP standard.

Assessor's conclusions on Quality

The quality data are acceptable. According to prequalification summary assessment report from WHO, the quality data on manufacturing and quality control of drug substances and drug product has been found satisfactory and in compliance with WHO recommendation.

Part 4: Non-clinical documentation

- **4.1 Pharmacokinetic (*ADME)***

  Not applicable for vaccine

- **4.2 Pharmacodynamics**

  Not applicable for vaccine

- **4.3 Toxicology**

  The 60-day toxicity study of DTwP-rHepB-Hib vaccine by intramuscular administration was performed in Wistar rats. The objective of the study was to evaluate the safety and reversibility of toxicity (if any).

  Conclusion

  Treatment of rats with DTwP-rHepB-Hib vaccine up to the dose of double SHD /rat body weight did not exhibit any significant treatment effects, on their hematology and biochemistry parameters.

  The No Observed Adverse Effect Level (NOAEL) of DTwP-rHepB-Hib vaccine in Wistar rats, following intramuscular administration on Day 1, 28, and 56 days was found to be double SHD/rat.

Reproduction Toxicity

Not applicable

Other toxicity studies

Not applicable

Assessor's conclusions on non-clinic aspect

No non-clinical pharmacokinetics, pharmacodynamics and pharmacodynamics drug interaction studies have been performed with the vaccine; this is acceptable since repeated dose toxicities studies were performed.

According to repeat-dose toxicity study, treatment of rats with DTwP-rHepB-Hib vaccine (liquid pentavalent combination vaccine) up to the dose of double SHD /rat body weight did not exhibit any significant treatment effects, on their hematology and biochemistry parameters. There is no observed adverse effect level (NOAEL) of DTwP-rHepB-Hib vaccine in Winstar rats. There are enough non-clinical evidences submitted to support efficacy and safety

profiles of DTwP-rHepB-Hib vaccine. The studies in animals are acceptable and follow the GLP standard. The prequalification summary assessment report from WHO also confirms the efficacy and safety profiles of DTwP-rHepB-Hib vaccine. There is no issue to reject the registration for marketing authorization of DTwP-rHepB-Hib vaccine in Thailand for the intended claim.

Part 5: Clinical Study Reports

Efficacy and safety data

Study 1

Study 1: A multicentric, single blind, parallel, randomized, phase-III study to evaluate the immunogenicity & safety of BEs combined pentavalent DTwP-rHepB-HIB liquid vaccine administered to 6-8 week old healthy Indian subjects at 6-10-14 weeks EPI schedule in comparison with marketed Shan5™

Study Code: BECT012

Design: Multicentric, single blind, parallel, randomized, phase III

Methodology:

This study was conducted at three study centres (n=30/centre) and all randomized 6-8 week old healthy infants of either gender (between 42-56 days at the time of first vaccination) underwent identical study procedures in both the study groups. All 90 subjects were randomized in 2:1 ratio, using a computer generated concealed randomized allocation sequence, either to the investigational or reference vaccine group. Study vaccine was administered single blinded for all the study participants as per WHO–EPI 6-10-14 week Schedule. A dose of 0.5 mL was delivered intramuscularly, as a three dose primary vaccination at Day 0, Day 28 and at Day 56 for all subjects. Subjects were evaluated for any adverse events during the entire period of the study.

Objective:

Primary: Seroprotection level at day 84

Secondary:

- GMTs at day 84
- Fold rise in antibody titer
- Safety and reactogenicity

Subject: 90 subjects of healthy Indian infants (6-8 weeks old)

Duration of treatment:

The duration of treatment for 6-8 week old infants in both study groups was 84 days (Time Window -4 +7 days). Overall study duration was 91 days for subjects in both the groups.

Place & Year: India, 2009

Conclusion	Efficacy - There were no significant differences in proportion of subjects achieving 4-fold rise in antibody titres against diphtheria, Pertussis, hepatitis-B and haemophilus influenzae type b components except for tetanus component where the p-value was significant (p0.0032). This difference in tetanus is because more number of subjects (40.35%) in BE group achieved 4-fold increase in antibody titres when compared with 10.0% in SHANTA group. Safety - Frequency of adverse events were similar between both vaccine groups and vaccine-related adverse events were mostly mild (66.18% in BE as against 66.67% in Shan5). - None of the subjects had any serious adverse events

Study 2

Study 2: A multicentric, single blind, parallel, randomized, phase-IV non-inferiority study to evaluate the immunogenicity & safety of BEs combined liquid pentavalent DTwP-rHepB-HIB vaccine administered to 6-8 week old healthy Indian infants at 6-10-14 weeks schedule in comparison with a marketed SIIL's Pentavac SD™ vaccine.

