PUBLIC ASSESSMENT REPORT
FOR
BEtt® (Ampoule presentation)

Common Name: **Adsorbed Tetanus Vaccine BP**

Application No. 1C 15086/60 (NB) (Initial)
Application No. 1C 15134/61 (NB) (Revised after the applicant was changed)

Assessment Report as adopted by the TFDA with
all information of a commercially confidential nature deleted

TABLE OF CONTENTS

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant **Biogenetech Co., Ltd.** submitted an application for Marketing Authorization as electronic dossier on September 5, 2017 and submitted the hard copies of the certificates and application forms on September 7, 2017 to the Thailand Food and Drug Administration (TFDA). At the time of submission and validation, **BEtt®** (Ampoule presentation) was designated as medicinal product in the following indication: For Tetanus prophylaxis, post exposure prophylaxis of Tetanus, neonatal tetanus prevention and Tetanus prophylaxis in wound management.

The legal basis for this application refers to: Drug Act 2510 B.E.

The application submitted was a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature substituting/supporting certain tests or studies.

Licensing status:

The product was licensed in the country of origin (India) and the other countries like Nepal, Nigeria, Colombia, Philippines, Pakistan, Niger, Uganda, Ivory Coast, Jordan, Egypt, Tanzania, Sri Lanka, Zimbabwe, Mozambique, Namibia, Kenya, Ghana, Syria at the time of submission of the application.

This vaccine uses the same bulk of vaccine that was approved and listed as WHO prequalified vaccine or BEtt® (Vial presentation) approved by WHO on July 12, 2012 (1 and 10 doses vial) and on December 21, 2009 (20 doses vial). Only difference is a container that the final bulk of Tetanus vaccine is filled.

TFDA Product Team Leader: (PTL)
Ms. Worasuda Yoongthong
TFDA External Experts

1.2 Steps taken for the assessment of the product

- The application was received by the TFDA on September 7, 2017
- The procedure started on September 2017
- A List of questions, the overall conclusion and review of the scientific data were prepared by the TFDA's PTL and sent to the applicant in March 2018
- The applicant submitted of the responses, including revised English SPC, Thai PIL and labeling (where required by Drug Act) during May 2018-January 2019.

- TFDA prepared preliminary Assessment Report based on responses from the applicant and dispatched the assessment report to external experts for their consideration and comments.
- Final draft of English SPC, Thai PIL and labeling was sent by applicant to the TFDA PTL in January, 2019.
- TFDA adopted the decision on marketing authorization on January 22, 2019.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Tetanus is a serious illness contracted through exposure to the spores of the bacterium, *Clostridium tetani*, which live in soil, saliva, dust, and manure. The bacteria can enter the body through a deep cut, wounds or burns affecting the nervous system. The infection leads to painful muscle contractions, particularly of the jaw and neck muscle, and is commonly known as "lockjaw".

People of all ages can get tetanus but the disease is particularly common and serious in newborn babies and their mothers when the mothers` are unprotected from tetanus by the vaccine, tetanus toxoid. Tetanus occurring during pregnancy or within 6 weeks of the end of pregnancy is called "maternal tetanus", while tetanus occurring within the first 28 days of life is called "neonatal tetanus".

The disease remains an important public health problem in many parts of the world, but especially in low-income countries or districts, where immunization coverage is low and unclean birth practices are common. WHO estimates that in 2018 (the latest year for which estimates are available), 25,000 newborns died from neonatal tetanus, 88% reduction from the situation in 2000. Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines (TTCV), which are included in routine immunization programmes globally and administered during antenatal care contacts.

To be protected throughout life, WHO recommends that an individual receives TTCV.

Neonatal tetanus can be prevented by immunizing women of reproductive age with TTCV, either during pregnancy or outside of pregnancy. Additionally, robust medical practices can also prevent tetanus disease including clean delivery and cord care during childbirth, and proper wound care for surgical and dental procedures.

2.2 Quality aspects

Introduction

BEtt® (Ampoule presentation) is Adsorbed Tetanus Vaccine which belongs to the pharmacotherapeutic group of J07AM01 (ATC CODE).

