Unit: Technical Assessment Unit

Public assessment report for biological products

ComBE Five (liquid)- Single and Ten dose vial

Administrative information:

Trade name of the medicinal product:	ComBE Five (liquid)- Ten dose vial ComBE Five (liquid) – single dose vial
INN (or common name) of the active substance(s):	Each dose of 0.5ml contains: Diphtheria Toxoid 25LF (≥30 IU) Tetanus Toxoid 5.5LF (≥60 IU) B. Pertussis (Whole cell) 16 IOU (≥4IU) r-HBsAg 12.5µg purified capsular polysaccharide of Hib (PRP) covalently linked to 20 to 36.7µg of Tetanus Toxoid 11µg Al+++ (as AlPO4) ≤1.25mg Preservative: Thiomersal Ph.Eur./BP 0.01% w/v
Manufacturer of the finished product	Biological E. Limited, plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District - 500 078, Telangana - India
Marketing Authorization holder	Biological E. Limited, plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District - 500 078, Telangana - India
Applied Indication(s):	
Pharmaceutical form(s) and strength(s):	Suspension for intramuscular injection
Route of administration	I,M
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations:

AEs: Adverse events
AEs: Adverse events

BE: Bioequivalence
BE: Bioequivalence
CI: Confidence interval
CI: Confidence interval
CQA: Critical quality ttributes
DP: Drug product
DS: Drug substance
GMT: Geometric mean titer
GMT: Geometric mean titer
IPCS: In-process controls
IV: Intravenous
IV: Intravenous
NOAEL: No Observed Adverse Effect Level
rDNA: Recombinant DNA
SAEs: Serious adverse events
SHD: SHD/rat: Sanhua Decoction treatment in rats to study conditions like ischemic stroke or other diseases
SIIL: Serum Institute of India

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Dossier initial submission and evaluation process:

The file evaluated according to normal track pathway & the company submitted data which are the Quality module-3 from the CTD file.

1. Introduction

- Combifive vaccine contains bulk purified Diphtheria Toxoid, Bulk Purified Tetanus Toxoid, Whole cell pertussis Antigen Bulk, Hepatitis B Purified bulk and Haemophilus type b conjugate bulk as active substance (bulk antigens) which are formulated with adjuvant (alumium phosphate), Thiomersal (preservative) and phosphate buffer (saline) as excipient in the final product.
- the final product appears as whitish turbid suspension in which the adjuvant tends to settle down on keeping.
- the product is supplied in two presentations as single dose vial (0.5ml liquid vaccine) and 10 doses vial (5ml liquid vaccine).
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- **Quality aspects:**

- General information:

a) Bulk Purified Diphtheria Toxoid: sterile, pale yellow to dark brown color clear liquid with antigenic purityof not less than 1500 Lf/mgPN_2 with shelf life 24 months stored at 2-8^{O}C

b) Bulk Purified Tetanus Toxoid: sterile, light to dark brown color clear liquid with antigenic purityof not less than 1000 Lf/mgPN_2 with shelf life 24 months stored at 2-8^{O}C

c) Whole cell Pertussis Antigen Bulk: Light to dark brown liquid with inactivated cells present in it. the shelf life is 12 months stored at 2-8^{O}C.

d) Hepatits B purified Bulk: Clear Colorless solution with shelf life 24 months stored at 2-8^{O}C

e)Haemophilus Influenza type b Vaccine Bulk Conjugate: Sterile liquid with the PRP-Protein

Manufacture, process controls and characterization:

- **Manufacturer:**

- Biological E. Limited, plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District - 500 078, Telangana – India (Diphtheria, Pertussis, r-HBsAg, Haemophilus influenza type b)
- Biological E.Limited , 7-4-114, Gaganpahad, Rajendra Nagar Mandal , Ranga Reddy District- 501 323 , Telangana- India (Tetanus toxoid)

* the manufacturer has been inspected and conforms to the cGMP requirements of the certifying authority.

