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 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product:	[TB222 trade name] *
Manufacturer of Prequalified Product:	Biocom JSC 54 Chapaevsky Cr 355016 Stavropol Russian Federation
Active Pharmaceutical Ingredient (API):	Cycloserine
Pharmaco-therapeutic group (ATC Code):	Antimycobacterial (J04AB01)
Therapeutic indication:	[TB222 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.* [TB222 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

1. Introduction

[TB222 trade name] is indicated in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis.*
[TB222 trade name] is only indicated as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed.

2 Assessment of Quality

The assessment was done according to SOP 20 of the WHO Prequalification programme.

Active pharmaceutical Ingredient (API)

Cycloserine (reference number WHOAPI-177) has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that cycloserine, used in the manufacture of [TB222 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

The API specifications include tests for description, solubility, identification, condensation products, specific optical rotation, heavy metals, residue on ignition, loss on drying, pH, related substances (HPLC), assay, residual solvents, microscopic examination and microbial limits.

Other ingredients

The other core capsule ingredient is talc. The capsule shells contain gelatin, ponceau 4R (cochineal red A), quinoline yellow and titanium dioxide

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture
[TB222 trade name] are size 0 hard gelatin capsules with a white body and orange cap, filled with a white or almost white powder. The capsules are packaged in an HDPE bottle with an HDPE screw cap, with a tamper-proof ring and induction foil sealing. 1 bottle with a leaflet in a carton.

The product was designed by technology transfer of the innovator product. The product is comprised of a simple formulation of API and purified talc, filled into gelatin hard capsule shells.

Appropriate in-process controls were set to ensure batch-to-batch reproducibility. Validation data presented on three batches demonstrated the consistency of the process and the quality of the product.

Specifications
The finished product specifications are pharmacopoeial based and include tests for description, identification (HPLC, TLC and chemical), average fill weight, uniformity of dosage units (by weight variation), dissolution, loss on drying, assay (HPLC), related substances (HPLC) and microbial limits. The test methods have been satisfactorily described and validated.

Stability testing
Stability studies have been performed at 25±2°C/60±5%RH as long-term storage condition. The data showed chemical degradation, though support the proposed shelf life and storage conditions, as well as the in-use period after first opening of the bottle, as defined in the SmPC. Excursions above 25°C should be avoided.

Conclusion
The quality part of the dossier has been accepted.

3. Assessment of Bioequivalence
The product was designed by technology transfer of the innovator product.

4. Summary of Product Safety and Efficacy
[TB222 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [TB222 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Seromycin® (Eli Lilly), for which benefits have been proven in terms of clinical efficacy.
The clinical safety of this product is considered to be acceptable when guidance and restrictions stated in the Summary of Product Characteristics are considered. Reference is made to the SPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion
Quality
Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [TB222 trade name] is used in accordance with the SmPC.

Efficacy and Safety
Regarding clinical efficacy and safety, [TB222 trade name] is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics are taken into consideration.

Benefit Risk Assessment
Based on the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit-risk profile of [TB222 trade name] was acceptable for the following indication: **"in combination with other antituberculosis agents for the treatment of all forms of tuberculosis caused by *Mycobacterium tuberculosis,* as a second line antimycobacterial drug when resistance to or toxicity from primary drugs has developed"** and has advised to include [TB222 trade name], manufactured at Biocom JSC, 54 Chapaevsky Cr, 355016 Stavropol, Russian Federation, in the list of prequalified medicinal products.