Unit: Technical Assessment Unit

Public assessment report for biological products

BCG Vaccine

Administrative information:

Trade name of the medicinal product:	BCG Vaccine (Freeze Dried)
INN (or common name) of the active substance(s):	Bacillus Calmette-Guerin
Manufacturer of the finished product	Serum Institute of India Pvt. Ltd., (SIIPL), 212/2, Hadapsar, Pune – 411028, India
Marketing Authorization holder	Serum Institute of India Pvt. Ltd., (SIIPL), 212/2, Hadapsar, Pune – 411028, India
Applied Indication(s):	BCG vaccine should be given routinely to all infants at risk of early exposure to tuberculosis. This vaccine should be given soon after the child is born. BCG administered early in life provides high level of protection particularly against severe forms of childhood tuberculosis and tubercular meningitis. In countries with low prevalence of tuberculosis, BCG vaccination should be restricted to high-risk groups such as hospital personnel and tuberculin negative contacts of known cases of tuberculosis. The vaccine can be given simultaneously with DTP, DT, TT, Measles, Polio, Hepatitis B, Haemophilus influenzae type b, yellow fever vaccines and vitamin A supplementation, but at a separate site.
Pharmaceutical form(s) and strength(s):	lyophilized powder to be reconstituted with the diluent. 1 ml = 0.05ml – 20 doses / 0.1 ml – 10 doses.
Route of administration	intradermal injection
Type of registration (EMA/FDA – Local)	Imported

List of abbreviations

BCG	Bacillus Calmette-Guérin vaccine
GMP	Good Manufacturing Practices
MA	Marketing authorization
WHO	World Health Organization
Ph. Eur	European Pharmacopoeia
BP	British Pharmacopoeia

USP	United state Pharmacopoeia
SIIPL	Serum Institute of India Pvt. Ltd
IP	Indian Pharmacopoeia
API	Active Pharmaceutical Ingredient
UNICEF	United Nations Children's Fund
PBS	Phosphate buffer saline
IHRS	In-House Reference Standard
FD	Finished Drug
ANOVA	Analysis of variance
CFU	Colony forming unit
HIV	Human Immunodeficiency Virus
ID	Intradermal
PMS	post-marketing surveillance
SAEs	Serious Adverse Events
TB	Tuberculosis

Table of contents

1. **General introduction about the product including brief description of the AI, its mode of action and indications:**
   - BCG Vaccine is a live freeze-dried vaccine derived from attenuated strain of Mycobacterium bovis. (Bacillus Calmette Guerin) used for the prevention of tuberculosis. The vaccine meets the requirements of WHO, BP & I.P.

2. **Quality aspects:**

2.2.1 Introduction

As mentioned in the aforementioned section.

2.2.2 Drug Substance (Active ingredient)

- **General information**

- Final BCG Vaccine for Filling" is indigenously manufactured at Serum Institute of India Limited; it contains attenuated strain of Mycobacterium bovis (Bacillus Calmette-Guerin). The various processes i.e. revival and propagation of seed, harvesting, Pooling and preparation of final bulk vaccine and all the vaccine production activities are carried out in manufacturing premises dedicated for the product and complying with prevailing WHO GMP conditions.
- **Nomenclature**:

- Recommended International Nonproprietary Name (INN): Not Applicable

Manufacture, process controls and characterization:

Manufacturer:

Serum Institute of India Pvt. Ltd., (SIIPL),212/2, Hadapsar, Pune – 411028, India

- **Description of Manufacturing Process and Process Controls.**
  BCG vaccine is manufactured by revival of Seed culture (Primary) on Sauton-potato medium, propagated on Sauton-potato medium with simultaneous subculture on Sauton's liquid medium by surface culture method. The production process of harvested suspension of BCG vaccine, along with the in-process control tests, is well represented in the MA file.
  Control of Materials.
  A summary of tests, specifications for the API "Harvested suspension of BCG Vaccine" is provided in MA file.
- **Controls of Critical Steps and Intermediates.**
  In-process controls are carried out performed on the harvested suspensions for BCG Vaccine: Description, Optical Density and Microscopic Examination/ Homogeneity.
- **Process Validation**
  Validation of the process is demonstrated by the consistency during production of BCG Bulk batches.
- **Manufacturing Process Development.**

The development of the initial BCG Harvest & BCG Bulk vaccine manufacturing process was performed by serum institute of India.
The number of experimental batches was produced to demonstrate successful technology transfer. During this period no principal changes were made than to

adopt the process to the procedure of the Serum Institute of India Ltd.
The current process was approved by the WHO for supply to the UNICEF vaccine program. Since then, the product has been continuously supplied to UNICEF.

