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REPORT OF THE MEETING OF THE OIE *AD HOC* GROUP ON REPLACEMENT OF THE INTERNATIONAL STANDARD BOVINE TUBERCULIN[1]

Paris, 6–8 June 2017

An *ad hoc* Group (hereinafter the Group) on Replacement of the International Standard Bovine Tuberculin (ISBT) was convened at the OIE Headquarters from 6 to 8 June 2017.

1. Opening

Dr Matthew Stone, Deputy Director General, International Standards and Science, welcomed the meeting participants on behalf of Dr Monique Eloit, Director General of the OIE. He thanked the participants for taking time to work on the project before and during the Group meeting. He acknowledged the progress made by the Group in selecting two candidate prospective donors of tuberculins and the importance of the current meeting to review and finalise the protocol for the preparation and validation of a replacement International Standard Bovine Tuberculin (ISBT-2).

Dr Stone reminded the Group of the importance of their engagement and tasks. He noted that OIE Member Countries rely on intradermal testing to control and eradicate bovine tuberculosis and that each national standard tuberculin should be validated against a good quality International Standard. An international standard tuberculin is an essential tool for OIE Member Countries to help them combat or eradicate bovine tuberculosis, a priority disease for both animal and human health.

Dr Steven Edwards noted that, in the previous meeting of the Group, a representative of the World Health Organisation (WHO) was invited and attended the meeting. However, the representative, Dr David Wood, retired recently, and an alternate representative had not been nominated to attend the current meeting. He considered that, since the WHO is supportive of the project, the presence of a representative was not strictly needed but that the OIE should continue reporting to the WHO on the progress of the project. He also informed the Group that Dr Douwe Bakker retired from the Group, and that Dr Ad Koets would be replacing him in the Group. The Group and the OIE welcomed Dr Koets as a new member of the Group and thanked the Dr Bakker for his significant contribution to the Group.

Dr Mei Mei Ho and Dr Ad Koets were not able to attend the meeting in person, however Dr Ho was able to provide responses to some questions during the meeting by email, and Dr Koets joined the meeting briefly by teleconference on June 7.

2. Appointment of chairperson and rapporteur

The meeting was chaired by Dr Steven Edwards, and Prof. Glyn Hewinson was designated as rapporteur, with the support of the OIE secretariat. The Group endorsed the proposed agenda.

The Terms of Reference of the Group, the Agenda and the List of Participants are presented as Appendix I, II and III respectively.

[1] Note: This ad hoc Group report reflects the views of its members and may not necessarily reflect the views of the OIE. This report should be read in conjunction with the September 2017 report of the Biological Standards Commission because this report provides its considerations and comments. It is available at: http://www.oie.int/en/international-standard-setting/specialists-commissions-groups/laboratories-commission-reports/meetings-reports/

3. Terms of Reference

3.1. Review progress to date, to acquire candidate bulk tuberculins and formulate into test fills for laboratory evaluation

Dr Glen Gifford gave an update on the progress made so far in the project implementation. He noted that milestones identified in the previous meeting of the Group had slipped by about one year, due to difficulties in obtaining funding. He recalled that in May 2017 the OIE, in collaboration with Dr Ho, MHRA-NIBSC[2], had contacted tuberculin manufacturers to solicit donations of tuberculins for consideration as candidate ISBT-2. Four enquiries were received and three manufacturers agreed to donate their tuberculins, including the provision to the OIE of a complete dossier including data required for evaluation. These data were reviewed by the Group against a predetermined set of endorsed criteria. Decisions on which candidates to take forward were made via a teleconference of the Group on 18 May 2017, as noted in Appendices V, VI, and VII.

The proceedings of this decision-making process are laid out in the 'Report of the Meeting of the OIE *ad hoc* Group on Replacement of the International Standard Bovine Tuberculin: Consultation by teleconference 18 May 2017'. The Group reviewed and adopted the report that will be annexed to the September 2017 Biological Standards Commission meeting report.

Two candidate tuberculins from manufacturers which were designated M1 and M2 were chosen for further evaluation, subject to satisfactory responses to further questions raised by the Group. Both suppliers had already confirmed their availability to provide tuberculin. In addition, both will need to provide data on lack of undesirable immunological sensitising effects of their products, before these are taken forward to the laboratory testing phase. The Group noted that there may be a limited capacity of laboratories to test the new standard using live *Mycobacterium bovis* to sensitise the test animals.

The Group also discussed the suitability of the currently available preparations from M1 and M2. Dr Ho confirmed that a slightly lower protein concentration of the bulk material could be acceptable, since the fill volume could be adjusted before lyophilisation to obtain the preferred final product protein concentration. She also informed the Group that the residual phenol in the available product from M1 (at approximately 0.03%) is lower than the phenol concentration present in the current ISBT-1, and this concentration did not adversely affect the lyophilisation. Therefore, the Group concluded that, rather than wait for the production by M1 of an alternative batch without phenol, considering the time slippages that have already occurred in the implementation of the project, the work on the International Standard should press ahead and suitability of the batches reviewed after evaluation of the trial fill preparations, as noted below.

3.2. Identify prospective collaborating laboratories, and finalize protocols and schedules to evaluate potency, specificity, and safety of candidate ISBTs, and prepare summary reports

The Group discussed and amended the 'Protocol for the evaluation and adoption of a replacement International Standard Bovine Tuberculin' Appendix III to the Report of the Meeting of the OIE *ad hoc* Group on Replacement of the International Standard Bovine Tuberculin, Paris, 24-26 November 2015 (Meeting Report 2015)[3]. The revised protocol is presented as Appendix IV to this report. The Group provided a rationale for these amendments in the relevant sections, as noted below.

