ANNEX

EU COMMENTS
ON THE PROPOSED CHANGES TO THE
WOAH MANUAL OF DIAGNOSTIC TESTS AND VACCINES
FOR TERRESTRIAL ANIMALS
PRESENTED FOR ADOPTION IN MAY 2024[1]

[1] The draft chapters are appended to the BSC Sept. 2024 meeting report available on the WOAH website at: https://www.woah.org/en/document/report-of-the-meeting-of-the-woah-biological-standards-commission-february-2024/

EU COMMENTS on the proposed changes to the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

SUMMARY

3.4.7. Bovine viral diarrhoea

General comment:

The EU can in general support this revised chapter. A specific comment is provided below.

Specific comments:

Pages 5-6, section B - Table 1 (Test methods available for diagnosis of bovine viral diarrhoea and their purpose): in the section "*Detection of immune response*", in the line *Antibody detection by ELISA*, column *Confirmation of clinical cases,* there is a reference to footnote ***g*** which, in our opinion, is not relevant for antibody detection but rather for antigen detection. Indeed, no reference to antigen detection is included in the relevant line for antibody detection ELISA in the table of Appendix 4 on p. 31, which refers to paired serum samples and seroconversion. This is also described in lines 200-202 on p. 4 without referring to antigen detection ("*Serology undertaken on paired acute and convalescent sera […] is worthwhile and gives a high probability of incriminating or excluding BVDV infection*."). For these reasons, footnote g should be deleted from Table 1 or, as an alternative, be replaced by a footnote referring to paired serum samples and seroconversion.

3.9.1. African swine fever (vaccine section only)

General comment:

The EU thanks the WOAH Biological Standards Commission for this work being moved forward. The EU can in general support this revised chapter. It appears that there are still several points that need to be clarified and we invite the Commission to review them.

As a general point, we note that throughout the text reference is sometimes made to either "licensing", "registration" or "authorisation". We would recommend to rather use the term "regulatory approval", which works in all jurisdictions across the world, and has been used systematically in other recently adopted Manual chapters. This would include the title of Section 2.3. "*Requirements for authorisation/registration/licensing*" (Line 297), that should be replaced with "Requirements for regulatory approval".

Further, specific comments are provided below.

Specific comments:

Lines 31-32: This text should be updated and aligned with the information given in lines 163-164.

Line 96: *immunogenicity (including spread)* - We would suggest referring to 'efficacy' which is the overarching term and it is mentioned later in the paragraph. Also referring to 'spread' here may be confusing as 'spread' is also a safety parameter.

Lines 105-106: *Demonstration of MLV safety and efficacy in pigs at different growth stages (suckling piglets, nursery pigs, fattening pigs), the safety in breeding-age boars …*

We do not think this is necessary and it is confusing (as tests are recommended in 4-10 week-old piglets, therefore categories mentioned in the brackets could be deleted)

Line 108: *….if ~~these~~ specific categories are included….*

Line 110: *….(the time point at which vaccine-induced immunity begins to decline and provides less protection)….*

In our opinion this sentence is not accurate, and we propose to change as follow: "Last time-point at which vaccine-induced immunity has been demonstrated."

Lines 122-123: editorial comment - This text should be aligned with the information given in lines 162-163 about currently authorised vaccines and others under development.

Lines 142-143: *….that could adversely affect the safety, potency or efficacy of the product:*

This text is not needed and can be deleted. If left, please delete 'potency' because this word is mostly linked to efficacy of the vaccine so using both is redundant.

Lines 239-241: This is not clear. General requirements in the EU (Ph. Eur. 0062) for example are that vaccine production is not undertaken using a virus more than 5 passages from the master seed lot, unless otherwise justified. In any case, demonstration of genetic stability is always required to the maximum passage level

used for vaccine production'; therefore, the requirement explained here is a general requirement rather than a special requirement.

An alternative wording is proposed: "Genetic stability of attenuation throughout the production process (i.e. to the maximum passage level to be used for vaccine production) should be confirmed by full genome sequencing and confirmation of virus phenotype (e.g. virus yield in cell line used for production)".

Lines 239-241: *"Additional demonstration……..safety requirement"*.

New proposed text: the text below would be preferable for clarity. Also, the existing vaccines in Vietnam could be authorised for use in breeding animals in the future, if relevant supporting safety data are presented to the authorities i.e. use in breeding animals not only for newly developed vaccines)

Proposed text:

"Additional demonstration of MLV safety in breeding age gilts and pregnant sows is preferred. When the vaccine is recommended for use or may be used in breeding animals, an evaluation of the impact of the vaccine on reproductive performance will be a standard safety requirement."

Lines 315-316: "….*piglets a minimum of 4 weeks old or not older than 10 weeks old"*

EU requirements for example are for general safety tests to be conducted in the most sensitive category of animals for which the vaccine is recommended, usually animals of the youngest age. Is there any reason as to why a prescriptive age range (4-10 weeks of age) has been defined?

