WHO-PQTm SCIENTIFIC DISCUSSION

This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 and 2 of this WHOPAR.

Name of the Finished Pharmaceutical Product:	SIILTIBCY (Cy-Tb)[1]
Manufacturer of Prequalified Product:	Serum Institute of India Pvt. Ltd. 212/2 Hadapsar Pune-411 028 India
Drug substance(s):	*Mycobacterium tuberculosis*-specific antigens rdESAT-6 and rCFP-10
Pharmaco-therapeutic group (ATC Code):	Tuberculosis diagnostics (V04CF)
WHO recommended therapeutic indication:	[BT-DX001] is indicated as a diagnostic aid for detection of *Mycobacterium tuberculosis* (Mtb) infection, including disease, in adults and children aged 28 days or older.

1 Introduction

Rapid, accurate and sustainable identification of Mtb infection is crucial to prioritize individuals for TB preventive treatment (TPT)—helping to stop progression to active disease and preventing transmission within communities. Diagnostic aids, therefore, play an important role in the control of this infectious disease.

SIILTIBCY (Cy-Tb) (BT-DX001) is a skin test for detection of Mtb infection. SIILTIBCY (Cy-Tb) contains the *Mycobacterium tuberculosis*-specific antigen proteins rdESAT-6 and rCFP-10. Both antigens are produced by recombinant DNA technology in *Lactococcus lactis*.

SIILTIBCY (Cy-Tb) induces a limited immune response to both current and previous infection. Mtb infection is recognized by an induration of the skin ≥ 5 mm at the injection site 48 to 72 hours after injection of Cy-Tb. The stronger the response, the more likely the infection is both recent and active.

The SIILTIBCY (Cy-Tb) formulation is: rdESAT-6 0.5 micrograms + rCFP-10 0.5 micrograms/mL solution for injection. It is presented as a multidose vial containing 10 doses of 0.1 mL each. Phenol is included as preservative.

The prequalification of this product by the WHO Prequalification Team: Medicines (PQTm) is based on the approval by a stringent regulatory authority (SRA), namely “European Medicines Agency”

[1]Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s responsibility.

(https://www.ema.europa.eu/en) in line with the "WHO Guidelines on submission of documentation for the procedure for prequalification of biotherapeutic product or their corresponding similar biotherapeutic products approved by stringent regulatory authorities"[2].

Hence, no assessment of the data underlying this approval has been undertaken within PQTm. However, according to the above-mentioned guidelines, WHO requested additional data for the safe use of the product in regions relevant for prequalified products and this information is included in this section of the WHOPAR.

2 Assessment of Quality

Product packaging and shipping

The assessment of the packaging and shipping of the product has been done according to the principles laid down in the WHO guidelines on the international packaging and shipping of vaccines (WHO/IVB/05.23), partially applicable also to biotherapeutics.

The Applicant submitted Installation Qualification (IQ) and simulated transport route qualification (TRPQ) demonstrating that the transport system can maintain appropriate conditions under test scenarios. In addition, operational qualification tests of the transport units were conducted under extreme ambient temperatures and time conditions, simulating worst-case situations, and confirmed that the product remains within the required temperature range for extended periods.

Performance qualification testing was also provided for transport by both air and sea freight. These tests were designed to reflect worst-case scenarios, taking into account the most challenging routes in terms of climate zones, duration, and handling. Three consecutive field tests were carried out by air and sea freight, using temperature loggers for continuous monitoring under real-time and actual temperature conditions.

During cold chain transport, temperatures were consistently maintained between 2–8 °C. During handling steps, short exposures outside this range were observed; however, these excursions remained within the limits defined in the Product Specific Requirements (PSRs), which are supported by stability data.

The Applicant also provided evidence that product transport complies with GDP requirements. Shipments are continuously monitored using calibrated temperature loggers from dispatch to final destination, and data are reviewed before release. Any deviations from the defined temperature limits are managed through a deviation report in line with the Applicant's procedures.

Finally, the Applicant demonstrated that the same shipment configuration has been successfully used for other products across multiple high-risk, temperature-sensitive routes in real-world conditions, with no reported temperature excursions to date.

Arrangements for handling complaints and product recalls

The procedure for handling product quality complaints and product recalls submitted by the applicant provides details, among others, on the product defects/serious quality issues definition, investigation process, process of recalls, established timelines for recall notification to National Medicines Regulatory Authorities and WHO, recall arrangements and actions to put in place at the distribution level as well as description of the annual mock-recall.

The applicant confirmed that the responsibilities for handling of complaints and recalls will also be clearly defined in the agreements or contracts between the manufacturer and relevant third parties.

[2] https://extranet.who.int/prequal/sites/default/files/document_files/03_Prequalification_general_AbridgedPathway.pdf

Stability of the product

The approved shelf-life for Cy-Tb is 24 months when stored at 2°C to 8°C.