The Group proposed adding details to the 'protocol for sensitisation of guinea-pigs with live *M. bovis'*, to ensure that the protocol is in line with the *European Pharmacopoeia*.

The Group highlighted the need for a statistician to review the protocols before commencing work, including the preliminary evaluation. This was discussed during the meeting in a teleconference with Dr Ad Koets. Dr Koets committed to take this aspect of the work forward by consulting with a statistician/epidemiologist, from his institute, regarding the experimental design and analytical procedures.

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2 Medicines and Healthcare products Regulatory Agency-National Institute for Biological Standards and Control, Potters Bar, Hertfordshire EN6 3QG, United Kingdom

3 Report of the meeting of the OIE *ad hoc* Group on replacement of the International Standard Bovine Tuberculin - Annex 5 of the Report of the meeting of the OIE Biological Standards Commission (http://www.oie.int/fileadmin/Home/eng/Internationa_Standard_Setting/docs/pdf/BSC/A_BSC_Feb2016.pdf)

a) Preliminary evaluation of candidate tuberculins and guinea-pig sensitisation with heat-inactivated *M. bovis*

The Group agreed that preliminary validation of the lyophilisation process and of the suitability of the candidate preparations will be performed by the two OIE Reference Laboratories (RL) for bovine tuberculosis in Argentina and France, as detailed in Appendix III of this report, using heat-inactivated *M. bovis* AN5. In particular, the OIE RL in Argentina will perform potency and specificity testing on the trial fill preparations while the OIE RL in France will perform only the potency testing. Dr Capsel informed the Group that the National Veterinary Services Laboratories of the USDA[4] would provide heat inactivated *M. bovis* AN5 sensitising agent to the OIE RLs and to the other International Collaborative Study participating laboratories, so that the same sensitising agent is used throughout the evaluation. USDA has sequenced the genome of the above-mentioned *M. bovis* AN5 strain. The Group noted that inactivation of *M. bovis* AN5 was achieved by heating the sensitising agent at 90°C for 35 minutes.

The Group discussed the conduct of the preliminary evaluation of candidate tuberculins.

Given the relatively high tuberculin protein concentration used in the USDA potency test protocol, the Group recommended that, for the preliminary evaluation of trial fills, the two reference laboratories will compare the USDA protocol with the procedure recommended by the OIE in Chapter 2.4.6, on bovine tuberculosis of the OIE *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual).* The aim will be to compare the effect of lyophilisation on potency and also to compare the two 'sensitising agent' formulations, which contain *M. bovis* AN5 blended with either mineral oil (USDA method) or Freund's incomplete adjuvant (OIE method). After evaluation of these results, the Group would then decide on the final protocol to be used for the International Collaborative Study. This comparative study will increase numbers of guinea pigs by 16 per laboratory.

b) Evaluation of heat-inactivated *M. bovis versus* live *M. bovis* for sensitisation in potency studies

The Group emphasised that the focus of the International Collaborative Study was to obtain a replacement of the ISBT-1 and not to validate heat-inactivated *versus* live *M. bovis* for sensitisation to assess tuberculin potency in guinea pigs. Nevertheless, the Group recognised the opportunity that the study offers to generate data to determine whether sensitisation with live AN5 could be replaced by an inactivated *M. bovis* AN5.

The Group therefore recommended that EDQM[5] should be informed of the study designs. EDQM could identify possible shortcomings that would affect the possibility to use the data for evaluation of heat-inactivated *M. bovis* for sensitisation in potency studies, and allowing EDQM to consider changing the current protocol in the *European Pharmacopoeia*[6].

c) International Collaborative Study to assess further fitness for purpose, using only heat-inactivated *M. bovis* for sensitization if results from preceding evaluation study are satisfactory

The Group noted that it would not be possible to make any recommendations on this question until data from the preliminary evaluation are available and analysed by a qualified statistician.

4. Discuss scheduling, budgeting and reporting

4.1 Scheduling, timeframes, deliverables.

The tentative timescale for producing an ISBT-2was revised as follows noting progress made on specific milestones:

- Approval of the proposal for production of an ISBT-2 for bovine tuberculin, by the OIE Biological Standards Commission – February 2016 [completed].
- Define selection criteria for bulk material – February 2016 [completed].

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4 United States Department of Agriculture

5 European Directorate for the Quality of Medicines & Healthcare (EDQM)

6 European Pharmacopoeia monographs for Tuberculin PPDs, (Tuberculin PPD, Bovine [01/2008:0536]

- OIE, in collaboration with NIBSC, write to manufacturers for materials requesting a written submission with technical data and to preliminary testing reference laboratories – March 2017 [completed].
- Selection of candidate ISBT-2 in teleconference of the Group – May 2017 [completed].
- Revision of protocol, timescales and budget – June 2017 [completed].
- Bulk material selected and supplied to NIBSC by July-August 2017.
- Preliminary fill of ampoules by August 2017.
- Statistician review protocol for the International Collaborative Study by September 2017.
- Call for participants for International Collaborative Study (contact OIE Delegates and Laboratory Focal Points) by September 2017.
- Prepare standardised sensitising agent – heat-inactivated *M. bovis* AN5 strain for guinea-pigs by end 2017.
- Evaluation of preliminary fill material by two OIE Reference Laboratories by end 2017.
- Main fill of 5000 ampoules by mid-2018.
- International Collaborative Study start mid-2018 end by mid- 2019.
- Data submitted to statistician for analysis-mid 2019.
- Written report submitted to OIE Biological Standards Commission January 2020 - and endorsement by the World Assembly – May 2020.
- NIBSC was designated as repository for ISBT-2 and will ensure secure appropriate storage and distribution.
- Peer-reviewed paper on characterisation of ISBT-2.