- **Description of Manufacturing Process and Process Controls**

a) Bulk Purified Diphtheria Toxoid:

- the production steps with the WCB (preparation of pre-seed and seed culture), Fermentation, Harvesting, concatenation of toxin and sterile filtration. Then detoxification with formaldehyde. After that purification and addition of amonium sulphate during pericipatation. Finally the filteration and concentrated and purified diphtheria toxoid.

b) Bulk Purified Tetanus Toxoid:
Tetanus Toxoid is manufactured through the fermentation of C. tetani, the toxin being harvested and then detoxified by formaldehyde. The resulting Crude Tetanus Toxoid is further purified through a selective precipitation by ammonium sulphate leading to the Purified Tetanus Toxoid.
c) Whole cell Pertussis Antigen Bulk:
- the production steps are as follows: pre-seed culture - seed culture - fermentation - harvesting - inactivation of pertussis culture - pooling of pertussis bulk antigen
d) Hepatits B purified Bulk:
- the production steps are as follows: pre-seed culture - seed culture - fermentation - harvesting - cell lysis - purification - concentration and filtration
e)Haemophilus Influenza type b Vaccine Bulk Conjugate:
- the production steps are as follows: Production and purification of Crude PRP - Conjugation of PRP-TT
* IPCs for the intermediates of the DS include tests with specified acceptance criteria and tests to monitor the process. All IPCs applied are in compliance with the international pharmacopieans, and with WHO giudelines.
* IPCs during the production process are well defined in the process schemes

- **Control of Materials**

-Sufficient information on seed bank system used in the DS manufacturing process has been submitted.
-Materials used in the manufacture of DS are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.
- IPCs applied during production of pre master, master, working seed bank and it's validation are included in details.

- **Controls of Critical Steps and Intermediates**

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

- **Process Validation**

-The DS manufacturing process has been validated adequately. All process parameters were maintained and all CQA were achieved.
- Tests results of critical quality attribute and results for critical parameter attribute in each stage of DS manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

- **Control of Drug substance:**

Specification
The release specification for the DS comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes. The

specification has been prepared in line with the requirements of pharmacopiean, WHO and ICH guidelines.

Analytical Procedures

All analytical procedures either pharmacopeia or in house developed were described. The analytical procedures that need validation are clearly mentioned and well described.

Batch analysis

The company submitted the summary protocol for the batches under analysis and the submitted data shows production consistency.

- **Container Closure System**

Primary closure system is described together with its specification

- **Stability of DS**

- The results of stability studies for three production batches of each DS component support the claimed shelf-life when stored in its proper container.

- **Drug product**
  - **Description and composition of DP**

- The DP is presented as whitish turbid suspension in which the adjuvant tends to settle down on keeping.
- the product is filled in USP type I glass vials (3ml/5ml) stoppered with nromobutyl rubber stoppers and sealed using royal blue flip off aluminium seals. The product is supplied in two presentations: single dose 0.5ml vial or 10 doses 5ml vial

  - **Manufacture of drug product**

- The Finished product is manufactured at Biological E. Limited, plot No.1, S.P. Biotechnology Park, Phase-II, Kolthur Village, Shameerpet Mandal, Ranga Reddy District - 500 078, Telangana - India

- All manufacturing steps and release of DP is conducted at this site. Besides the filling and packaging of DP final container vaccine is done their too.

- **Description of Manufacturing Process and Process Controls**

- manufacturing process is simply divided into two processes: formulation or blending process and filling of the vial process.

- **Control of critical steps and intermediates**

There is only one intermediate in the manufacturing process before filling, which is the blended bulk

The critical steps of the DP manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- **Process validation and / or evaluation**

- process and cleaning validation: carried out in three manufacturing consistency batches and the study reports enclosed
- Media fill simulation study: the aseptic media fill simulation study report for blending and filling process are enclosed

- **Control of excipients**

- excipients and their use during the DP manufacturing are mentioned. All excipients comply with BP except aluminium phosphate gel which is in-house..
- no excipient of human or animal origin are used during DP manufacture. No novel excipients were used

- **Control of drug product**

-The specifications include physical characters, general tests, tests for identity, tests for purity, activity, quantity, tests for contaminants.
- Justification of the DP specifications at the release and during stability studies are provided.
- the analytical procedures, principles and validity criteria used for control testing of the vaccine were provided.