- **Specification**
  All test specifications have been finalized based on WHO references and in house specification. Wherever required analytical method has been developed and successfully completed.
  - **Analytical Procedures.**

  Details of the test methods are provided.
  - **Reference Standards or Materials.**
    COA of In-house working standard for BCG vaccine IHRS which is used for testing of BCG final bulk vaccine for filling and the final drug product is enclosed.
  - **Container closure system**
    Desirable pack: 50.0 lit. Stainless-Steel Vessel
  - **Stability of drug substance**

  Recommended storage condition: 2-8°C.

2.2.3 Drug product:

- **Manufacture of the drug product:**
  - Description of manufacturing process and process controls along with manufacturers and responsibilities
  Manufacturer:
  Serum Institute of India Pvt. Ltd., (SIIPL),212/2, Hadapsar, Pune – 411028, India
  - Control of critical steps and intermediates
  The manufacturing process is controlled through critical process parameters, in process testing and release testing.
  A summary of the critical process parameters and tests for the finished product is provided in the dossier.
  - Process validation and / or evaluation.
  All critical manufacturing processes are validated.
  All critical process steps, critical process parameters, in-process checks are monitored and evaluated based on risk assessment.
- **Product specification:**
  - Analytical procedures for excipients are described in Ph. Eur, BP, IP
  - Pharmacopoeia analytical procedures are carried out as per recent edition of USP and are therefore considered to be validated.
  - There is no excipient of human or animal origin in the vaccine.
  - No novel excipient has been used in the formulation of BCG Vaccine (Freeze dried)
    - **Reference Standards or Materials.**

In house Reference Vaccine for BCG FD is used in Quality Control test of BCG vaccine.

- **Container closure system.**
  The primary packaging material for BCG vaccine (Freeze Dried) is a hydrolytic class-I glass, Tubular, Amber vial with 40 mm height.
- Vials are closed with 13 mm slotted Bromobutyl rubber stopper.
- The closure is sealed to the container using 13 mm aluminium seal with blue Pantone 300C colored flip-off cap.
- The diluent, Sodium Chloride Injection B.P. is filled in 1 ml clear glass Type I ampoule having snap-off band to its constriction and 65 mm in height.

Stability of the drug product.

-Based on available stability data,
approved Shelf Life: 24 months
approved Storage Conditions: 2-8 °.
It is even more stable if stored in temperatures as low as -20°C.
Store in a dark place.
The diluent should not be frozen, but should be kept cool.

1. **Non –clinical aspect:**

Bacillus Calmette-Guerin (BCG) is an attenuated live bacillus that was derived in 1908 from strain of Mycobacterium bovis by Calmette and Guerin in France. It is used immunization against tuberculosis past 55 years. The BCG strain Danish 1331 was used for the immunization against tuberculosis. The strain extensively used in the immunization programs for the past 55 years.
Non Clinical studies on BCG Vaccine have been established as per guidelines of Vaccines and Requirement for dried BCG Vaccine (revised 1985) (WHO Technical Report Series No. 745, 1987, Annexure 2).

Pharmacology

Vaccination with BCG Vaccine elicits a cell-mediated immune response that confers a variable degree of protection to infection with Mycobacterium Tuberculosis. The duration of immunity after BCG vaccination is not known, but there are some indications of waning immunity after 10 years. Vaccinated persons normally become tuberculin positive after 6 weeks. A positive tuberculin test indicates a response of the immune system to prior BCG vaccination or to a mycobacterial infection. However, the relationship between the post vaccination tuberculin test reaction and the degree of protection afforded by BCG remains unclear.
Pharmacokinetic studies are not applicable for vaccines in accordance with the WHO TRS 927.
Toxicology
Safety test in Guinea pigs was conducted to assess the safety of BCG Vaccine when administered to the guinea pigs through subcutaneous route at the dose of 50 human