After first opening, the product may be stored for a maximum of 28 days at 2°C to 8°C.

Conclusion: The quality part of the dossier is accepted.

Pharmacovigilance - WHO Prequalification-Specific Addendum to the RMP

WHO assessed the latest SRA-approved Risk-Management Plan (RMP) and post-marketing safety reports together with a WHO PQ-specific addendum to the RMP according to the structure detailed on the WHO-PQT website[3].

The WHO-prequalification-specific addendum to the RMP is reported below. Conclusion:

The pharmacovigilance part of the dossier is accepted.

[3] https://extranet.who.int/pqweb/sites/default/files/documents/RMP_AddStructureDec2019-2.pdf

Risk Management Plan Addendum for WHO Prequalification

1. INTRODUCTION

The objective of this RMP Addendum is to describe how the RMP (Version 2, dated 29 January 2025) will be applied in WHO regions.

Cy-Tb RMP submitted with this Addendum includes a description of the risk management system based on all information Serum Institute of India Pvt. Ltd. (SIIPL) deems relevant to the safety profile of Cy-Tb.

Indication: Cy-Tb is indicated as a diagnostic aid for detection of *Mycobacterium tuberculosis* infection, including disease, in adults and children aged 28 days or older. This medicinal product is for diagnostic use only.

Posology: The dosage is 0.1 mL administer via intradermal injection using the Mantoux technique.

The applicability of safety concerns, pharmacovigilance activities and risk minimization measures in the WHO regions is mentioned in the relevant sections of this addendum. All the RMP Annexes are also applicable to WHO regions.

SIIPL acknowledge that healthcare settings and infrastructure may vary between countries, and following product prequalification, we will evaluate the adequacy of the safety concerns, pharmacovigilance (PV) activities, risk minimization measures and traceability of the product at a national level where the product is registered.

To meet these requirements, we enter into Safety Data Exchange Agreements (SDEA) with our business partners (like distributors, local representatives etc. who market the product in the specific countries) to ensure the reporting of safety data based on local practices or specificities in the area where the product is intended for use.

2. DETAILS OF THE EUROPEAN MEDICINES AGENCY (EMA) APPROVED RMP

The EU RMP version 1.0 for SIILTIBCY was approved by EMA on 17 October 2024 with ref. no. EMEA/H/C/006177/0000.

3. SAFETY CONCERNS

The safety concerns for Cy-Tb are described in RMP Part II: Module SVIII. Cy-Tb has been found safe in clinical trials of more than 3,000 participants. There are no safety concerns reported. Therefore, there are no important identified or potential safety concerns for the product.

The safety concerns are indicated in the table below:

Important identified risk	None
Important potential risk	None
Missing information	None

To ensure that, no additional safety concerns are identified at the national level based on local practices or specificities in the area, the continuous safety monitoring of the product would be conducted through the global pharmacovigilance processes already in place, which involves:

1. Adverse event report management: as per the SOPs, we have system in place for handling of adverse events (AEs) for all the products. We receive the reports of AEs and SAEs through spontaneous reporting from patients, parents, physicians, state and central government authorities or any other source. All these AEs/SAEs are processed, investigated, causality assessment is done and records are maintained.

   An exclusive email address **pharmacovigilance@seruminstitute.com** has been created specifically for reporting adverse events globally. The details are already placed on the website.

   Any adverse event related information published in online newspaper /digital media, whenever available, is also logged and investigated.

2. Literature surveillance: the worldwide literature is searched weekly as per the regulatory guidelines and any safety cases detected are processed and reported. In case of inadequate information, additional information is sought from the authors of the paper for clinical evaluation and causality assessment of the AE/SAE.

3. Safety Data Exchange Agreements (SDEA): We also enter into SDEA with our business partners (like distributors, local representatives etc. who market the vaccines in the specific countries) to ensure the reporting of safety data within the timelines.

4. Signal detection: The signal detection activities are performed at SIIPL to determine whether, based on the examination of individual case safety reports (ICSRs), aggregated data including studies, literature information or other data sources, there are new risks associated with a medicinal product or whether risks have changed.

   The primary data sources for signal detection and the minimum frequency of review are outlined below.

Activity/Data source	**Frequency of review**
ICSR (Individual Case Safety Report) medical review of adverse events	Each business day
Triage and review of signal notifications from sources other than ICSRs	Each business day
Global literature surveillance	Weekly
Line listing review	Along with PSUR preparation
Review of SIIPL's post-authorisation Safety Database, including all spontaneous and solicited ICSRs, aggregated data including studies, regulatory reports etc.	Along with PSUR preparation
Aggregate review of Clinical Trial Database	Along with PSUR preparation
Dose distribution data	Along with PSUR preparation

At SIIPL, the pharmacovigilance team uses Qualitative method for signal detection. Data for signal detection is reviewed along with the PSUR. Case-by-case manual review of all the PSUR interval ICSRs is done for relatedness and expectedness. All the drug-event combinations (related ICSRs) are evaluated and each suspected drug-event combination is described for eligibility to call it as a suspected signal.

