European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 5th meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 05/11/2013, WEB meeting

(Agreed on 15 11 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Aline de Koeijer (chair), Arjan Stegeman (vice-chair), Caroline Guittre, Eamonn Gormley
- **EFSA:**
  - Frank Verdonck (AHAW)

1. Welcome and apologies for absence

The chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], EFSA screened the Annual Declaration of Interest (ADoI) and the Specific Declaration of Interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

4. Adoption of minutes

The minutes were agreed by written procedure on 15/11/2013 and published on the EFSA website 21/11/2013.

[1] The publication of the minutes shall be made without delay in compliance with the Founding Regulation and no later than 15 working days following the day of their agreement.
[2] Indicate first full name and them surname(John Smith) all throughout the document

[3] http://www.efsa.europa.eu/en/keydocs/docs/independencepolicy.pdf
[4] http://www.efsa.europa.eu/en/keydocs/docs/independencerules.pdf

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5. Scientific topics for discussion

The comments received from the Panel and the European Commission were discussed and the draft opinion was adapted accordingly. The conclusions and recommendations were reviewed in detail and modified where required.

6. Next meeting

Not foreseen.

European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 5th meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 21/10/2013, WEB meeting

(Agreed on 06 11 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Aline de Koeijer (chair), Arjan Stegeman (vice-chair)
- **Hearing Experts:**
  - Glyn Hewinson
- **EFSA:**
  - Frank Verdonck (AHAW)

1. Welcome and apologies for absence

The chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes.

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests [4], EFSA screened the Annual Declaration of Interest (ADoI) and the Specific Declaration of Interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

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4. Adoption of minutes

The minutes were agreed by written procedure on 06/11/2013 and published on the EFSA website 08/11/2013.

5. Scientific topics for discussion

The WG received background information on the UK bTB vaccination program and discussed the content of the draft opinion to understand its practical implications. The text under discussion did not contain elements that would make the design, implementation and analysis of bTB vaccination field trials impossible. However, the discussion made clear that rephrasing of some sentences was required to improve the clarity of the scientific opinion.

It is clear that field trials on bTB vaccination have to provide data to fulfil the current legal requirements (e.g. for market authorization). The aim of this EFSA opinion is to give guidance on data that need to be provided to allow an assessment on DIVA performance, vaccine performance and vaccine safety. For instance, a comparison of the tuberculin skin test (current trade test) with the DIVA test is not strictly required for the assessment of the DIVA performance and hence is not mentioned in the scientific opinion. However, field trials should provide data to compare both tests if this is required for use of the test based on the current legislation.

These additional data should include continuous test signals at the level of the individual animal and data normally registered in cattle identification and registration systems. At the herd level, annual official bTB status in the previous five years should be provided as well as possible risk factors associated with the risk of bTB introduction and associated with within-herd transmission of bTB. The field trials should provide data to measure the reduction of transmission (eg incidence, prevalence). This could be used in models to estimate the effect towards eradication of bTB.

The use of BCG in a field trial raises legal problems since the vaccinated animals (or a proportion of these) will become skin test positive and should be culled in order to comply with the current legislation. It should be considered to seek derogation from this test and to allow retention in the herd of test-positive animals involved the field trial to enhance the power of the study for quantifying transmission parameters, while recognizing the potential for increased risk of spread of bTB, due to infected animals remaining in the herd for a longer time period. The use of the DIVA test to identify infected vaccinated animals is not ideal as without prior validation in the field, the determination of the cut off points would be arbitrary. Thus any test and cull program to be applied in the field trial will surely differ from the present control measures, since a different test (or set of tests) will be applied. However, it was suggested that the use of the tuberculin skin test should be avoided, to allow for double blinding in field trials.

At slaughter, all trial animals should be examined in greater detail as compared to the established routine post-mortem analysis (e.g. procedure currently applied for reactor animals), in order to increase diagnostic sensitivity of the procedure and enable better estimation of the performance of the DIVA test. Supplementary tests (histology and bacteriology) should be applied when appropriate. SOPs and quality control should be developed for all procedures.