4.2 Projected costs, current funding and in-kind support, activities not yet funded.

The Group discussed the budget with Dr Emily Tagliaro, Head of the OIE World Fund Unit. The Group considered that part of the costs would be covered by in-kind contributions by OIE Member Countries and that the remainder of the budget would need to be secured by the OIE. Dr Tagliaro will investigate further options for funding.

4.3. Internal reporting, communication of results.

The Group recommended that a peer-reviewed paper on characterisation of ISBT-2 should be published, in addition to the internal report to the Biological Standard Commission.

4.4. Contingencies

The Group identified the following contingencies:

- If there are insufficient laboratories able to participate in the International Collaborative Study, then the number of animals tested in each participating laboratory should be increased, as advised by the statistician.
- If there is insufficient funding following an initial round of requests, then other funding agencies should be approached.
- If neither of the candidate batches are found to be satisfactory, then the OIE will need to identify other candidate batches for evaluation.

5. Other matters

The Group addressed a number of additional questions raised by the OIE as below:

a) Does the Group support conducting a comparative genomic analysis to characterise each of the *M. bovis* isolates that were used as seeds to produce the candidate tuberculins?

The Group endorsed this proposal and recommended that the genomes of *M. bovis* AN5 seeds be sequenced by the providers of the candidate tuberculins, or that the manufacturers provide DNA to the OIE Reference Laboratory for bovine tuberculosis in the UK for sequencing.

b) Does the Group support recommending that National Regulatory Authorities consider conducting a genomic analysis of *M. bovis* isolates used for production of bovine tuberculins?

The Group supported this suggestion and further recommended that genomic sequencing be used to characterise an AN5 reference strain.

In order to identify the reference strain, the Group recommended that laboratories participating in the International Collaborative Study using live *M. bovis* AN5 to sensitise guinea-pigs should be asked to provide the genomic sequence of the AN5 strain used to sensitise the guinea pigs. Alternatively, the participants could provide genomic DNA from these strains to the OIE Reference Laboratory for bovine tuberculosis in the UK for sequencing.

c) Does the *ad hoc* Group support conducting a proteomic analysis of the *M. bovis* AN5 islolates? Are there technical limitations to conducting or interpreting proteomic studies on heat-inactivated *M. bovis*?

The Group did not recommend the use of proteomic analysis of *M. bovis* AN5 isolates as part of this study.

d) Should the OIE consider providing standardised reference reagents (e.g. *M. bovis* AN5 seed cultures and heat-inactivated reagents) for use by National Regulatory Authorities in calibrating National Reference Standard bovine tuberculins and product batches against the new ISBT-2?

The Group endorsed this suggestion and recommended that this activity be linked to the OIE Biobank Initiative. The Group recommended that this reference material be held by the OIE Reference Laboratories for bovine tuberculosis and cost recovery fees be charged for supplying reagents to others.

The Group also recommended that the *M. bovis* AN5 working seed should undergo no more than five passages for production and that the relevant Chapter of the *Terrestrial Manual* should be revised to include this recommendation.

6. Conclusions

6.1. Comments and Recommendations

1. There is concern that supplies of ISBT-1 are running out. The Group, therefore, recommends that the timeline of the project be strictly respected;
2. The Group strongly recommends that the OIE World Fund explore funding options as a matter of urgency, including raising awareness among OIE Delegates;
3. The Group recommends that the supply of ISBT-2 be considered as fundamental for the implementation of the tripartite Zoonotic Tuberculosis Road Map, under the 'One Health' initiative;
4. The Group recommends that the Chapter on Bovine tuberculosis in the OIE *Terrestrial Manual* be revised, including the section on tuberculin.

7. Finalisation and adoption of the draft report

The *ad hoc* Group finalised and adopted the draft report.

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…/Appendices

Appendix I

MEETING OF THE OIE *AD HOC* GROUP ON
REPLACEMENT OF INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 6-8 June 2017

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Terms of Reference

- Review progress to acquire candidate bulk tuberculins and formulate test fills at NIBSC.
- Identify prospective collaborating laboratories for testing candidate ISBTs.
- Finalize protocols for characterizing candidate ISBTs, and evaluating their potency, specificity, and safety.
- Discuss scheduling, budgeting, and reporting.

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Appendix II

MEETING OF THE OIE *AD HOC* GROUP ON

REPLACEMENT OF INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 6-8 June 2017

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Agenda

1. Opening

2. Appointment of chairperson and rapporteur

3. Terms of Reference

3.1. Review progress to date, to acquire candidate bulk tuberculins and formulate into test fills for laboratory evaluation

3.2. Identify prospective collaborating laboratories, and finalize protocols and schedules to evaluate potency, specificity, and safety of candidate ISBTs, and prepare summary reports

4. Discuss scheduling, budgeting and reporting

4.1 Scheduling, timeframes, deliverables.

4.2 Projected costs, current funding and in-kind support, activities not yet funded.

4.3. Internal reporting, communication of results.

4.4. Contingencies

5. Other matters

6. Conclusions

6.1. Comments and Recommendations

7. Finalisation and adoption of the draft report

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Appendix III

MEETING OF THE OIE *AD HOC* GROUP ON REPLACEMENT OF INTERNATIONAL STANDARD BOVINE TUBERCULIN

Paris, 6-8 June 2017

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Protocol for the Evaluation and Adoption of a Replacement International Standard Bovine Tuberculin (Revised June 2017)

The 1st International Standard for purified protein derivate (PPD) of bovine tuberculin was designated by WHO[7] in 1986[8], and is currently held at the WHO International Laboratory for Biological Standards, MHRA-NIBSC[9], UK. Due to the declining stocks of the International Standard Bovine Tuberculin, a proposal has been developed for the evaluation and calibration of a replacement standard. The aim is to produce a new International Standard Bovine Tuberculin sufficient to meet global requirements for the next 20 years. The task will require animal studies, and therefore funding. It is agreed that the OIE should take the lead in evaluating and designating the replacement standard. A study expert panel should direct and oversee the study. Partners in the study will include the OIE Reference Laboratories for bovine tuberculosis, other recognised experts, and MHRA-NIBSC (as holders of the current standard and experts in the evaluation, designation and storage of standard reference preparations). The protocol for the proposed study is outlined below.

