Assessment report for biological medicinal product
Diphtheria, tetanus and pertussis vaccine (Adsorbed), Tripvac 28 August 2018
Division of Health Product Enterprise Services
Thai Food and Drug Administration

ชื่อผลิตภัณฑ์ **Name of product**	Tripvac
ชื่อตัวยาสำคัญ **Active Substance(s)**	Diphtheria toxoid, tetanus toxoid, B. Pertussis
รูปแบบยา **Pharmaceutical form**	Suspension for injection
ความแรง **Strength**	Diphtheria toxoid 25 Lf (>30 IU) Tetanus toxoid 5.5 Lf (≥60 IU)* B. Pertussis 16 IOU(≥4.0 IU)** * ≥ 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.
ช่องทางการบริหารยา **Route(s) of administration**	Intramuscular injection
ข้อบ่งใช้ที่ขอขึ้นทะเบียน **Therapeutic indication(s)**	<u>Patient information leaflet</u> กระตุ้นให้เกิดการสร้างภูมิคุ้มกันต่อโรคคอตีบ บาดทะยัก ไอกรน ในทารกที่มีอายุตั้งแต่ 6 สัปดาห์ขึ้นไป
	<u>SmPC</u> Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) (DTwP) is indicated for primary immunization of infants, above the age of six weeks against diphtheria, tetanus and whooping cough diseases. The vaccine can be safely and effectively given at the same time as BCG, Measles, Polio (OPV and IPV), Hepatitis B, Yellow fever, *Haemophilus influenzae* type b vaccines and Vitamin A supplementation.
เลขรับคำขอขึ้นทะเบียนตำรับยา และ วันที่รับคำขอ	2C 15108/60 (B) 7 พฤศจิกายน 2560
E-Identifier Number	e6000063

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Abbreviations

DTP	Diphtheria, tetanus toxoid and pertussis
DTPa	Diphtheria, tetanus toxoid and pertussis, acellular

DTPw	Diphtheria, tetanus toxoid and pertussis, whole cell
DTwP	Diphtheria, tetanus toxoid and whole cell pertussis
HBV	Hepatitis-B virus
HCV	Hepatitis-C virus
Hib	Haemophilus Influenzae type B
OPV	Oral Polio Vacccine
Ph. Eur.	European Pharmacopoeia
SAE	serious adverse event
TEAE	treatment-emergent adverse event
VVMs	Vaccine Vial Monitors
USP	United States Pharmacopoeia
WHO	World Health Organization

Assessment report for biological product
Diphtheria, tetanus and pertussis vaccine (Adsorbed)
Tripvac
2C 15108/60 (B) E-identifier: e6000063
(Manufacturing site: Biological E. Limited)
28 August 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.

Reported cases of vaccine preventable diseases, 2011-2016 Thailand

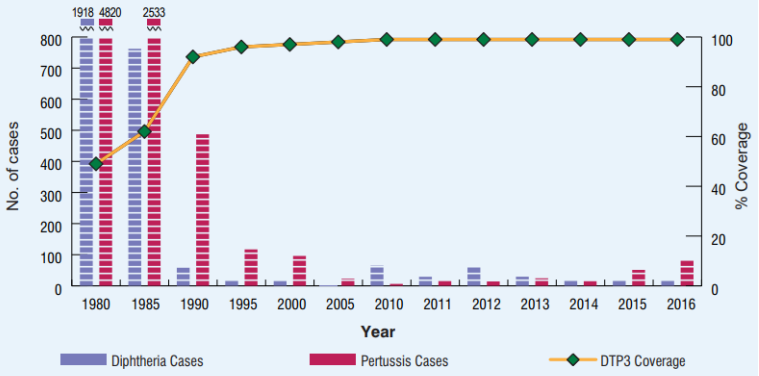
Year	Diphtheria	Pertussis	NT: neonatal tetanus (% of all Tetanus)
2011	28	12	1 (1%)