Use of Bayesian techniques for test validation without a gold standard can be helpful, especially since a perfect test will not be available. The analysis will profit from multiple modelling methods including latent class analysis.

The term ‘vaccine performance’ will be used consistently throughout the scientific opinion since the term ‘vaccine efficacy’ is not clearly defined. The term ‘re-vaccination’ will be defined in the glossary and will be used instead of the term ‘boosting’.

The analysis of DIVA test performance and vaccine performance can be performed at the same time. However, if the sensitivity of the DIVA test is low, then the results of the vaccine performance might be underestimated. This potential risk should be taken into account during the design of the field trial and an estimate regarding the test performance should be obtained as soon as possible. Since vaccination in the field is essential to validate the DIVA test in the field, it will not be possible to validate the test completely before starting the field trial.

When different options are available for the design, implementation of analysis of field trials, the scientific opinion describes the pros and cons of the different options and leaves all possibilities open. For instance, the consequences of selecting the animal level, herd level or region level as the unit of interest to assess the vaccine performance are discussed without suggesting a best choice ‘level’ to select. This step lies beyond the terms of reference of the mandate.

The contribution of badgers to the local epidemiology of bTB will need to be considered in the analysis of field trial data as they may impact on the estimated performance of the vaccine in cattle. By selecting the animal as unit of interest for the assessment of vaccine performance, this problem can be dealth with, but due to the expected low infection pressure in the herds, this requires sufficient attention in the power analysis of the trials.

The field trials should provide safety data to confirm the results obtained in laboratory conditions according to the requirements of the Commission Directive 2009/9/EC. Specifically, data regarding the potential shedding of the BCG vaccine Danish strain via the respiratory route and milk should be provided in order to allow risk assessment of trade in vaccinated animals.

6. Next meeting

5/11/2013, web meeting

European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 4rd meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 15/10/2013, WEB meeting

(Agreed on 18 10 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Aline de Koeijer (chair), Arjan Stegeman (vice-chair), Eamonn Gormley, Caroline Guittre, Javier Bezos (EURL)
- **EFSA:**
  - Frank Verdonck (AHAW)

1. Welcome and apologies for absence

The chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests [4], EFSA screened the Annual Declaration of interest (ADoI) and the Specific Declaration of interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

4. Adoption of minutes

The minutes were agreed by written procedure on 18/10/2013 and published on the EFSA website 21/10/2013.

[1] The publication of the minutes shall be made without delay in compliance with the Founding Regulation and no later than 15 working days following the day of their agreement.
[2] Indicate first full name and them surname(John Smith) all throughout the document

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5. Scientific topics for discussion

The last scientific details on DIVA test performance, vaccine performance and vaccines safety were discussed and agreed upon. The conclusions and recommendations were reviewed and reworded where required.

6. Next meeting

5/11/2013, web meeting

European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 3rd meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 01/10/2013 , Parma

(Agreed on 08 10 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Aline de Koeijer (chair), Arjan Stegeman (vice-chair), Eamonn Gormley, Javier Bezos (EURL)
- **EFSA:**
  - Frank Verdonck (AHAW) and Jose Cortinas (SAS, via teleconference)
- **European Commission:**
  - Francisco Reviriego-Gordejo

1. Welcome and apologies for absence

Caroline Guittre had to apologise for the WG meeting.

The chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], EFSA screened the Annual Declaration of interest (ADoI) and the Specific Declaration of interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

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4. Adoption of minutes

The minutes were agreed by written procedure on 08/10/2013 and published on the EFSA website 10/10/2013.

5. Scientific topics for discussion

All sections of the document were discussed in detail and the most important items are listed below:

- Ireland did not invest in the development of a bTB vaccine or a DIVA test and was therefore excluded as example in the background provided by the European Commission.
- The pro's and con's of keeping DIVA test positive animals in a field trial to assess the vaccine performance were discussed.
- Analysis of vaccine performance should examine (1) the decline of susceptibility and impact on infectiousness as well as (2) the added value of a vaccine in addition to other control measures.
- Movement of animals during a field trial has to be defined and recorded.
- Influence of wildlife should be taken into account in the analysis of the bTB vaccine performance.
- A field trial could assess the DIVA test performance and the vaccine performance at the same time, but the scientific opinion will describe the risks that this brings with it.
- Safety aspects of the candidate bTB vaccine in relation to trading vaccinated animals.