The results and raw data will be submitted to MHRA-NIBSC for statistical analysis and evaluation by the study expert panel.

1. Production

Tuberculin manufacturers will be invited to donate a bulk candidate material along with certificates of analysis that should include toxicity, sterility, sensitising effect, specificity and potency. At least two candidate materials will be selected for further processing and evaluation using methods that are in conformity with recognised production processes. The tuberculin will be obtained from the water-soluble fractions prepared by heating in free-flowing steam and subsequently filtering cultures of *M. bovis* strain AN5 grown in a liquid synthetic medium. The active fraction of the filtrate, consisting mainly of protein, will be isolated by precipitation, washed and re-dissolved in glucose-phosphate buffer without preservative. The final sterile preparation will be stored at MHRA-NIBSC as bulk material pending calibration of the new standard. A small number of lyophilised test ampoules, each containing 2 mg of protein, will be produced for initial analysis. The bulk stock of candidate preparations that give satisfactory performance in the preliminary evaluation will then be lyophilised into 2 mg ampoules. These will be used in an International Collaborative Study to determine the unitage/potency of the preparations, one of which will be selected as the replacement International Standard Bovine Tuberculin. It will be defined in International Units by calibration against the current Standard.

2. Preliminary evaluation

The aim of the preliminary evaluation is to check the lyophilisation process and the suitability of the candidate preparations. Two OIE Reference Laboratories for bovine tuberculosis will carry out a preliminary evaluation in guinea-pigs sensitised with heat-inactivated *M. bovis* AN5 strain. They will be supplied with the current International Standard and the pre-lyophilised and freeze-dried preparations of the two candidate preparations, which will be evaluated as follows.

2.1. Potency

For each candidate preparation, sensitise not fewer than eight albino guinea-pigs, each weighing 300 g to 500 g, by the deep intramuscular injection of a suitable dose of heat-inactivated *M. bovis* strain AN5 suspended in buffer and made into an emulsion with Freund's incomplete adjuvant or mineral oil in order to compare possible differences in the preparations. Not less than 4 weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for not more than four injection sites on each side. Prepare dilutions of the candidate tuberculin to be evaluated and of the reference standard preparation using isotonic phosphate-buffered saline (pH 6.5–7.5) containing 0.005 g/litre of polysorbate 80. Use not fewer

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7 World Health Organization

8 WHO - Proposed international standard for purified protein derivative (ppd) of bovine tuberculin - THE INTERNATIONAL COLLABORATIVE ASSAY: http://apps.who.int/iris/bitstream/10665/78132/1/WHO_BS_86.1518_eng.pdf

9 Medicines and Healthcare products Regulatory Agency - National Institute for Biological Standards and Control, Potters Bar, Hertfordshire EN6 3QG, UK

than three doses of the standard preparation and not fewer than three doses of the candidate preparation for evaluation. Choose the doses such that the lesions produced have a diameter of not less than 8 mm and not more than 25 mm. Allocate the dilutions randomly to the sites using a Latin square design. Inject each dose intradermally in a constant volume of 0.1 ml or 0.2 ml. Measure the diameters of the lesions after 24 to 28 hours and calculate the result of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the tuberculins.

The test is not valid unless the fiducial limits of error ($p = 0.95$) are greater 50% and less than 200% of the estimated potency, where the stated potency of the standard represents 100%. The estimated potency is not less than 66% and not more than 150% of the stated potency. The stated potency is not less than 30 000 IU/mg.

This will require 38 albino guinea-pigs per laboratory.[10]

The preliminary evaluation will also include the testing of a protocol, provided by USDA, for the sensitisation of guinea pigs with heat-inactivated *M. bovis* blended in mineral oil. This will require 16 guinea-pigs per laboratory (32 in total).

2.2. Specificity

The candidate standards are assayed, in one OIE Reference Laboratory for bovine tuberculosis, against the standard for avian PPD tuberculin by a four-point assay in guinea-pigs sensitised with heat-inactivated *M. avium* (strain D4ER), comprising two dilutions at 25-fold intervals of each tuberculin. Quantities of 0.03 mg and 0.0012 mg of test avian PPD tuberculin corresponding to approximately 1500 and 60 IU, are chosen because these doses give good readable skin reactions. In one assay, the candidate standards are compared with the International Standard Bovine Tuberculin in eight guinea-pigs by applying eight intradermal injections per animal and employing a balanced complete Latin square design. The reading of the results and the statistical evaluation are identical to the potency test. The response to bovine PPD in guinea-pigs sensitised with *M. avium* should be 10% or less in comparison with avian PPD.

This will require eight albino guinea-pigs.

3. International collaborative study

The study will be coordinated by MHRA-NIBSC, under the guidance of the study expert panel and under the supervision of the OIE Biological Standards Commission. A questionnaire will be sent by MHRA-NIBSC to potential participants, including questions such as which potency assay they can perform using guinea-pigs or cattle, using live or heat-inactivated *M. bovis* sensitisation, and in the case of cattle with either experimentally infected or natural reactors. Participants will also be asked their capacity and willingness to perform the required assays using a common study protocol within a specified timeframe. The participants will be chosen by the study expert panel on the basis of the responses. The target number of participating laboratories would be as follows: ten for guinea-pigs sensitised with live *M. bovis,* ten for guinea-pigs sensitised with heat-inactivated *M. bovis* strain AN5, five for naturally sensitised reactor cattle and four for cattle sensitised by experimental infection. If these numbers are not achieved, the study expert panel will reconsider the study design.