Study Code: BECT011

Design: Multicentric, single blind, parallel, randomized, phase IV

Methodology:

This study was conducted at eight study centres (n=51/centre) and all randomized 6-8 week old healthy infants of either gender (between 42-56 days at the time of first vaccination) underwent identical study procedures in both the study groups. All 408 subjects were randomized in 2:1 ratio, using a computer generated concealed randomized allocation sequence, either to the investigational or reference vaccine group. Study vaccine was administered single blinded for all the study participants as per WHO–EPI 6-10-14 week Schedule. A dose of 0.5 mL was administered intramuscularly, as a three dose primary vaccination at Day 0, Day 28 and at Day 56 for all subjects, with a dosing interval of 28 days. Subjects were evaluated for any adverse events during the entire period of the study.

Objective:

Primary: Demonstrate non-inferiority of BE Pentavalent vaccine with Pentavac SD (DTwP-rHeB-Hib) (seroprotection at day 84)

Secondary:

- Fold rise in antibody to D, P, T, HB and Hib above seroprotection cut off level between BE vaccine and Pentavac SD at day 84
- Comparison of GMTs to D, T, P, HB and Hib between both groups at day 84
- Assess safety and tolerability of BE vaccine and Pentavac SD for 84 days

Subject: 408 subjects of healthy Indian infants (6-8 week old)

Duration of treatment:

The duration of treatment for 6-8 week old infants in both study groups was 84 days (Time Window -4 +7 days). Overall study duration was 91 days for subjects in both the groups.

Place & Year: India, 2011

Conclusion	Efficacy: - There were no statistically significant differences in proportion of subjects achieving 4-fold rise in antibody titres against diphtheria, tetanus, pertussis and hepatitis-B except for haemophilus influenzae type b component (p 0.0390). Safety: - Frequency of adverse events were similar between both vaccine groups, and vaccine-related adverse events were mostly mild in severity (76.47% in BE against 77.94% in SIIL). - None of the subjects had any related serious adverse events

Study 3

Study 3: A multicentric double blind single arm randomised phase-IV study to evaluate the safety, reactogenicity & lot consistency of three production lots of BE"s combined liquid pentavalent DTwP-rHepB-HIB vaccine administered at 6-10-14 weeks schedule to 6-8 week old healthy Indian infants.

Study Code: BECT014

Design: Multicentric, double blind, single and randomized, phase IV

Methodology:

This study was conducted at nine study centres (n=66/center) and all randomized 6-8 week old healthy infants of either gender (between 42-56 days at the time of first vaccination) underwent identical study procedures in all the study groups. All 660 subjects were randomized in 1:1:1 ratio, using a computer generated concealed randomized allocation sequence, either to Lot-A, Lot-B and Lot-C vaccine groups. Study vaccine was administered double blinded for all the study participants as per WHO–EPI 6-10-14 week Schedule.

A dose of 0.5 mL was administered intramuscularly, as a three dose primary vaccination at Day 0, Day 28 and at Day 56 for all subjects with a dosing interval of 28 days. Subjects were evaluated for any adverse events during the entire period of the study.