BEtt® (Ampoule presentation) is a sterile preparation of refined tetanus toxoid. The toxoid is purified by chemical methods and is adsorbed onto aluminium phosphate. Thiomersal (0.01% w/v) is added as preservative. The vaccine is a white turbid suspension in which the mineral carrier tends to settle down slowly on keeping. The vaccine meets the requirements of WHO and BP.

Active Substance

Each dose (0.5 ml) contains:

Tetanus Toxoid	≥ 40 IU
Adsorbed on Aluminium phosphate (AlPO4)	≥ 1.5 mg
Preservative: Thiomersal BP	0.01% w/v

Manufacturers

Manufacturing facility	Operations
Biological E. Limited 7-4-114, Gaganpahad, Rajendra Nagar Mandal Ranga Reddy (District), India-501323	Manufacture of bulk purified tetanus toxoid
Biological E. Limited Plot No. 1, S.P. Biotechnoclogy Park Phase-II, Kolthur Village, Shameerpet Mandal Ranga Reddy District. – 500078, Telangana India	Formulation of Adsorbed Tetanus Vaccine
Biological E. Limited 18/1 & 3, Azamabad, Hyderabad, Telangana, India – 500020	Filling, labelling, packing and distribution of Adsorbed Tetanus Vaccine

I. DRUG SUBSTANCE(S)

1. *General Information, Starting Materials and Raw Materials*

BEtt® (Ampoule presentation) is a sterile preparation of refined tetanus toxoid. The toxoid is purified by chemical methods and is adsorbed onto aluminium phosphate. Thiomersal (0.01% w/v) is added as preservative.

2. Manufacturing Process of the Drug Substance(s)

2.1 Seed Virus Process

Master seed lot preparation

Seed of *Clostridium tetani* is used in the production of Tetanus Vaccine (Adsorbed). Lyophilized cultures of the master seed were received from Central Research Institute (CRI) Kasauli, and the production was started in 1968. Seed of *Clostridium tetani* is maintained in the production laboratory in test tubes under appropriate condition and is tested before use.

Working seed lot preparation

Master seed is used for production of working seed. Each working seed lot is used for production batch and is tested before use.

2.2 Bulk Process

The seed virus passes to the fermentation, clarification, concentration, sterile filtration, detoxification, purification, dia-filtration and pre-filtration before getting bulk purified tetanus toxoid (BPTT). Thiomersal is calculated and added to the targeted volume of BPTT based on the estimated concentration to get a desired final concentration. After that, BPTT is sterile filtered under laminar flow unit and stored in cold room.

2. *Characterization of the Drug Substance(s)*

Tetanus Toxin produced by the organism *Clostridium Tetani*, is a single polypeptide chain with a mean molecular weight of around 150 KDa. Basic characterization study was done on different batches to study the protein profiles by several techniques.

3. *Quality Control of the Drug Substance(s)*

Several tests are included in drug substance specification. Appropriate validation data have been submitted in support of the test procedures.

4. *Reference Standards or Materials*

Working Standard is used for estimation of Lf in BPTT. This working standard is standardized before use.

5. *Packaging and Container Closure System of the Drug Substance(s)*

BPTT is stored in polypropylene bottles at 2-8°C.

6. *Stability of the Drug Substance(s)*

Three batches of BPTT manufactured at commercial production scale were charged for stability at accelerated (21-25°C) for 6 months and real time conditions (2-8°C) for 36 months.

All the three batches of BPTT manufactured have completed the stability studies and are complying with the specifications and no significant trend changes have been observed during the stability.

Also three batches manufactured in year 2012/2013 are placed on stability at real time (2-8°C) and accelerated (25±2°C) conditions.

II. DRUG PRODUCT

1. *Description and composition of the Drug Product*

BEtt® (Ampoule presentation) is a sterile preparation of refined tetanus toxoid. The toxoid is purified by chemical methods and is adsorbed onto aluminium phosphate. Thiomersal (0.01% w/v) is added as preservative. The vaccine is a white turbid suspension in which the mineral carrier tends to settle down slowly on keeping.