3.1 Guinea-pig heat-inactivated *M. bovis* sensitisation

The proposed protocol will be finalised after Preliminary Evaluations and statistical analyses have been completed.

Each participant will be asked to test each of the candidate preparations in three separate experiments. A total of 10 guinea-pigs will be used for each candidate preparation for each experiment. A standard stock of sensitising agent (heat-inactivated AN5) will be produced as an aqueous suspension at a concentration of 50 mg (wet weight) of heat-inactivated AN5 per ml of aqueous buffer. A working preparation of heat-inactivated AN5 in mineral oil will be prepared at each participating laboratory from provided stock reagents. Combine 2 ml stock sensitising agent with 3 ml of sterile light mineral oil adjuvant (Fisher Scientific Sigma Chemical Company or equivalent supplier, MDL Number: MFCD00131661) for a final concentration of 20 mg/ml.

[10] The proposed numbers of animals include spares for contingencies.

For each candidate preparation, sensitise eight albino guinea-pigs, each weighing 300 g to 500 g, and allocate the two additional guinea pigs to be used as unsensitised controls.

Heat and maintain the working stock preparation to approximately 45°C and withdraw the warmed sensitising agent into a syringe. Inject 8 guinea-pigs by deep intramuscular injection with 0.05 ml sensitising agent in each hind leg (total volume per animal equals 0.1 ml).

Inject the non-sensitised guinea-pigs by intramuscular injection (0.5ml per hind leg) with 0.1 ml sterile saline previously warmed to 45°C.

Thirty-five +/- 2 days after sensitisation, clip the hair from the abdomen and sides of each guinea-pig and allow the guinea-pigs to rest in their cages a minimum of four hours prior to administering tuberculin injections. Prepare dilutions of the candidate tuberculins to be evaluated and of the reference preparation using isotonic phosphate-buffered saline (pH 6.5–7.5) containing 0.005 g/litre of polysorbate 80 to contain 50, 10, 2, and 0.4 µg protein/ml this correspond to 1625 IU/ml, 325 IU/ml, 65 IU/ml and 13 IU/ml respectively. Allocate the dilutions randomly to the injection sites using a Latin square design. Laying the guinea-pig on its side, inject each dose intradermally in a constant volume of 0.1 ml. Four injections are administered to each side of each guinea pig. Similarly, inject the four dilutions of the reference and candidate tuberculins on the two unsensitised control guinea-pigs. Measure the diameters of the lesions using calipers after 24 to 28 hours and again at 48–52 hours post-injection. Take two perpendicular diameter readings of the erythema of each injection site. Calculate the result of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the tuberculins.

This will require a total of 60 guinea-pigs per laboratory.

3.2 Guinea-pig live *M. bovis* sensitisation

Each participant will be asked to test each candidate tuberculins in three separate experiments. For each candidate tuberculin, sensitise eight albino guinea-pigs, each weighing 400 g to 600 g, by the deep intramuscular injection of 0.0001 mg of wet mass of living *M. bovis* AN5 suspended in 0.5 ml of a 9 g/litre guinea-pig live *M. bovis* sensitisation solution of sodium chloride. Four weeks after the sensitisation of the guinea-pigs, shave their flanks to provide space for four injection sites on each side. Prepare dilutions (40, 20, 10 and 5 IU/ml) of the candidate tuberculin to be evaluated and of the reference tuberculin using isotonic phosphate-buffered saline (pH 6.5–7.5) containing 0.005 g/litre of polysorbate 80. Allocate the dilutions randomly to injection sites using a Latin square design. Inject each dose intradermally in a constant volume of 0.2 ml. Measure the diameters of the lesions after 24 hours using calipers and calculate the results of the test using the usual statistical methods and assuming that the diameters of the lesions are directly proportional to the logarithm of the concentration of the injected tuberculins.

This will require a total of 50 guinea-pigs per laboratory.

3.3 Reactor cattle

In accordance with the OIE *Terrestrial Manual*, cattle should be procured from infected herds containing confirmed field cases that have reacted positively between 3 mm and 15 mm in the tuberculin skin test, and preferably also positive in the interferon gamma release assay. Infected cattle should be held in isolation for at least 8 weeks. The candidate tuberculins are evaluated against the International Standard Bovine Tuberculin by a four-point assay using two dilutions at five-fold intervals of each candidate tuberculin. For the standard, 0.1 and 0.02 mg of PPD tuberculin are injected, as these volumes correspond with about 3250 and 650 IU. The candidate tuberculins are diluted in such a way that the same weights of protein are applied. The injection volume is 0.1 ml, and the distance between the middle cervical area injection sites is 15–20 cm. In one assay, the candidate tuberculins are compared with the International Standard Bovine Tuberculin in eight reactor cattle, applying eight intradermal injections per animal in both sides of the neck, and employing a balanced complete Latin square design. The thickness of the skin at each injection site is measured with callipers in tenths of a millimetre, as accurately as possible before and 72 hours after injection

The results are statistically evaluated using the same standard methods for parallel-line assays as employed in the potency tests in guinea-pigs.

Each participant will be asked to test each of the candidate preparations in three separate experiments. This will require at least 24 reactor cattle of at least 6 months of age.

3.4 Experimentally infected cattle

Participants will be asked to propose their method of experimental infection, including the dose and strain of *M. bovis* to be used for sensitisation. At least 6 weeks post-infection, the tuberculin test is conducted, as noted above. This will require at least 8 animals of at least 6 months of age.