Lines 353-355: "*If a label claim……..should be completed*"

It is suggested to revert the order of the sentences i.e. first the general statement on requirements (if a label claim…) and then the specific info on existing published info.

Lines 367-369: We ask to rationalize the sentence *"….contact piglet is measured on at least the 3 consecutive days preceding co-mingling with vaccinated piglets. The body temperature of each naïve, contact piglet is then measured daily for at least 45 days, preferably 60 days*".

Lines 383-384: Please rationalise the changes to the following sentence: "*Quantitative PCR may be used to detect positive samples, but results should be confirmed by infectious virus titration as described above"*

Lines 387-388: Please rationalise the following sentence: "Collect blood (serum) samples from the naïve contact pigs at least at day 21 and day 28 days and carry out an appropriate test to detect vaccine virus antibodies"

Line 410: Please note that whilst quantitative PCR is mentioned in line 393 as optional, then one of the compliance criteria is based on it.

Perhaps a more neutral wording could be used here as the suitable testing methods are described above:

"No or a low percentage of naïve, contact piglets test positive to the vaccine virus and/or to antibodies against the vaccine virus"

Line 412: A general, more neutral heading would be preferrable as the details are then given in the actual text.

'*Dissemination in the vaccinated animal'*

Line 423: Please substitute "*final product of the vaccine*" with "commercial vaccine".

Line 501-502: "….release dose…". Please change to '*maximum release virus titre'*. Dose is mentioned later in the sentence referring to vaccine dose, so it is confusing.

After "*1 dose of vaccine"*, please add: if needed. Indeed, often the titre of the virus recovered after passage is lower than the original virus titre inoculated.

Lines 544-550: In line with the compliance criteria of the safety tests described above the following minimum requirement is missing and should also be added: "Absence of abnormal (local or systemic) reactions"

It is understood that the absence of acute/chronic clinical signs/gross pathology are related to ASF.

Local/systemic reactions refer to more general observations (injection site reactions, anaphylactic reactions, etc.).

Lines 551-553: This needs to be clarified. As it reads there must be absence of mild clinical signs. Is this the intention? Is it necessary this part?

Lines 555-556: "*…. both real-time PCR positive and seropositive….."* Please see the previous comment on this point.

Line 570: *"…..by evaluating ~~their resistance~~ protection against live virus challenge…."*

Line 582: Please delete *(minimum release dose).* Please note that the minimum release titre may be higher than the minimum efficacious titre, to compensate for the potential losses in titre during shelf life (overage).

Line 625-628: The aim of the validity criterion is to validate the suitability of the challenge. It needs to be reminded that one of the key minimum standards for efficacy has been set for protection against mortality. Therefore, it would be expected that the challenge model used is suitable to evaluate such efficacy endpoint.

The proposed validity criterion is not considered appropriate: 1) the number of vaccinated piglets dying or reaching the humane endpoint should always be 0 (to fulfil the compliance criterion); 2) it might be challenging to prove statistical significance with the minimum number of animals that can be included per group; 3) even if statistical significance is proven, it may not be meaningful from a biological point of view e.g. 0% mortality in vaccinated vs. 15% mortality in controls might render a statistically significant difference, but it is not considered appropriate to validate a challenge aimed at demonstrating protection against mortality (low severity of the challenge). The severity of the challenge should be suitable to evaluate the efficacy endpoints that are then required as minimum standards. Ideally, a minimum percentage of control piglets dying/reaching humane endpoint should be defined (e.g. minimum 80%, meaning that 1 out of 5 controls may not die or reached the humane endpoint). The experts on the disease may provide advice on which would be a realistic percentage (representative of field conditions).

Please also note text in lines 668-670 where validity criterion is also set at 100% mortality in control piglets.

Line 657: Please delete *(minimum dose*). Not necessary and it might be confusing as reference to "dose" is made in the same sentence with a different meaning.

Lines 667-668: *"….for TCID…….less than 21 days"*. This text will need to be revised to align with the final decision on the validity criterion.

Line 723: *"shows abnormal (local or systemic) reactions".* Please delete: Reference to abnormal (local or systemic) reactions is normally used relating safety

observations after vaccine administration which is not the case. The point (clinical signs of disease) is covered in the next bullet point.

Lines 739-742: "*(none of or a reduced number of naïve, contact exposed piglets shows abnormal [local or systemic] reactions, reaches the humane endpoint or dies from causes attributable to ASF, displays fever accompanied by typical acute disease signs caused by ASF) and test positive for antibodies to the challenge virus.*"

We would suggest deleting this part. The key compliance criteria for transmission are already given above and specifically in lines 731-733, so the info would appear redundant and makes reading more difficult.

Lines 751-752: *"….are required…."*. Perhaps to cater for possible differences in different regulatory jurisdictions, "in general" could be added: "Manufacturers are in general required to (…)"

Lines 755-759: Change proposed: The text can be simplified and rationalised as:

"Although not included in the standards for first generation MLV ASF vaccines, manufacturers are required, as part of the authorisation procedure, to generate data (including potency) showing that the vaccine remains stable over the shelf life recommended for the product."