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

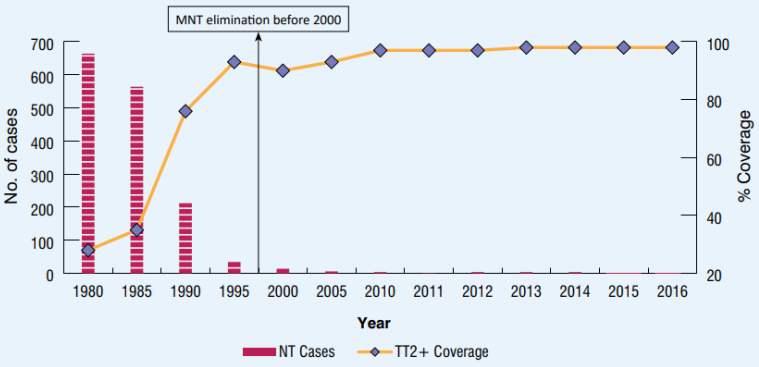
Thailand Immunization schedule, 2018

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) (Adsorbed) is a sterile suspension for injection which contains diphtheria (D), tetanus (T) toxoids, whole cell inactivated pertussis bacteria (wP). It is a whitish turbid liquid in which the mineral carrier tends to settle down slowly on keeping. 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.

Mechanism of action

Active immunization against diphtheria, tetanus and pertussis disease.

Registered Countries

Country	Approval date	Indication	Registration Name
India	03.10.1979	Active immunization against diphtheria, tetanus and pertussis in infants above 6 weeks of age.	Diphtheria, tetanus and pertussis vaccine adsorbed
Iran	14.02.2016		
Sri Lanka	21.07.2017		

Part 2: Summary of the dossier

2.1 Type of marketing authorization application

- **Product type:** Biological product
- **Application type:** Full assessment

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 quality part was also evaluated by expert panel.

2.2 Administrative data

2.2.1 Product

Name of Product: Invented name	Tripvac
Active Substance(s)	Diphtheria toxoid, tetanus toxoid, B. Pertussis
Strength	Diphtheria toxoid 25 Lf (>30 IU) Tetanus toxoid 5.5 Lf (≥60 IU)* B. Pertussis 16 IOU(≥4.0 IU)** * ≥ 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.
Therapeutic class	ATC code: J07AJ51
Pharmaceutical form	Suspension for injection
Route of administration	Intramuscular injection
Drug Characteristics	Whitish turbid liquid in which the mineral carrier tends to settle down slowly on keeping
Packaging/Package size(s)	Vial, glass type I: 0.5 ml (1 dose 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

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 and also licensed as GMPc from Bureau of drug control, Food and drug administration, Thailand. Therefore, the manufacturer has acceptable GMP standard.

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

3.1 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 ℃
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℃
Time frequency (Months)	0, 1, 2, 3 and 6 months
Result	All 3 batches of BPDT comply with the specifications up to 6 months.

Three Bulk Purified Diphtheria Toxoid batches which are manufactured at commercial scale were placed on stability at 2-8℃ (real time) for 42 months and 25±2℃ (accelerated) for 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℃) and stable up to 42 months, when stored at Real time storage conditions (2-8℃).

Container closure system

USP monograph <660> CONTAINERS—GLASS: Type I glass containers are suitable for most products for parenteral and non-parenteral 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 ℃
Time frequency (Months)	0, 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℃
Time frequency (Months)	0, 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℃ (real time) for 42 months and 21-25℃ (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℃) and up to 42 months, when stored at Real time storage conditions (2-8℃).

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 non-parenteral 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.

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 guidelines.

3.2 Drug product

3.2.1 Manufacture

Name and Address of Site	Responsibility
M/s Biological E. Limited Plot No. 1, Phase II, Shapoorji Pallonji Biotech Park, Kolthur Village, Shameerpet Mandal, Ranga Reddy (District), INDIA - 500078	Formulation, Filling, Packing & Distribution of Diphtheria, Tetanus and Pertussis Vaccine Adsorbed (Drug Product).