Each participant will be asked to test each of the candidate tuberculins in three separate experiments. This will require at least 24 cattle of at least 6 months of age.

3.5 Stability testing

MHRA-NIBSC will prepare samples for the thermal stability test. Ampoules from final definitive fill preparations will be incubated at various temperatures (i.e. –20°C, 4°C, 37°C) for different durations (i.e. 3, 6, 12, 24 months). These samples will only require testing once by one Reference Laboratory using guinea-pig sensitised with heat-inactivated AN5. Depending on progress with the International Collaborative Study, the longest duration of stability test may not be complete by the time that all other data in support of the adoption of the new standard are ready. In this case, samples from further time points can be tested after the adoption and the expiry date can be adjusted according to the results (this is a common practice for other standards).

A stability test on two candidate preparations, using three temperatures and four time points will require a total of 144 guinea-pigs, comparing samples of two incubation temperatures (4°C or 37°C) with the sample stored at –20°C.

4. Report of the international collaborative study

The study expert panel will prepare a draft report. A copy of the draft report is sent to each participant together with the code used to identify their own laboratory. The participants should confirm that:

i) Their data have been correctly interpreted in the analysis;

ii) The proposed material is suitable to serve as a reference standard for the purpose defined; and

iii) The proposed unitage is appropriate.

The final report will be submitted to the OIE Biological Standards Commission.

A manuscript will be prepared for publication in a peer-reviewed appropriate international journal.

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Appendix V

Original: English
May 2017

REPORT OF THE MEETING OF THE OIE AD HOC GROUP ON REPLACEMENT OF THE INTERNATIONAL STANDARD BOVINE TUBERCULIN
Consultation by Teleconference 18 May 2017

The OIE *ad hoc* Group on Replacement of the International Standard Bovine Tuberculin (hereinafter referred to as the Group) evaluated the dossiers provided by three manufacturers, as potential donors of candidate tuberculins for the production of the new International Standard Bovine Tuberculin (ISBT-2).

The Biological Standards Commission (hereinafter referred to as the Commission), agreed that this evaluation could be conducted by correspondence among the experts of the Group. The OIE secretariat facilitated the communication, which took place via electronic means. A teleconference was organised on 18 May 2017 to facilitate the discussions, and to prepare the report.

The Group members conducted preliminary analyses of the dossiers prior to the teleconference. The experts presented their key findings to the other participants of the Group, initially by electronic means and then during the teleconference. The Group had an in-depth discussion on prospective suppliers of bulk tuberculin's compliance, based on the selection criteria that had been developed during the first meeting of the Group, in November 2015.

Prior to the teleconference the Group had requested additional information from the potential donors, and had received clarification from two of them.

1. Opening

On behalf of Dr Monique Eloit, Director General of the OIE, Dr Simona Forcella, of the Status Department and Dr Glen Gifford, of the Science and New Technologies Department, welcomed and thanked the Group for their commitment and support towards the OIE. Dr Forcella acknowledged the work done, not only during the meeting, but also prior to the meeting in reviewing the dossiers submitted by prospective donors.

Dr Forcella restated the objective of the teleconference and reiterated the importance of replacing the current ISBT (ISBT-1) as soon as possible, before current stocks run out. Participants were also reminded of the importance of the sensitivity and confidentiality issues pertaining to the meeting and highlighted that the report of this meeting should be transparent, with each decision science-based and clearly documented so that it can be used to communicate the Group's decision to the Biological Standards Commission and eventually to the OIE Member Countries.

2. Adoption of the agenda and appointment of chairperson and rapporteur

The Group was chaired by Dr Steven Edwards, and Prof. Glyn Hewinson was designated as rapporteur, with the support of the OIE Secretariat. The Group endorsed the proposed agenda.

The Terms of Reference of the Group and the agenda are presented as Appendix I and the list of participants is presented as Appendix II.

3. Consideration of Terms of Reference.

3.1. Background and Terms of Reference

The Group was convened for the first time by the OIE from 24 to 26 November 2015. The main objective of this Group was to develop a protocol to produce a new replacement ISBT (ISBT-2), as the current ISBT-1 is becoming depleted.

The Commission at its February 2017 meeting endorsed the proposal for the National Institute for Biological Standards and Control (NIBSC) to contact prospective suppliers of bulk tuberculin on behalf of the OIE. Subsequently, a number of manufacturers were contacted, and among them, three potential donors for replacement tuberculin have been identified.

According to the timescale of the protocol, as developed by the Group in November 2015, the initial screening of candidate tuberculins was to be done on the basis of the summary documents provided by the prospective donors. The *ad hoc* Group teleconference was required to discuss the submissions from prospective donors of candidate bulk tuberculins, and to select two candidates for further evaluation.

The objective of the teleconference was to review the documentation and test results provided by prospective donors of candidate bulk tuberculins, and to select two candidates which will be formulated into test fills at the NIBSC. These candidate tuberculins will be further evaluated in laboratory studies conducted at the OIE Bovine Tuberculosis Reference Laboratories and collaborating laboratories.

3.2. Summary of the completed procedures to contact manufacturers of bovine tuberculins, to solicit donations of candidate bulk tuberculins

Dr Glen Gifford summarised the completed procedures to contact manufacturers of bovine tuberculins, to solicit donations of candidate bulk tuberculins.

He informed the Group that 18 prospective donor manufacturers were contacted and provided with an explanation of the project, data requirements around the potential donated material, and decision making process including the score sheet that would be used by the Group to assess the candidates. The OIE received responses from four prospective donors, and three out of four provided the required documents. These were identified as Manufacturer 1, Manufacturer 2 and Manufacturer 3 to protect their confidentiality. The experts reviewed the application and summaries of these have been provided to the Group.