- **Container closure system**

- the product is filled in USP type I glass vials (3ml/5ml) stoppered with nromobutyl rubber stoppers and sealed using royal blue flip off aluminium seals. The product is supplied in two presentations: single dose 0.5ml vial or 10 doses 5ml vial
- Identity of materials of construction together with their specifications are described

- **Stability**

-Approved shelf life for the Finished product: 24 months.
-Approved Storage Conditions:
- Store at temperature 2-8ºC,
- after opening: store at temperature 2-8 ºC for 28 days
- don't freeze and discard if the vaccine has been frozen
- shake well before use

- **<u>Non –Clinical aspect & Clinical aspect:</u>**

Adventitious agents

1. **Non –clinical aspect:**

Diphtheria, Tetanus, Pertussis (Whole cell), Hepatitis B (rDNA) and Haemophilus type b conjugate vaccine (Adsorbed) - Liquid Pentavalent Vaccine contains Bulk Purified Diphtheria Toxoid, Bulk Purified Tetanus Toxoid, Whole cell Pertussis Antigen Bulk, Hepatitis-B Purified Bulk and Haemophilus type b conjugate bulk as active substances (Bulk Antigens), which are formulated with Adjuvant (Aluminum Phosphate), Thiomersal (Preservative) and Phosphate Buffer (saline) as Excipients.

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.
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.

2. **Clinical aspect:**

➢ **Clinical Efficacy including Immunogenicity**

- The studies included phase III and phase IV multicentric, randomized, single-blind and double-blind trials conducted in India.
- The vaccine was compared to marketed comparators: Shan5™ (Shantha Biotechnics) and Pentavax SDT™ (SIIL). To demonstrate non-inferiority/equivalence in seroprotection rates (SPR) and geometric mean titers (GMTs) for all five antigens Diphtheria, Pertussis, Tetanus, Hepatitis B, and Haemophilus influenzae type B at Day 84 (28 days after the 3rd dose).
- Seroprotection rates for all five antigens exceeded 87–100% across all lots and comparator groups.
- No statistically significant differences in antibody responses between BE and comparator vaccines, except: a slightly higher fold increase in anti-Tetanus antibodies in BE group (p=0.0032), explained by high maternal antibody levels at baseline. The GMTs at Day 84 were comparable between BE and comparator vaccines. For Pertussis and Tetanus components, BE group GMTs were slightly higher but clinically not significant.
- Equivalence was confirmed among the three BE production lots (Lot A, B, C), with all pairwise 95% CI of GMT ratios between 0.5–2.0.
- The vaccine met the non-inferiority margin of 10% when compared with licensed comparators for all antigens.

➔ BE's liquid pentavalent DTwP-rHepB-HIB vaccine demonstrated strong immunogenicity, seroprotection, and equivalence to marketed comparators (Shan5™ and Pentavax SDT™) and consistency among production lots.

➢ **Clinical Safety**

- Across all studies, no vaccine-related serious adverse events (SAEs) or deaths were reported.
- Overall incidence of TEAEs (treatment-emergent adverse events):
    - Ranged between 21–35% across groups, mostly mild or moderate.
- Most common local AEs: Injection site pain (42–52%), erythema (24–30%), swelling (30–35%), and tenderness (10–12%).
- Most common systemic AEs: Fever (60–67%), irritability (10–15%), crying (7–12%), chills (~2%), and somnolence (~10%).
- No clinically relevant differences in AE frequency or severity between BE and comparator groups (Shan5™ / SIIL).
- No life-threatening AEs, no withdrawals due to AEs, and no new or unexpected safety signals observed.
- Physical exams, vitals, and laboratory findings were comparable between all groups.

➢ **Overall Conclusion**

- Immunogenicity: Non-inferior and equivalent to licensed comparators (Shan5™ and Pentavax SDT™) with robust immune response against all antigens.
- Lot consistency: Demonstrated across three independent production lots.
- Safety: No serious or unexpected adverse events; good overall tolerability.

Finally, The BE liquid pentavalent DTwP-rHepB-HIB vaccine (Combe-5) is safe, well-tolerated, and immunologically equivalent to existing licensed pentavalent vaccines, fulfilling criteria for clinical comparability and non-inferiority

General Conclusion and Recommendations if any:
Based on the review of CTD modules and other supplementary documents, the product is approved.