6. Next meeting

15/10/2013, web meeting

European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 2nd meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 04-05/09/2013, Parma

(Agreed on 18 09 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Arjan Stegeman (vice-chair), Eamonn Gormley, Caroline Guittre (EMA – CVMP)
- **Hearing Experts:**
  - Rowland Kao, Fabian Tibaldi (via web conference on 05/092013 in the afternoon)
- **EFSA:**
  - Ana Afonso, Justyna Jaskiewicz, Frank Verdonck (AHAW) and Jose Cortinas (SAS)

1. Welcome and apologies for absence

Aline de Koeijer had to apologise for the WG meeting.

The vice-chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests[4], EFSA screened the Annual Declaration of interest (ADoI) and the Specific Declaration of interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

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4. Adoption of minutes

The minutes were agreed by written procedure on 18 09 2013 and published on the EFSA website 23/09/2013.

5. Scientific topics for discussion

Wednesday

5.1 Feedback from SOG meeting

FV summarized the scientific overview on bTB vaccination and DIVA testing that was presented at the SOG meeting (30-08-2013, London). Feedback was given on the discussion that took place in the SOG meeting regarding the presentation of EFSA's mandate on bTB vaccination and what could be expected/non-expected from the scientific opinion. The WG agreed that the scientific opinion should be delivered according to the agreed timelines (December 2013).

5.2 Discussion on the approach of the mandate

Discussions during the previous WG meeting and the work done in preparation of this second WG meeting made clear that it is very complex to validate a diagnostic test to assess the bTB infection status and to assess the performance of a bTB vaccine in the field. For instance, vaccination will induce skin test sensitivity of the animals. The current legislation indicates that skin test reactors should be culled, meaning that all vaccinated animals should be removed from the trial. One could ask exemption for skin testing during the trial but how will infected animals then be detected knowing that the DIVA test could not be used as long as it is not validated. In addition, the induction of skin test sensitization will hinder blinding of the study.

After long discussions, the WG had to conclude that there is no way to solve major questions related to the design of a field trial based on scientific grounds only (non-scientific aspects are behind the remit of EFSA). Therefore, the WG suggest to present the ideal conditions to validate the DIVA test (e.g. based on OIE guidelines to validate a diagnostic test) and the ideal conditions to test bTB vaccine performance (e.g. double-blind randomized controlled field trial). Based on these ideal situations, the opinion will list the data that should be delivered by the field trial to allow assessments of the DIVA test performance and the vaccine performance in the future. Any deviations from the ideal situation should be justified and accounted for as they will introduce bias in the results. This approach will highlight the scientific issues related to bTB vaccination but will not take any decision in the design of the trial as this is beyond the scope of the mandate.

Thursday

5.3 Vaccine safety

It was agreed that the chapter on vaccine safety in this scientific opinion will focus on the human safety aspect since it is very specific for bTB and is behind what is described in the current legislation. Shedding of the BCG vaccine strain by vaccinated animals and characterization of the obtained BCG isolates will probably be the main aspects to be analysed in a field trial.

5.4 DIVA test performance

The available DIVA tests in the field of bTB are able to detect responses to antigens that are expressed and/or secreted by *M. bovis* field strains but not by the BCG vaccine strain. Therefore, the DIVA tests allow detection of infected animals but not

their vaccination status. The WG suggests that a field trial should provide data on the sensitivity and the specificity of a DIVA test. This should be done both in vaccinated and in non-vaccinated animals if the test will be used to analyse the performance of a candidate bTB vaccine.

5.5 Vaccine performance

Vaccine performance could be analysed in different ways (presentation by FT). The WG suggests describing some methods that have been or could be used. Every method has is advantages and disadvantages and there is no scientific consensus on what is the preferred method.