doses (5 mg). There is no mortality throughout 42 days study period. All the animals were found healthy, normal feeding, watering behavior and body weight of animals was noticed. Necropsy findings showed the scar formation at the site of inoculation. All the animals were found healthy, normal feeding, watering behavior and body weight of animals was noticed. Necropsy findings showed the scar formation in all 10 animals. The regional lymph nodes of inguinal, auxiliary and cervical have shown mild to light swelling. Liver, kidneys and intestine did not show any lesion of abnormalities. The lunges of two animals showed slight congestion in its both lobes. The spleen of 7 animals showed rough surface and diffused black discoloration and the spleen of 3 animals showed rough surface and focal black discoloration. The range of spleen weight was between 0.86 to 1.51g.
In conclusion, the test substance is found to be safe and free from contaminating microorganisms, including virulent Mycobacterium tuberculosis. Hence, the test substance is considered for safe use as a therapeutic drug in human beings.

2. Clinical aspect:

Clinical overview:

Clinical Overview

BCG Vaccine is a live attenuated vaccine derived from *Mycobacterium bovis* and is indicated for active immunization against tuberculosis (TB), particularly severe forms of childhood TB such as tuberculous meningitis and miliary tuberculosis. The vaccine is administered intradermally as a single dose, preferably soon after birth in populations at high risk of tuberculosis.
The protective effect of BCG vaccination is primarily mediated through induction of cell-mediated immunity. Vaccinated individuals typically develop a positive tuberculin skin test response within approximately six weeks following vaccination. Although the duration of protection is not fully established, available evidence suggests that protection may persist for at least 10–15 years. International recommendations support the use of BCG vaccination in neonates and infants in countries with a high burden of tuberculosis.
The submitted clinical package included a randomized, open-label, controlled, multicenter Phase III comparative study evaluating the safety, reactogenicity, and immunogenicity of the applicant's BCG vaccine compared with a licensed reference vaccine manufactured by Serum Institute of India Limited, as well as a multicenter post-marketing surveillance (PMS) study evaluating safety and tolerability under routine conditions of use.

Clinical Efficacy

The efficacy of BCG vaccination is primarily supported by extensive published literature and long-standing clinical experience. Meta-analyses and observational studies have demonstrated that BCG vaccination provides substantial protection against severe forms of childhood tuberculosis, particularly tuberculous meningitis and miliary tuberculosis, with reported protection rates approaching 80%.

Protection against pulmonary tuberculosis has been shown to vary across different geographical regions, with overall estimates of approximately 50% in several analyses. The protective effect appears to be greater when vaccination is administered during infancy or shortly after birth.

The submitted Phase III study enrolled 120 healthy children aged 0–14 years who were randomized to receive either the investigational BCG vaccine or the licensed reference vaccine (60 subjects per treatment arm). The primary objective was to compare safety and reactogenicity, while immunogenicity was evaluated through post-vaccination Mantoux testing.

Mantoux testing was performed on Day 90 and assessed on Day 93. Of the 120 enrolled subjects, 116 underwent Mantoux testing and 114 subjects were evaluable for immunogenicity assessment. Approximately 88% of evaluable subjects demonstrated a positive Mantoux response (≥10 mm induration), indicating successful induction of an immune response. No statistically significant difference was observed between the investigational and reference vaccines ($p = 0.99$), supporting comparable immunogenic performance.

Clinical Immunogenicity

The Phase III study was conducted at two centers using a randomized, open-label, controlled design. Subjects received intradermal administration of BCG vaccine according to age-appropriate dosing (0.05 mL for children below one year of age and 0.1 mL for children aged 1–14 years).

Immunogenicity was assessed through post-vaccination tuberculin skin test conversion and evaluation of local vaccine reactions. Local reactogenicity assessments included erythema, papule formation, ulceration, and scar development at 30 minutes, 72 hours, Day 10, Day 30, Day 60, and Day 90 following vaccination. Subjects were further followed until Week 26 for assessment of scar formation and safety.

Statistical analyses were performed using SAS version 9.2. Comparative analyses included t-tests, Chi-square tests, Wilcoxon rank-sum tests, and ANOVA where appropriate.

Among evaluable subjects, the mean Mantoux induration was 14.16 mm in both treatment groups, demonstrating comparable immune responses. The proportion of subjects achieving positive tuberculin conversion was high in both groups, and no statistically significant difference was observed between the investigational and reference vaccines ($p = 0.99$).