2. *Pharmaceutical Development*

The manufacturing process (blending, filling and packing) of Adsorbed Tetanus Vaccine is developed and optimized in-house at BE.

Critical process parameters and in-process controls have been identified during the process development activities and the same were validated through process validation studies at commercial scale.

3. *Manufacturing Process of the Drug Product*

Calculation of the amount of material for adjuvant preparation and then preparation. Blending of BPTT with thiomersal and adjuvant preparation to produce final bulk and filling into the final container.

4. *Control of the Adjuvant(s), Preservative(s), Stabilizer(s), and Excipients(s)*

All excipients are controlled by the specification according to the requirements in the British Pharmacopoeia, United States Pharmacopoeia or In-house. Only excipients tested and released by the Quality Control Department/Production Department are used for the production.

5. *Quality Control of the Drug Product*

Several tests are included in drug product specification. Appropriate validation data have been submitted in support of the test procedures.

6. *Reference Standards and Materials*

Tetanus: At Biological E. Limited, internal reference standard for Tetanus Toxoid is established in-house and calibrated against the NIBSC standard of Tetanus Toxoid.

7. *Packaging and Container Closure System of the Drug Product*

BEtt® as per this application is filled in glass ampoule (USP type I).

8. ***Stability of the Drug Product***

The three consistency batches of vaccine were placed on stability study at real time condition (2-8°C) for 42 months and accelerated condition (25±2°C) for 6 months. According to the stability results, the shelf life for BEtt® (Ampoule presentation) is 36 months at the temperature of +2 to +8 °C.

The TFDA recommended on The Quality Dossiers as The followings:

Drug substance

1. Please provide the molecular structure, molecular weight and others of Tetanus toxoid in S1.2.
2. Please also indicate the type of fermentor used for Tetanus culture
3. Please send the result from biochemistry test of master seed and working seed lot of Tetanus.
4. Please declare the impurity from the detoxification of Tetanus toxin by formaldehyde..

Drug product

1. Please send the declaration letter to confirm that the detailed information i.e. production scheme, lot no. of master seed and working seed, seed test results and control of critical steps will be added in the summary lot protocol of product to be sent to Thailand.
2. Please provide transport validation report for transportation of bulk.
3. Please consider the tests on final bulk and finished product as per WHO TRS 980, 2014.

Other concerns

1. Information about holding time of final bulk before filling should be provided.

The company responded to the above recommendations as the followings:

Drug substance

1. The information on structure and molecular size of Tetanus Toxoid Bulk was provided. Revised completed sections related to drug substance were also enclosed herewith.
2. The details of the fermenter used for Tetanus Bulk manufacturing was provided.
3. The certificates of current Master and Working standards of Tetanus strain along with the biochemistry results were provided.
4. The information on impurities of Tetanus Toxoid Bulk was provided.

Drug product

1. The declaration to provide the information as requested as part of Summary Lot Protocols of TT Vaccine for all commercial shipments to Thailand was provided.
2. The validation report was provided.
3. Justification for the specification was provided and confirmed that all tests align with WHO TRS 980, 2014. SOPs and validation reports of the concerned tests including related information were also provided.

Other concerns

1. Information about holding time of final bulk before filling was provided.

TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON QUALITY ASPECTS

All documents are completed.

BASED ON THE RESULTS, THESE QUALITY ASPECT COULD BE ACCEPTED

2.3 Non-Clinical aspects

Introduction

I.PHARMACOLOGY

1 Pharmacodynamic studies (immunogenicity of the vaccine)

Not applicable.

2 Pharmacodynamic studies of adjuvant(s) (if applicable)

Not applicable.

II.PHARMACOKINETICS

Not applicable.

III. TOXICOLOGY

1. General toxicology

No toxicity studies were conducted on BEtt®.