6. Next meeting

01/10/2013, Brussels

European Food Safety Authority

AHAW UNIT

Scientific Panel on AHAW

Minutes of the 1st meeting of the Working Group on bovine tuberculosis vaccination

M-2013-0152, EFSA-Q-2013-00241

Held on 27/06/2013 , Parma

(Agreed on 08 07 2013)[1]

Participants

- **Working Group (WG) Experts**[2]**:**
  - Aliine de Koeijer (chair), Eamonn Gormley, Edith Authie, Caroline Guittre (EMA –CVMP)
- **Hearing Experts:**
  - Rebecca Jones
- **European Commission representatives:**
  - Francisco Reviriego Gordejo (DG SANCO)(by teleconference)
- **EFSA:**
  - Ana Afonso, Justyna Jaskiewicz (AHAW)

1. Welcome and apologies for absence

The Chair welcomed the participants.

2. Adoption of agenda

The agenda was adopted without changes

3. Declarations of interest

In accordance with EFSA's Policy on Independence and Scientific Decision-Making Processes[3] and the Decision of the Executive Director implementing this Policy regarding Declarations of Interests [4], EFSA screened the Annual Declaration of interest (ADoI) and the Specific Declaration of interest (SDoI) filled in by the experts invited for the present meeting and no conflict of interest was identified for working group members.

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4. Adoption of minutes

The minutes were agreed by written procedure on 08 07 2013 and published on the EFSA website 15/07/2013."

5. Scientific topics for discussion

5.1 Presentation of the EFSA Mandate

The objective of the mandate is to provide guidance to the development of the field trial design necessary for bovine TB vaccine authorization process. Since vaccination against bovine tuberculosis (bTB) is currently prohibited by EU legislation the authorization and use of the vaccine in a MS will require legislative changes. Such changes will need to be supported by the best scientific evidence. EFSA was therefore requested to issue an opinion about which aspects must be taken into consideration when designing the vaccine field trial for collecting information that will allow to assess the performance of the vaccine and associated DIVA test as well as the effectiveness of the vaccine as a control measure. The target of this and other control measures in place is always the eradication of bTB from EU. The issues related with vaccine safety are not to be specifically addressed as far as public health but only when they may have an impact on disease spread between animal populations.

5.2 Presentation of AHVLA ongoing and future work

RJ gave a presentation on DEFRA-AHVLA work on bTB vaccination. The presentation is available to the WG and highlights timetable and milestones for the UK project. It is expected that a procurement will be launched for the design in Autumn 2013. Future contractors will need to take into consideration AHAW opinion while designing the trial.

DEFRA has appointed a scientific advisory working group to guide the preparation of a field trial and assess the feasibility of vaccination for bTB in the UK. DEFRA is interested in the participation of EFSA WG members/staff in their meetings to promote collaboration.

5.3 Approach to the mandate

EFSA's role is to highlight issues and data gaps that have to be addressed and answered by the field trial. EFSA will not participate in the field trial design per se. The terms of reference of the mandate comprise of an assessment of the vaccine performance, safety, conditions of use and associated candidate DIVA test. After clarifications by the commission it was agreed that the focus of the mandate is on the assessment of the vaccine and DIVA test performance. These will be addressed and will contain assessment of conditions of use. Theoretical concepts such as definitions of: i)efficacy of the vaccine on the animal level, ii) efficiency on the herd level, iii) effectiveness of the vaccine as a control measure and iv) infected animal for the DIVA testing need to be addressed. The safety assessment will only concern shedding of the attenuated live pathogen and risk of its spreading outside the vaccinated population. The WG agreed in developing a draft containing the current state of knowledge both on vaccine and test and existing data gaps. On the basis of the gap analysis a list of priorities to be addressed by the trials will be presented.

5.4 Data and expertise needs

The expertise within the WG was considered sufficient and tasks were distributed among the group members. In regards of transmission model parameters elaboration, AK is to consult the hearing expert Rowland Kao.

6. Next meeting

4 - 5 September 2013 (14-19 and 9-17h, respectively), Parma