Any potential signal identified through the signal detection processes are then thoroughly evaluated (utilizing all sources of data available) to validate the signal. The validated signal, if any, is presented in PSURs and is shared with regulatory authorities.

4. PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are described in the RMP.

To ensure compliance with regional regulations and facilitate timely reporting of adverse events, the global PV system of SIIPL will be connected at local level through the local Safety Data Exchange Agreements (SDEA) partner where the product is registered. A global PV system have a central database for collecting and managing safety data reported from all the sources.

Local SDEA partner will be responsible for collecting safety data reported at a national level, ensuring compliance with country-specific regulations, and communicating with local health authorities.

The SDEA document clearly defines the roles and responsibilities of each party and also the mode of exchange of the safety information, which is generally through an email.

Wherever there is a local regulatory requirement of a PV qualified person, we ensure that, the local Safety Data Exchange Agreements (SDEA) partner would have the same. The details would also be mentioned in the SDEA. If there are no such requirements at national level, all the pharmacovigilance activities, as described above in section ‘Safety Concerns’, are handled globally by SIIPL PV qualified team.

If required by the SDEA partner, the local PV person will also be trained on the basics of PV by SIIPL PV team to comply with the local regulatory requirements.

Communication plan:

All the safety information will be processed in the global safety database of the product by SIIPL. As per the local requirements, the safety data will be shared with the local SDEA partners who in turn will submit the same to the local NRAs.

All the regulatory safety communications received either directly or through the local SDEA partners will be appropriately and timely managed through the global PV system processes.

In case, there is any safety concern is identified with the product, it will be notified to the local SDEA partners within 5 business days.

Since Cy-Tb was granted marketing authorization from Indian NRA on 09 May 2022, Periodic Safety Update Reports (PSURs) are being prepared in line with recommendations of the regulatory authorities. The PSURs will be submitted in accordance with the national requirements.

4.1 Additional pharmacovigilance activities

Based on the various available clinical studies, Cy-Tb was found safe and well tolerated. The pooled safety analysis of Cy-Tb, including data on 3,109 participants from 07 clinical trials (phase I – Denmark and UK, phase II – UK and South Africa and USA and phase III – Spain and South Africa), did not report any safety concern. Therefore, no additional pharmacovigilance activities are planned for WHO regions.

The requirement of any additional PV activities will be assessed through routine surveillance, factoring in the local specificities such as epidemiology, healthcare infrastructure, clinical practice and other factors. Only routine risk minimization measures in the form of the summary of product characteristics (SmPC) and the corresponding product leaflets (PLs) are presently implemented. The distribution of the SmPCs and PLs of the product Cy-Tb is in accordance with applicable national requirements. Effectiveness of risk minimization measures is also assessed through routine pharmacovigilance activities. There is a continuous monitoring of the safety profile and related benefit-risk balance of the product. Appropriate and diligent communication to the regulatory bodies is governed by procedures in place.

4.2 Traceability

Where regional practices permit, the batch/lot number for Cy-Tb, if not already provided in the source document by the reporter, will be systematically followed-up with the reporter for each post marketing ICSR. When available, batch/lot information will be included in the global safety database.

In addition, as per the "Annex B – UNICEF Guidelines for Vaccine Barcode Specifications", we apply bar codes on the secondary packaging levels. These bar codes conform to GS1 standards, allowing through a unique company prefix to identify vaccines available in the global supply chain. The bar codes include Global Trade Item Number (GTIN), lot number, expiry date and unique serial number.

5. RISK MINIMISATION MEASURES

Routine risk minimisation measures for the use of Cy-Tb are addressed in Local Prescribing Information (PI/ SmPC), in line with those described in the RMP.

There are no important potential or identified risks associated with Cy-Tb. Routine risk minimisation measures are considered sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are planned in WHO regions.

SIIPL will provide the Summary of Product Characteristics (SmPC)/ Package Insert (PI) or non-promotional education material (if applicable) whenever requested by the healthcare professionals (HCPs) in the WHO regions.

5.1 Assessment of Effectiveness of Local Risk Minimisation Measures

There are no effectiveness measures for routine risk minimisation measures other than routine pharmacovigilance activities.

6. REFERENCES

None.

ABBREVIATIONS

Abbreviation	Definition / Explanation
HCP	Health care professional
EMA	The European Medicines Agency
ICSR	Individual Case Safety Report

MAH	Marketing Authorization Holder
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
Cy-Tb / SIILTIBCY	Mixture of rdESAT-6 + CFP-10
WHO	World Health Organization