The 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 are acceptable. According to prequalification summary assessment report from WHO, the manufacturing and control of the ready to use DTwP 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 DTwP vaccine manufacturing by Biological E Ltd.

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 non-parenteral uses.

DTwP 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 DTwP with the container closure system.

Reviewer's assessment

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

3.2.5 Stability

Stability summary and conclusion (Diphtheria, Tetanus and Pertussis Vaccine [Adsorbed], 1 dose and 10 doses)

Three batches of Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) single dose and ten dose were placed on stability at 2-8 °C (real time) and at 25±2 °C (accelerated conditions).

Conclusion: The results of the stability studies proved that the vaccine is stable up to 24 months, when stored at 2-8°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 stored 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.

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 the vaccine

- **4.2 Pharmacodynamics**

Not applicable for the vaccine

- **4.3 Toxicology**

DTwP vaccine has been used for a long time. However, Biological E. Limited company enclosed the studies using combined vaccine with the same antigens.

Study 1: Single dose toxicity: Using DTwP+r-Hepatitis B vaccine in mice and rabbits for 14 days. There was no any serious adverse event.

Study 2: Repeat dose toxicity: Using DTwP-rHepB-Hib vaccine (liquid pentavalent combination vaccine) in Wistar for 60 days. There was no any serious adverse event.

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.

The prequalification summary assessment report from WHO also confirms the efficacy and safety profiles of DTwP vaccine. Overall non-clinical evidence is acceptable**.**

Part 5: Clinical Study Reports study

DTwP vaccine has been used for a long time. There is none of the study for supporting. So the company used other vaccines study which using the same antigen as DTwP vaccine. *(Show on table 21)*

Table 21Clinical studies

Study number [Reference]	Study design/ study population	Description/Doses studied/Duration of treatment	Conclusions
STUDY 1 (Fully Liquid Pentavalent) Study Code: BECT012 Protocol No.: BECT012/DTwP-rHepB-HIB-PIII/CTP-01 Phase – III (Immunogenicity & Safety Study) Study Completed: 10th July,2009-30th Oct., 2009	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™ vaccine. **90 Subjects**	- Randomized 2:1 ratio, 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. Duration: 91 days	**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).

Study number [Reference]	Study design/ study population	Description/Doses studied/Duration of treatment	Conclusions
			- None of the subjects had any serious adverse events
STUDY 2 (Reconstituted Pentavalent) Study Code: BECT008 Protocol No.: BE/Penta/DTwPrHepB +HIB/ CTP-01 Phase – III (Immunogenicity&Safety Study) Study Completed 02nd Feb.2009-16th June 2009	A multicentric, single blind, parallel, randomised phase-III study to evaluate the immunogenicity & safety of BE's reconstituted pentavalent vaccine [Haemophilus influenza type b Tetanus conjugate vaccine reconstituted with DTwP-Hepatitis- B vaccine] administered to 6-8 week old healthy Indian infants at 6-10-14 weeks in comparison with GSK's HiberixTM reconstituted with TritanrixTM-HB vaccine – A noninferiority study. **270 Subjects**	- Randomized 1:1 ratio, either to the experimental 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. Duration: 91 days	**Efficacy:** - There were no statistically significant differences in proportion of subjects achieving 4- fold increase between BE and GSK groups at Day 84 in all the four antigens except in Haemophilus influenzae where the p-value is 0.0403. No clinical significance is attributable as no significant difference in proportion of subjects seroprotected (≥1.0 µg/mL) between both the groups was noted for HIB. **Safety:** Frequency of adverse events were similar between vaccine groups, and vaccine related adverse events were generally mild.