The observed local reaction pattern was consistent with the expected biological response following BCG vaccination, progressing from papule formation to ulceration and subsequent scar development. By Week 26, subjects available for follow-up demonstrated characteristic BCG scar formation, indicating successful vaccine take.

Overall, the immunogenicity findings were consistent with the established mechanism of action and biological activity of BCG vaccines and supported comparability between the investigational and reference products.

Clinical Safety

Safety was evaluated through both the Phase III comparative study and a large multicenter post-marketing surveillance study.

In the Phase III study, all 120 enrolled subjects received vaccination and were followed for up to 26 weeks. No deaths, serious adverse events (SAEs), or treatment-related adverse events were reported during the study period. Both the investigational and reference vaccines were well tolerated, and no clinically significant safety concerns were identified.

The applicant also submitted results from a multicenter, prospective, open-label, single-arm PMS study conducted across six cities in India. A total of 1,017 children were enrolled and vaccinated, of whom 1,000 completed study follow-up. The primary objective was to evaluate safety and tolerability, while the secondary objective was to assess local injection-site reactions.

Safety assessments were conducted at 30 minutes post-vaccination, Day 3, and Week 6. At Day 3, papule formation was observed in 478 subjects, one subject developed an ulcer, and the remaining subjects had no local lesions. At Week 6, papules were reported in 933 subjects, ulcers in 28 subjects, scars in 6 subjects, and no lesion was observed in 33 subjects.

No deaths, serious adverse events, or unexpected safety signals were reported during the PMS study. The observed local reactions were consistent with the expected reactogenicity profile of BCG vaccines and represented normal vaccine responses. Published literature indicates that adverse reactions following BCG vaccination are generally uncommon and include local ulceration, abscess formation, regional lymphadenitis, and scar formation. Rare cases of osteomyelitis and disseminated BCG infection have been reported predominantly in immunocompromised individuals. Consequently, BCG vaccination is contraindicated in individuals with severe immunodeficiency, including HIV infection and those receiving immunosuppressive therapy.

Overall, the available evidence demonstrates that the vaccine is well-tolerated and exhibits a safety profile consistent with the established safety profile of licensed BCG vaccines.

Benefit–Risk Analysis

Tuberculosis remains a significant public health concern, particularly in countries with a high disease burden. Severe forms of childhood tuberculosis, including tuberculous meningitis and miliary tuberculosis, are associated with substantial morbidity and mortality.

The benefits of BCG vaccination are supported by:

• Extensive global clinical experience and long-term use in national immunization programmes.

• Established protection against severe forms of childhood tuberculosis.
• Demonstrated induction of cell-mediated immune responses following vaccination.
• Comparable immunogenicity to a licensed reference BCG vaccine, as demonstrated by equivalent Mantoux responses in the Phase III comparative study.
• Favorable safety findings from both the controlled Phase III study and the PMS study involving more than 1,000 vaccinated children.

The identified risks are predominantly limited to expected local reactions at the injection site, including papule formation, ulceration, and scar development. Serious vaccine-related complications are rare and are generally restricted to individuals with underlying immunodeficiency, for whom vaccination is contraindicated.

Considering the demonstrated immunogenicity, acceptable safety profile, comparability with a licensed reference vaccine, and the established public health benefit of preventing severe childhood tuberculosis, the overall benefit–risk balance of the BCG vaccine is considered favorable.

Overall Conclusion

The submitted data, together with extensive published evidence and post-marketing experience, support the safety and effectiveness of the BCG vaccine for active immunization against tuberculosis.

The randomized Phase III comparative study demonstrated immunogenicity comparable to the licensed reference vaccine, with no statistically significant difference in Mantoux responses between treatment groups ($p = 0.99$). The vaccine exhibited an acceptable safety and reactogenicity profile, with no deaths, serious adverse events, or clinically significant safety concerns reported during follow-up.

The PMS study, involving 1,017 vaccinated children, further confirmed the favorable safety profile of the vaccine under routine clinical use, with no unexpected safety signals identified.

Overall, the submitted clinical evidence demonstrates that the vaccine induces an appropriate immune response, exhibits expected local reactogenicity consistent with BCG vaccination, and possesses an acceptable safety profile.

Based on the totality of available evidence, the benefit-risk balance of the BCG vaccine is considered positive for its approved indication in the prevention of severe forms of childhood tuberculosis.

General Conclusion and Recommendations if any:

Based on the review of CTD modules and other supplementary documents, the product is approved.