European Medicines Agency
Veterinary Medicines and Inspections

London, 13 July 2005
Doc. Ref. EMEA/CVMP/IWP/214680/2005

OVERVIEW OF COMMENTS RECEIVED ON DRAFT REVISED GUIDELINE ON REQUIREMENTS AND CONTROLS OF BOVINE SERUM USED IN THE PRODUCTION OF IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Organisation
1	IFAH Europe
2	Invitrogen

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.eu.int http://www.emea.eu.int

Table 2:Discussion of comments

1. Introduction	
Comment	Outcome
Bovine viral diarrhoea antibodies should be replaced by Bovine viral diarrhoea **neutralising** antibodies	IWP did not agree to restrict the type of detected antibodies to neutralising antibodies because ELISA can include neutralising antibodies and is easily used and quickly performed. It is up to the manufacturer to know what is the best way to conduct its risk analysis and how to interpret the results.
Recommendation to change the statement to be expanded to read "…in accordance with GMP, GLP or ISO 9001 principles"	IWP agreed
Basic regulation on substances of animal origin for the production of veterinary vaccines is Ph. Eur. section 5.2.5. Here it is prescribed that substances of animal origin should EITHER be tested for the absence of extraneous organisms OR subjected to a validated sterilisation or inactivation procedure "shown to be capable of reducing the titre of certain potential contaminants in the substance concerned by at least 10^6". For BVDV, infectivity reduction factors of $10^6 – 10^7$ have uniformly been found. The present guideline still follows a different principle ('test AND inactivate'). As no reason is given a justification for keeping the double requirement will be welcomed.	IWP did not agree and clarified that the starting point of this guideline was a very important BVD type II problem induced by an IBR live vaccine contaminated. In that case, the manufacturer tested AND inactivated the bovine serum AND missed the contaminant!! This is due to a particular difficulty to handle in a proper way the pestiviruses.
A major change in the proposed revision of the guideline is the omission of the 'comparative titration test'. This is welcomed because this test has caused a lot of confusion regarding its nature and the test result requirement was impossible to comply with as soon as the bovine serum contained significant antibody levels against the reference strain of BVDV used. We do not agree with the revision proposal that bovine serum with considerable BVD antibody titres should not be used for the production of pestivirus vaccines. Indeed, this depends on the production procedure. For instance, if the serum is only used at cell culture stage but is absent at virus production stage, antibodies present in the serum may not interfere with the virus production. Also production systems using specific strains or high inoculation doses may not be affected by the presence of antibodies. The aim of the guidelines is not to decide where serum must be used but what serum must be used. IFAH-Europe kindly asks that this requirement is removed from the introduction part. However, if still seen as necessary the following sentence should be introduced: "Manufacturers should take into account that the production of the vaccine virus in pestivirus vaccines may be influenced by interfering BVD antibodies in the bovine serum used for production".	IWP agreed and text was amended

33.1 General and Specific Tests	
Comment	Outcome
Proposal to include the statement "The OIE code and Volume 9 of the US Code of Federal Regulations can be used for guidance in selecting what viruses to test for"	IWP did not agree as this statement is too vague
Proposal to specifically mention the viruses to be screened	IWP agreed and amended the text to specify viruses inducing viraemia and transplacental infections such as Bovine adenovirus, BVD Virus (see below), Parvovirus, Bovine Respiratory Syncytial Virus, Reovirus, Parainfluenza 3, IBR and those responsible for diseases exotic to Europe (such as Bluetongue).
33.2 Tests to detect Bovine Viral Diarrhoea Virus	
Comment	Outcome
Amend the text to read "…to ensure it is below the level that has been shown to be effectively validated inactivated in the validation test for inactivation treatment."	IWP agreed and text was amended
33.3 Tests to detect BVD antibodies	
Comment	Outcome
The statement on "when high levels of antibodies are detected…" should be revised to say "…If it cannot be demonstrated that the level of antibodies does not interfere with the detection of a low titre of BVD virus(e.g. by bvalidated spiking techniques), a procedure has to be written by the vaccine manufacturer…"	IWP did not agree clarified that this comment was not related to the problem as it is not an interference with the detection of a low titre of BVD virus (it was in the previous version of the guideline and has already been amended).
Please remove "When high level of antibodies are detected…. hampering the quality of the vaccine by these bovine sera".	The IWP inserted a slightly more restrictive proposal because the manufacturer has to demonstrate there is no interference with a pestivirus production of vaccines because even when the serum with high level of antibodies is used only in the first stages of production, it is not always evident that the washing of the cells could remove all the antibodies and in consequence they are not interfering with the adsorption of the pestivirus vaccinal strain onto the sensitive cells.
Annex I	
Comment	Outcome

The footnote in Annex I can be amended into ("*If the test for BVDV is negative before inactivation, the test for BVD antibodies ~~testing~~ ~~should~~ may be carried out before inactivation*"), as the inactivation procedure will not affect the antibodies and the test procedure may become much better logistically manageable if BVD antibody testing is carried out at the same stage under all circumstances.	IWP did not agree to replace should by may; indeed, according to the difficulty to identify a pestivirus contamination, a negative result has to be part of a process of risk assessment . How to conduct this risk analysis if one does not know what are the factors involved? The presence of BVD antibodies has certainly a high impact on the ability to isolate or identify a pestivirus contaminant.. It has to be known to assess the quality of the product before inactivation.
Annex II	
Comment	Outcome
For live virus vaccines the document should describe the number of doses to be tested	IWP did not agree as it is the responsibility of the manufacturer or the vaccine supplier to know the number of doses to be tested to ensure the quality of the product. Annex II has been deleted from the guideline and a new separate guideline will be written on the subject.
This Annex does definitely NOT fall within the scope of this guideline.	IWP agreed and Annex II has been deleted from the guideline and a new separate guideline will be written on the subject.