<table>
<tr><td colspan="2">Objective:
Primary: Evaluation of safety and reactogenicity at 28 days after the 3rd dose (6-10-14 weeks schedule)
Secondary:
Demonstrate equivalence between 3 production lots of the following parameters at day 84 (28 days after the 3rd dose)
- GMT
- Seroprotection
- Fold rise above the seroprotection cut off value
Subject: 660 subjects of 6-8 weeks old healthy Indian infants
Duration of treatment:
The duration of treatment for 6-8 week old infants in both study groups was 84 days (Time Window -4 +7 days). Overall study duration was 91 days for subjects in both the groups.
Place & Year: India, 2011</td></tr>
<tr><td>Conclusion</td><td>Efficacy:
- There were no clinically significant differences between the three lot groups in terms of local and systemic adverse events reported (p<0.05)
- There were no clinically significant differences in seroprotection rates (SPR) between the three lot groups and the SPRs were adequate and comparable. (p<0.05)

Safety:
- No related serious adverse events were reported in any of the three lot groups.</td></tr>
</table>

Assessor's conclusions on Clinic aspect

According to prequalification summary assessment report from WHO, all the three studies vaccine lot groups demonstrated an acceptable safety profile and were well tolerated at each vaccination administration time point. No deaths occurred during the entire period of study. None of the subjects experienced any other serious. There were no clinically relevant differences between the three lot groups in terms of safety.

There were no clinically significant differences in seroprotection rates (SPR) between the three lot groups. Efficacy is assessed using the surrogate of immunogenicity to each of the vaccine antigenic components. The assays used for these require some additional information or justification. The cut-off antibody levels for seroconversion appeared acceptable. The results indicated acceptable and similar seroconversion rates for the components of the test vaccine and comparator vaccines.

There is sufficient data to support the efficacy of pentavalent vaccine at the applicated indication; the vaccine is indicated for the active immunization against diphtheria, tetanus, pertussis, hepatitis B and diseases caused by Haemophilus influenza tybe b in infants from 6 weeks of age.

Part 6 Risk Management Plan

Risk Management Plan: there is more deep detail in annex 1 (eCTD module: 1.8.2). The main points are

1. Summary of the safety concerns
2. Pharmacovigilance plan
3. Risk minimization measures

Overall Benefit/risk assessment

External expert reviews the documents submitted to support the quality of DTwP+HB+Hib vaccine, along with prequalification summary assessment report from World Health Organization (WHO) conclude that that the quality, efficacy and safety issues of the vaccine is acceptable and pass the standard criteria.

Based on the supported documents on quality, safety and efficacy, thai FDA considers the benefit over risk of DTwP-HB-Hib vaccine in the active immunization against diphtheria, tetanus, pertussis, hepatitis B (HB) and *Haemophilus influenza* tybe b disease infants > 6 weeks by concensus. Therefore recommends the granting of the marketing authorization subject to the following conditions:

1) This medicine will only be prescribed in the hospitals and clinic as stated on the label.
2) Drug safety profile will be monitored according to the protocol as proposed in the Safety monitoring programme (SMP).
3) Submit the complete version of patient information leaflet (PIL) after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval)
4) Submit the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

References

1. Vaccines Handbook, 9th International Congress of Tropical Pediatrics. 2011. Available at: http://www.pidst.or.th/A203.html
2. Expanded Programme on Immunization (EPI) Fact Sheet, Thailand. 2017. Available at: http://www.searo.who.int/immunization/data/thailand_2017.pdf

Annex

Annex 1

Summary of the safety concerns

Important identified risks:

- Common AEs, Hypersensitivity to any component of vaccine, Child has experienced an encephalopathy of unknown etiology occurring within 7 days following previous dose of vaccine with a pertussis containing vaccine, Infants with known family history of Sudden Infant Death Syndrome (SIDS).
- Immunocompromised person/persons receiving immunosuppressive therapy, the expected immune response may not be achieved.
- Subjects with thrombocytopenia or bleeding disorder, bleeding may occur following intramuscular injection.

Important potential risks:

- Possible interference of maternal antibodies with active immune response to its corresponding antigen in the vaccine resulting in inadequate immune.

Miss information:

- Information for use during pregnancy or lactation is not available.

Vaccine has not been evaluated for carcinogenic or mutagenic potential or for impairment of fertility.

Pharmacovigilance plan

The surveillance system proposed in this PV plan focuses on safety surveillance with two components:

1. Routine Pharmacovigilance practice based primarily on spontaneous reporting

Routine Pharmacovigilance practices of Biological E. Limited (BE LTD.) would include the elements outlined below:

- Spontaneous Reporting Systems and Processes
- Expedited adverse drug reaction (ADR) reports
- Periodic safety Update Reports (PSUR)

2. Active Pharmacovigilance Surveillance through targeted clinical investigation