Annex I

OVERVIEW OF THE WOAH PROJECT TO REPLACE THE FIRST INTERNATIONAL STANDARD AVIAN TUBERCULIN

In 1951, the World Health Organization (WHO) established the international standard for purified protein derivative (PPD) of mammalian tuberculin, intended for the diagnosis of both bovine and human infections despite being from a human strain of the tubercle bacillus.[i] At the same time, WHO's Expert Committee on Biological Standardization (ECBS) decided to establish an international standard preparation of avian tuberculin (ISAT) and the first international standard was established in 1954. This material has been prepared from the Mycobacterium strain called D4 and was characterised by the Statens Serum Institut (SSI), Copenhagen, Denmark.[ii]

Both the avian and the bovine standards have been stored and distributed by, the National Institute for Biological Standards and Control (NIBSC), currently the main custodian of WHO biological reference materials since the late 1990s. The avian PPD is intended to be used in the potency assay of M. avium tuberculin preparations.

In June 2022, World Organisation for Animal Health (WOAH, founded as OIE) was notified by NIBSC that the stock of the ISAT is exhausted, and around 20 ampoules were remaining. WOAH was informed that the archived stock could be used to develop replacement material, but it would not be sufficient to supply to national laboratories to calibrate their in-house standards. NIBSC has been distributing ISAT to around fifteen organisations mainly in Asia and South America with some in Europe and the US but is currently declining all requests and has removed the PPD from their catalogue. While NIBSC is providing facilities and advisory support, they cannot deliver the replacement of ISAT by themselves.

Before this, in 2014, WOAH became aware that the stock of the international standard bovine tuberculin (ISBT) was running low. In response, WOAH convened an *ad hoc* Group in November 2015 entitled 'Replacement of the International Standard Bovine Tuberculin' ('the Group' hereafter). The Group proposed the evaluation and calibration of a new ISBT, and the development of a suitable replacement ISBT is still ongoing. This Group further recommended that the status and future requirements for the ISAT should be reviewed and monitored, therefore the new development related to ISAT was unexpected.

The issue was presented to the WOAH *Ad Hoc* Group on replacement of the International Standard Bovine Tuberculin on 4th July 2022. The Chair (Steven Edwards) reminded the Group that in 2015, WOAH initiated the work to identify a replacement candidate for the current ISBT since it is a product for veterinary use. The Group recommended that the same approach could be considered for ISAT and if so, it should be undertaken by the same ad hoc Group based on their experience with ISBT.

The first phase of the project will involve acquiring documentation on the avian tuberculins produced from manufacturers, willing to donate for this project. The experts of the WOAH *Ad Hoc* Group, under the supervision of the WOAH Biological Standards Commission, will examine the documentation and select two or more candidate tuberculin for further evaluation based on the selection criteria. The manufacturers will be informed about the selected candidate bulk material.

In the second phase of the project, the selected candidate bulk tuberculins will be shipped to a designated laboratory where formulation will be performed by small-scale test fills, which will be evaluated by experts at the WOAH Mammalian Tuberculosis Reference Laboratories who will, preliminarily, assess the performance of test filled candidate ISAT in a guinea pig model.

In the third phase, based on the results of the evaluations in the WOAH Mammalian Tuberculosis Reference Laboratories, one or two formulated candidate tuberculin will be selected for further evaluation/validation through a study to confirm the candidate tuberculin's suitability to serve as a potential new WOAH International Standard which will be scheduled in 2025.

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[i] World Health Organization & Expert Committee on Biological Standardization (1986 : Geneva, Switzerland). (1986). Proposed international standard for purified protein derivative (PPD) of bovine tuberculin. World Health Organization. https://apps.who.int/iris/handle/10665/78132

[ii] Guld, J., Bentzon, M. W., Bleiker, M. A., Griep, W. A., Magnusson, M., & Waaler, H. (1958). Standardization of a new batch of purified tuberculin (PPD) intended for international use. *Bulletin of the World Health Organization*, *19*(5), 845-951. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2537760/