21 September 2018
EMA/CHMP/BWP/652969/2018
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on "Questions and answers on the Haemagglutination Inhibition (HI) test for qualification of influenza vaccine (inactivated) seed preparations" (EMA/CHMP/BWP/426390/2017)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Vaccines Europe

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1. General comments – overview

Stakeholder no.	General comment	Outcome
1	Can the Agency clarify what the additional principles/considerations are in relation to LAIVs and if they will be published either as a separate document or addendum to the current draft version? When might this be?	The preparation and qualification of LAIV seed virus from donor/parent strain is different from the TIV/QIV, e.g. a 2-way HI testing is required at certain stages. For consistency purposes, the EMA Guideline on Influenza vaccines – Quality module was already modified in this regard (EMA/CHMP/BWP/310834/2012 Rev.1). The Agency will consider the need for further updates in due time.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
48-49	1	Comment: Given the objective that the seed preparations are antigenically identical to the approved CVV, and HI tests have technical challenges, would the comparison of the sequences (between the different strains as well as within the different passages of 1 strain) also be considered as an acceptable alternative suitable method? Proposed change: Include the option to compare sequences as a method.	Rejected since reference to existing guidance documents is already included. As indicated in the EMA Guideline on Influenza vaccines – Quality module (EMA/CHMP/BWP/310834/2012 Rev.1), antigenic confirmatory tests for identity are the preferred option when suitable reagents are available. However, in the event that reagents are not available or insufficient reagent specificity is demonstrated, alternative tests to identify seed virus (e.g. PCR) should be developed. As regards to the use of sequence analysis to be used as a single identity test, it is noted that positive identity testing may not be straightforward in case differences in the genetic sequence are detected.
58-59	1	Comment: HA identification test (HAI) is performed by each manufacturer by using in-house reference Antigens and Antisera because such specific identity (HA) reagents, produced from ferrets, are not available on the market, from official suppliers such as ERLs (Essential Regulatory Laboratories) or WHO CC. To address a lack of precision of the method as well as a constraint on the quantity of prototype strain received, Vaccine manufacturers would like to engage	Rejected. Manufacturers are encouraged to engage ERLs / WHO CCs to further optimise HAI testing.

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		some discussions with ERLs (e.g.: NIBSC, TGA, CBER) and WHO CC to assess the possibility to be supplied with official specific HAI reagents (ferret antiserum and reference antigen) as it is done already for SRD reagents.	
58-59	1	Comment: The objective of performing the HI test on the seed virus prepared by each manufacturer is to check whether the antigenicity of the virus has remained unchanged during passages performed during the preparation of the seed virus. It is the understanding of vaccine manufacturers that the prototype strain against which the antigenic distance of the manufacturers working seed must be determined is the approved CVV received by manufacturers and neither the wild type strain from which the reassortant is derived nor the reference strain recommended by WHO if it is different from the wild type from which the reassortant virus is derived. Example of Manufacturers working seed and related CVV, wild-type strain and WHO recommended reference strain: WHO recommended reference strain: A/California/7/2004 (H3N2) Selected A/California/7/2004-like wild-type strain: A/New York/55/2004	Accepted. In principle, the manufacturer's seed virus should be HI tested against the CVV used for seed preparation in order to meet the objective of the HI testing for seed preparations. The use of a different type of antiserum (e.g. produced by the manufacturer) could be acceptable if justified, e.g. by demonstrating the appropriate specificity of the antiserum in HI testing using a panel of appropriate viruses. Similarly, the use of a different comparator virus, e.g. a WHO recommended virus, other than the approved CVV could be acceptable if justified by the MAH, e.g. 2-way HI testing may be needed to support use. In this case, an appropriate antiserum raised against the comparator should be used. The Q&A document is updated accordingly Annex 2. Example of presentation of Haemagglutination Inhibition (HI) testing results has been amended accordingly. In addition, the type of antiserum that is normally used for HI testing, e.g. post-infection ferret antiserum, is further detailed.

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		CVV: A/California/7/2004-like reassortant A/New York/55/2004 X-157 Manufacturer's Working seed: A/New York/55/2004 X-157, Lot 123456 In the above example, the Manufacturers Working Seed Virus lot 12456 would be compared with the A/New York/55/ X-157 reassortant CVV. The use of a prototype virus other than the approved CVV should be acceptable if justified. This may be indicated, for example, if the first passage of the CVV is used to generate ferret antiserum and also as working seed for production. The use of an earlier passage of the reassortant, the wild-type parent or the reference strain may be acceptable in those cases. Alternatively ferret serum could be supplied by a WHO laboratory/ERL. Proposed change: The use of a prototype virus other than the approved CVV should be justified by the MAH.	
64-66	1	Comment: RBCs from different species may not be available routinely in manufacturing site or external testing laboratories and the use of RBCs from different species may require to adapt existing validated procedures. To enable the use of matched RBCs by testing labs (manufacturing site or external laboratory) the	Rejected. Industry needs for harmonised CVV documentation is being addressed by other parties, which may also include information on red blood cells. However, it should be noted that the responsibility of an appropriate HI test lies with the manufacturer.

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		information which RBCs should be used must be provided to manufacturers as early as possible and at the latest as part of the CVV documentation, so that assay results for the release of seed virus, can be generated in a timely manner. The documentation should also state clearly whether the use of RBCs of only one species is acceptable or whether RBCs from several species can be used.	
99 - 100	1	Comment: Industries have on several occasions raised concerns about the <4-fold acceptance criteria being applied to the HI testing of working seeds prepared by manufacturers. This is due to: • The precision of the HI method in most laboratory settings is ±2 fold, therefore there is a risk that the result of an HI test will be OOS due to the precision of the method rather than an antigenic difference • If a test is recorded as being OOS and then accepted after discussion with EMA, difficult to reconcile with manufacturing and quality procedures.	Rejected. The Agency has taken note of Industries' concerns but considers the <4-fold acceptance criteria scientifically justified because only limited passages from the CVV is expected and a HI test result of $\geq$ 4-fold would indicate a change in antigenic profile in the seed virus.
103-112	1	Comment: WHO have described on several occasions that antigenic characterization of recent A(H3N2) viruses remains technically difficult and that they are required to use modified HI methods and/or virus neutralization assays for antigenic analysis. If this	Accepted. The Agency recognises the technical challenges of the HI test for antigenic characterisation of H3N2 viruses. However, as long as red blood cell agglutination occurs, the HI method is to be used. Otherwise, alternative tests may need to be

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		continues to be an issue, how will this be addressed? Will alternative assays be considered?	considered. Companies are encouraged to develop VN assays which can be applied if the HI assay is not feasible. The Q&A document is amended accordingly. In addition, slight editorial changes are introduced to clarify that companies should consult regulatory authorities for further guidance in case further testing does not resolve the issue of unexpected HI results.