4. Discussion of the *ad hoc* Group's evaluations of the documentation and test results that were submitted by prospective donors.

The Group discussed and evaluated each of the documents provided by the three prospective donors, to demonstrate compliance with the selection criteria for bulk material.

1) Description of manufacturing protocol and quality control system for the production of purified protein derivative (PPD) of bovine tuberculin.

The Group considered that Manufacturer 1 (M1) provided very detailed and clear documentation substantiating a clear protocol and good track records.

Manufacturer 2 (M2) provided a short description but clear enough to demonstrate a good protocol.

Manufacturer 3 (M3) provided detailed and clear information. However, the Group noted that this manufacturer no longer used chemical precipitation methods, e.g. ammonium sulphate or trichloroacetic acid, but concentrates by ultrafiltration instead, using (20kDa) membrane. The ultrafiltration molecular weight cut off is important, as many lower molecular weight proteins are highly immunogenic (e.g. ESAT-6 and CFP10, which are approximately 10kDa). The Group commented that, if the cut-off was too high, the manufacturer might lose these important low molecular weight antigens. The Group determined that an International Standard must be produced by the standard procedure, and that the procedure adopted by M3 was not yet an accepted procedure, although it might become one in the future. The group regretted that M3 did not provide the requested additional information, including the molecular weight cut-off specifications.

The Group acknowledged that all manufacturers reported that they conform to the *European Pharmacopoeia* standard for manufacturing bovine tuberculin, as demonstrated by the quoted references provided in the dossiers.

2) Summary demonstrating long-term consistent production history with use of product in bovine tuberculosis (bTB) control programmes.

The Group acknowledged that the three manufacturers all had a history of long-term production: M1 since 1982; M2 since 1996. M3 also had a long-term production history, however has only been producing tuberculin with the above mentioned new ultrafiltration methodology since 2005, and had a new master seed since 2013.

3) Summary of use in a large-scale or statistically significant number of animals.

The Group agreed that the three manufacturers complied with the requirements, and that each had supplied the bovine tuberculin product to millions of animals.

4) Regulatory oversight of the products released including: release criteria and identification of responsible regulatory authority.

The Group agreed that the three manufacturers complied with the requirements, and were legally registered by countries' Competent Authorities.

5) For continuity of quality criteria, the replacement International Standard Bovine Tuberculin-2 (ISBT-2) should have performance characteristics as close as possible to the current International Standard Bovine Tuberculin-1 (ISBT-1).

The Group considered that the ISBT-1 had a potency of 32,500 IU/mg and noted that M1 had a tuberculin with performance characteristics similar to ISBT-1. M2 had a standard product with a lower potency (25,000U/mg), however M2 informed the Group that, if selected, would produce a batch of tuberculin with potency similar to ISBT-1. The characterisation of the tuberculin produced by M3 versus ISBT-1 was not clear. The Group noted that M3 had a higher reported potency (50,000 IU/mg).

6) Certificate of Analysis. Should include toxicity, sterility, sensitising effect, specificity and potency data passing the European Pharmacopoeia requirement for Tuberculin purified protein derivative, bovine monograph (01/2008:0536) or equivalent in other regulatory standards.

The Group agreed that the submitted dossier was compliant with the format of the questionnaire in Article 1.6.7.

The Group agreed that the most important critical characteristics were sterility, specificity and potency and that two out of the three prospective donors of candidate bulk tuberculins provided detailed information. M3 did not provide information regarding specificity.

7) Quantity per single batch production. Bulk tuberculins should be in the range of 10-12 g of protein content; with concentration suitable for dilution further for filling at 2 mg/1 ml/ ampoule in glucose-phosphate buffer (pH 6.5 – 7.5).

The Group noted that, according to the information provided, M1 and M2 would be able to achieve the range of 10-12 g of protein content; with concentration suitable for dilution further for filling at 2 mg/1 ml/ ampoule in glucose-phosphate buffer (pH 6.5 – 7.5). The Group noted that M3 reported that protein concentration of their product was variable depending on the produced batch. The Group agreed that the protein content of an International Standard should be constant.

8) Uniformity. The bulk material should be sufficient to fill 5000 to 6000 ampoules. The product should be presented as a single homogenous bulk or filled in clear/neutral glass ampoules. All documentation and labelling should be in English.

The Group agreed that according to the information provided by M1 and M2, their products would be compliant with the requirements. The Group noted that, in its answer, M3 replied that this characteristic was not applicable nor performed by M3.

9) Potency. The estimated potency per mg should be as close as possible to the old (current) ISBT-1, ± 32,500 International Units (I.U.) per mg. as estimated in guinea pigs.

The Group noted that potency of field preparations currently in use, depending on local legislation, is variable: B2000 (the minimum required dose), B2500 and B3000 contains 2000, 2500 and 3000 I.U. per dose of 0.1 ml, respectively. For an optimal specificity a concentration of 1mg per ml has always been recommended. Hence, a potency of 32,500 IU/mg would be just slightly higher than e.g. the B3000, thus allowing a better comparison in the parallel line assay. Contents of each ampoule should be ± 2mg, allowing the present dilution schemes in use to remain in place.

The Group agreed that all manufacturers were compliant with European Pharmacopoeia standard.

10) Specificity. Specificity should comply with the requirements given by the OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, Chapter 2.4.6, Bovine Tuberculosis (Terrestrial Manual).

The Group agreed that the international standard should be standardised in this respect. The Group noted that none of the manufacturers complied with the OIE requirement for specificity testing, and agreed that the manufacturers should be asked to do specificity tests for the candidate tuberculin, if they are chosen for further evaluation.

11) Lyophilisaton. For lyophilisation, the bulk material should contain no phenol. Traditionally, bulk material is stored often at +4oC in the presence of phenol, used as preservative. It is recognised that companies may need to adapt procedures specifically in order to supply bulk material without phenol.