Study number [Reference]	Study design/ study population	Description/Doses studied/Duration of treatment	Conclusions
STUDY 3 (Fully Liquid Pentavalent) Study Code: BECT011 Protocol No.: BECT011/DTwP-rHepB-HIB-PIV/CTP-01 Phase – IV (Immunogenicity & Safety Study) Study Completed 25th April, 2011-13th Sept. 2011	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. **408 Subjects**	- Randomized 2:1 ratio, 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. Duration: 91 days	**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 4 (Fully Liquid Pentavalent) Study Code: BECT014 Protocol No.: BECT014/DTwPrHepB-HIBPIV/ CTP-01	A multicentric double blind single arm randomised phase-IV study to evaluate the safety, reactogenicity & lot consistency of three production lots of BEs combined liquid pentavalent DTwP-rHepB-HIB vaccine administered at 6-10-14 weeks	- Randomized 1:1:1 ratio, 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	**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

Study number [Reference]	Study design/ study population	Description/Doses studied/Duration of treatment	Conclusions
Phase – IV (Study to evaluate the safety, reactogenicity & lot consistency) Study Completed 23rd April 2011-14th Sept.2011	schedule to 6-8 week old healthy Indian infants. 660 Subjects	56 for all subjects with a dosing interval of 28 days. Durations: 91 days	SPRs were adequate and comparable. ($p<0.05$) **Safety:** - No related serious adverse events were reported in any of the three lot groups.
STUDY 5 (Reconstituted Pentavalent) Study Code: BECT017 Protocol No.: BECT017/DTwP-rHepB +HIB- PIV/CTP-01 Phase – IV (Safety & Reactogenicity study) Study Completed 4th Oct.2010-25th Feb.2011	A multicentric open label non-comparative phase-IV observational study to evaluate safety and Reactogenicity of BE's reconstituted Pentavalent DTwP-rHepB+HIB vaccine in 6-8 week old healthy infants as per routine EPI Schedule. 640 Subjects	- Study vaccine was administered for all the study participants as per WHO–EPI 6-10-14 weeks dosing schedule. A dose of 0.5 mL of reconstituted study vaccine was administered intramuscularly, as a three dose primary vaccination at Day 0, Day 28 and at Day 56 for all subjects. Duration: 91 days	**Efficacy:** - As this is a phase-IV safety study no immunogenicity assessment was performed. **Safety:** - Most of the reported adverse events were mild to moderate in severity and there were no serious adverse reactions reported during the entire course of the study

Commented [DN1]: For other studies, you use total study period. Then we changed this point to 91 days.

Assessor's conclusions on Clinical aspect

According to prequalification summary assessment report from WHO, all the five 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 DTwP vaccine at the applicated indication; Diphtheria, Tetanus and Pertussis Vaccine (Adsorbed) (DTwP) is indicated for primary immunization of infants, above the age of six weeks against diphtheria, tetanus and whooping cough diseases. The vaccine can be safely and effectively given at the same time as BCG, Measles, Polio (OPV and IPV), Hepatitis B, Yellow fever, *Haemophilus influenzae* type b vaccines and Vitamin A supplementation.

Part 6 Risk Management Plan

Risk management plan consists of three key topics as following

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

Please see annex 1 for details

Overall Benefit/risk assessment

External quality expert reviews the documents submitted to support the quality of DTwP vaccine, along with prequalification summary assessment report from World Health Organization (WHO) conclude 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, the benefit of DTwP vaccine is over risk when indicated for primary immunization of infants, above the age of six weeks against diphtheria, tetanus and whooping cough diseases. The vaccine can be safely and effectively given at the same time as BCG, Measles, Polio (OPV and IPV), Hepatitis B, Yellow fever, *Haemophilus influenzae* type b vaccines and Vitamin A supplementation.

Therefore recommends the granting of the marketing authorization subject to the following conditions:

1) 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)
2) 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

Risk Management Plan

Summary of safety concerns

Important identified risks	Common AEs, Hypersensitivity to any component of vaccine including anaphylaxis reaction.
Important potential risks	Possible interference of maternal antibodies with active immune response to its corresponding antigen resulting in inadequate immune.
Missing 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

Planned PV actions:

Passive (spontaneous and stimulated reporting) and Active PV Practices

Planned Risk Minimization Actions:

Routine PV activities

Warning and information included in the leaflet

Proper training to field force personnel to collect ADR information

Direct contact available for HCP