Tetanus Toxoid Vaccine Adsorbed was license in India in 1979. There were no prevalent regulations existing during that time for requirement of preclinical trials for vaccines. By the way, BE has conducted pre-clinical trials on other combination vaccine like DTwP-rHepB Vaccine (Tetravalent Vaccine), DTwP-rHepB-Hib (Pentavalent Vaccine) where the same Tetanus antigen is part of the formulation.

Based on the review of the quality data and assessing the pre-clinical and clinical aspects, WHO pre-qualified Adsorbed Tetanus Vaccine (the same product but in vial presentation) in December 2009.

2. Special toxicology for vaccines (when applicable)

Not applicable.

2.1 Special immunological investigations

- Toxicity studies in special population

Not applicable.

- **Genotoxicity and carcinogenicity studies, when applicable**

Not applicable.

- Reproductive toxicity studies for vaccines to be administered to pregnant women or individuals of fertile age.

Not applicable.

3. SPECIAL CONSIDERATIONS (if applicable)

3.1 Live attenuated vaccines.

Not applicable as BEtt® is not live attenuated vaccine.

3.2 New substances incorporated into the formulation

None of new substances are used in vaccine formulation.

4. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

The labels are acceptable.

English SPC and Thai PIL will be used as product information.

5. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSIONS ON NON-CLINICAL ASPECTS

This vaccine has been manufactured according to the international standard and has been registered in many countries. The vaccine with same component (BEtt® (Vial presentation)) was also pre-qualified by WHO. Therefore, it can be acceptable to register and market in Thailand.

BASED ON THE STUDIES DESIGN AND RESULTS THESE NON-CLINICAL ASPECT COULD BE ACCEPTED

2.4 Clinical aspects

Introduction

1. REPORTS OF CLINICAL STUDIES

1 Phase I Studies

Not available.

2 Phase II Studies

Not available.

3 *Phase III Studies*

Not available.

4 Special Considerations

Not available.

5 Adjuvant(s)

Aluminium phosphate is used as an adjuvant. It is an adjuvant widely used in vaccine preparation.

6 Phase IV Studies and / or Pharmacovigilance plan (if applicable)

Phase IV, prospective, open-label clinical study has been performed on BE's Adsorbed Tetanus Vaccine to study the safety and efficacy of the vaccine in 100 healthy children and adults (Aged between 10-50 years excluding pregnant women) in comparison with a commercially available vaccine.

Two phase IV-bridging studies are also performed on BE's Adsorbed Tetanus Vaccine to prove safety and efficacy of the vaccine.

- A prospective, open label bridging study in sixty pregnant women aged between 18-44 years, during 13-20 weeks of gestation.
- A prospective, open label bridging study in 72 healthy children and adults aged between 10-50 years.

TT vaccine manufactured by BE was found to be safe at the given dose and immunization schedule studied in healthy children an adult in the age group of 10-50 years.

7 Non-inferiority Studies (for combined vaccines, or approved vaccines prepared by new manufacturers)

Not applicable.

8 Co-administration Studies with other Vaccines

The vaccine can be given safely and effectively at the same time as Measles, Polio (OPV and IPV), Hepatitis B, Yellow fever vaccine and Vitamin A supplementation.

2. TFDA PTL AND EXTERNAL EXPERT'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

The labels are acceptable.

English SPC and Thai PIL will be used as product information.

3. TFDA PTL AND EXTERNAL EXPERT'S OVERALL CONCLUSION ON CLINICAL ASPECTS

This vaccine has been manufactured according to the international standard and has been registered in many countries. The vaccine with same component (Vial presentation) was also pre-qualified by WHO. Therefore, it can be acceptable to register and market in Thailand.

<u>BASED ON THE STUDIES DESIGN AND RESULTS THESE CLINICAL ASPECT COULD BE ACCEPTED</u>

2.5 Pharmacovigilance (If applicable)

Spontaneous AE reporting system will be used for product safety monitoring.

2.6 Overall Conclusion and Recommendation

Recommendations

The TFDA and external experts have reviewed the clinical studies and found them evidently supportive; therefore positive opinion was given towards the approval of marketing authorization of **BEtt**® (Ampoule presentation).