The Group noted that M1 would supply bulk tuberculin but with low concentration of phenol, stating that that this would not affect lyophilisation. According to this statement M1, if selected, would be asked to supply data to justify that the level of phenol would not affect lyophilisation or to produce a batch without phenol. M2 and M3 reported that they could supply a phenol free batch.

The Group considered that time scale for supplying phenol free batches from each supplier should be clarified and that NIBSC should address with evidence based scientific justification if a product with low phenol concentration could be accepted.

12) Production strain. *Mycobacterium bovis* (*M. bovis*) AN5:

The Group agreed that all manufacturers used a live, adequately referenced strain of *Mycobacterium bovis* AN5.

13) Certified seed lot system should be in place to guarantee future continuity of the ISBT-2.

The Group noted that the all three manufactures had a certified seed lot system in place.

14) Bovine PPD production strain should be sequenced.

The Group considered that *M. bovis* has not been sequenced by the three manufacturers, but that the sequencing should be required for the candidate tuberculins that are selected for laboratory evaluation, so that the sequence of the strain used to produce the ISBT-2 is well defined. The Group proposed have a further in-depth discussion on this issue during the next ad hoc meeting that will be held from 6 to 8 June 2017, at the OIE Headquarters. The Group agreed that they will also discuss whether to make available a standard strain for tuberculin production, and corresponding reagents for potency testing

15) The origin and passage history of the *M. bovis* AN5 should be provided.

The Group considered that this topic was comprehensively covered by topic 12.

16) Details of production methods should be provided.

The Group noted that out of the three manufacturers, M1 and M2 provided a detailed and satisfactory description of the production protocols, while M3 had provided an incomplete description and, therefore, would need to be requested to provide additional information.

17) Guinea pig assays performed according to the basic guidelines from the OIE Terrestrial Manual.

The Group agreed that the guinea pig potency assay was performed according to the European Pharmacopoeia standard by M1and M2 that provided satisfactory details.

M3 did not provide information on this topic, however stated to be compliant with the European Pharmacopoeia.

On this regard, the Group noted that the European Pharmacopoeia required potency testing using live *M. bovis* to sensitise guinea pigs, but the *OIE Manual* accepts potency testing using live or inactivated *M. bovis* to sensitise animals, and the United States Code of Federal Regulations Title 9 (9 CFR) requires sensitisation with inactivated *M. bovis*. A study designed by the ad hoc Group will address the question as to whether either method is acceptable. The Group appreciated that the European Pharmacopoeia is aware of the OIE project to replace the current International Standard Bovine Tuberculin, and is willing to consider the data resulting from the International Collaborative Study, overseen by the Group, to update their requirements accordingly.

18) Strict description of the guinea pig assays provided.

The Group noted M1 and M2 provided additional information to describe the guinea pig assay.

5. Select two manufacturers that will donate candidate tuberculins to be formulated into test fills at NIBSC for laboratory evaluation.

The Group agreed that, although the product from M3 had many strong points, it was the candidate that, for the reasons highlighted in the above discussions, less fully complied with the requested characteristics. The key issue is that the International Standard should be made in a standard way (*i.e.* the currently accepted manufacturing methods). The Group regretted that M3 product did not meet this requirement, and that the requested supplemental information to characterize the tuberculin was not made available.

With respect to the M1, although it seems to be a good candidate, an important issue is the inclusion of phenol in the batch. The Group agreed to require science-based evidence on the impact of phenol. The Group agreed that, on the basis of the evidence provided, M2's product appears to be a suitable candidate, but some points of clarification were required.

The Group unanimously agreed that the products from M1 and M2 should be selected, subject to satisfactory supplementary answers to issues to be discussed at the forthcoming meeting in June 2017.

6. Other business.

The Group will meet again at the OIE Headquarters in Paris from 6 to 8 June 2017 to finalise the selection of the potential donors.

7. Adoption of report.

The Group agreed that the report would be circulated for finalisation.

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Appendix I

MEETING OF THE OIE AD HOC GROUP ON REPLACEMENT OF THE INTERNATIONAL STANDARD BOVINE TUBERCULIN
Consultation by Teleconference 18 May 2017

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Background

An *ad hoc* Group teleconference is required to discuss the submissions from prospective donors of candidate bulk tuberculins, and to select two candidates for further evaluation.

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Terms of Reference

1. The objective of the teleconference is to review the documentation and test results provided by prospective donors of candidate bulk tuberculins, and to select two candidates which will be formulated into test fills at the National Institute for Biological Standards and Control (NIBSC). These candidate tuberculins will be further evaluated in laboratory studies conducted at the OIE Bovine Tuberculosis Reference Laboratories and collaborating laboratories.

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Provisional Agenda

1. Opening.
2. Designation of the Chair and Rapporteur.
3. Adoption of agenda.
4. Consideration of Terms of Reference.
   - 4.1 Briefly summarise the completed procedures to contact manufacturers of bovine tuberculins, to solicit donations of candidate bulk tuberculins.
   - 4.2 Discuss the *ad hoc* Group's evaluations of the documentation and test results that were submitted by prospective donors.
   - 4.3 Select two manufacturers that will donate candidate tuberculins to be formulated into test fills at NIBSC for laboratory evaluation.
5. Other business.
6. Adoption of report.

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Appendix II

MEETING OF THE OIE AD HOC GROUP ON REPLACEMENT OF THE INTERNATIONAL STANDARD BOVINE TUBERCULIN
Consultation by Teleconference 18 May 2017

List of participants

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Note: Dr. El Harrak did not participate in the teleconference to evaluate the manufacturer's data for the candidate tuberculins.

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