European Medicines Agency
Veterinary Medicines and Inspections

London, 17 November 2008
Doc. Ref. EMEA/CVMP/IWP/521211/2008

**OVERVIEW OF COMMENTS RECEIVED ON
DRAFT GUIDELINE ON GUIDELINE ON REQUIREMENTS FOR AN AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES FOR VACCINES FOR EMERGENCY USE AGAINST BLUETONGUE**

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

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	IFAH - Europe	Belgium

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

Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
IFAH-Europe welcomes the "*Guideline on Requirements for an Authorisation under Exceptional Circumstances for Vaccines for Emergency Use against Bluetongue*" and likes to express appreciation for the opportunity to comment on the previous Concept Paper and on the current Guideline. IFAH-Europe appreciates that the need for guidelines on DIVA, change of strains and vaccine banks are recognised in section *2. Scope*. Nevertheless we would like to emphasize that as long as the multistrain approach is not endorsed and the change/addition of new strain is not considered, there remain considerable costs and timelines associated with varying the numerous existing marketing authorisation (MAs). Therefore, IFAH-Europe would like to request that CVMP/EMEA works toward this with the EU Commission in order to have the multistrain approach validated as soon as possible. As the aim of the guideline is to speed up the MA process in face of a disease outbreak, IFAH-Europe is also quite supportive towards the use of a benefit-risk assessment instead of a general report. Therefore, it should be considered that when requesting analytical requirements it is important to take into account that the finished product potency test is the most demanding and lengthy part of the development of a vaccine.
SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Page 4 ***3. Legal Basis* - 1st sentence**	The word *"with"* is missing after *conjunction*.	Agreement and correction to: This guideline has to be read in conjunction <u>with</u> the introduction and general principles (4) and Title II of the Annex I to Directive 2001/82/EC as amended
Page 5 ***4.1 General Requirements*** **1st paragraph**	Please insert *"ly"* after "*maternal"*.	Agreement and correction to: *(*e.g. maternall<u>y</u> derived antibodies impact)
2nd paragraph	Please change *"is"* to *"are"*.	Agreement and correction to: If only incomplete but relevant safety and efficacy data ~~is~~ <u>are</u> available

[1] Where applicable

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
3rd paragraph	*The vaccine must only contain suitable bluetongue virus serotypes (one or more).* Working with other serotypes than *only suitable bluetongue virus serotypes* should be recognised as valid for some aspects of the production process (except inactivation kinetics). This should be mentioned as it allows a quicker development. In situations where speed is important, additional data from other serotypes can be useful to support regulatory decisions (e.g. shelf-life) As an example for the possibility to work with other serotypes, IFAH-Europe suggests adding the following to the paragraph on 'stability' (Page 6, 3rd paragraph): *The usual requirements for stability should be put in place as soon as possible for the vaccine. In the meantime the use of data for BTV vaccines with other serotypes in the formulation may grant a shelf-live not exceeding 2 years and in the absence of data, a maximum shelf-life of 12 months may be granted.*	Agreement but modification of proposal to: The use of stability data of a BTV vaccine containing other serotypes but having the same composition in adjuvants and excipients may be used to define the shelf life.
Page 5 ***4.2 Analytical (Quality) Requirements*** **2nd bullet point**	*A description of the […] However, if an appropriate antigen quantification is not available, the virus titre before inactivation may be considered as long as a correlation with vaccine efficacy can be demonstrated.* Although it is stated that an alternative for antigen quantification can be performed before inactivation by determination of the virus titre, a possibility for antigenic mass determination should also be mentioned. IFAH-Europe suggests adding the following: *However, if an appropriate antigen quantification is not available, the virus titre or the antigenic mass determination before inactivation may be considered as long as a correlation with vaccine efficacy can be demonstrated.*	Not accepted since it is important to avoid a quantification in mL which is not relevant and gives no idea of the Ag quantity
Page 6 ***4.3 Safety***	*For inactivated vaccines representative experimental batches or standard production batches can be used.*	Not accepted but clarification of wording with a new sentence added:

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Requirements **3rd paragraph**	It is understood that use of standard production batches allows for use of batches at non maximum potency/titre. IFAH-Europe suggests adding the following: *For inactivated vaccines representative experimental batches or standard production batches can be used, i.e. it is not necessary to use maximum antigen content batches.*	"The use of standard production batches is possible if the vaccine contains a fixed antigenic amount that is controlled at the formulation step."
4th paragraph	*Due to the expected large use of this type of vaccine, the examination of reproductive and lactating performances after vaccination should be carried out.* For the reproductive performance and lactation, some rough orientating ideas may be useful (methods, field trial, minimum number of animals etc.) as these tests may be heavy or long to carry out. Please provide orientating ideas of methods, field trial, and minimum number of animals.	Not accepted since the existing guidance applies
Page 6 ***4.4 Efficacy Requirements*** **- 1st paragraph**	*The efficacy of the vaccine should be demonstrated in laboratory conditions by a challenge model aimed to define the onset and duration of immunity for each category of the indicated target species (e.g pregnant animals).* The example given on target species is not the most suitable one and may also misguide people that pregnant animals are one of the primary targets. The transplacental infection is today not seen as the most probable route of spread of the disease, and in addition those challenge models are the worst to develop and validate. IFAH-Europe suggests the following change: *The efficacy of the vaccine should be demonstrated in laboratory conditions by a challenge model aimed to define the onset and duration of immunity for each category of the indicated target species (e.g ~~pregnant animals~~ minimum age).*	Accepted in part as the mention of pregnant animals was voluntary and has now been deleted.

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Page 6 **Last sentence**	*The challenge virus should be relevant to the current epidemiological situation in the E.U.* The use of an appropriate and validated challenge strain should be emphasized since there are several strains in sheep, which cannot cause disease. IFAH-Europe suggests adding the following: *The challenge virus should be relevant to the current epidemiological situation in the E.U. <u>It is advisable to use a challenge strain of the serotype that corresponds to the serotype in the vaccine.</u>*	Not accepted as this is considered obvious.
Page 7 **1st paragraph**	*For inactivated vaccines representative experimental batches or standard production batches can be used.* It is understood that use of standard production batches allows for use of batches at non minimum potency/titre. IFAH-Europe suggests adding the following: *For inactivated vaccines representative experimental batches or standard production batches can be used, <u>i.e. it is not necessary to use minimum antigen content batches for efficacy studies</u>.*	Not accepted but clarification added in the form of a new sentence: "The use of standard production batches is possible if the vaccine contains a fixed antigenic amount that is controlled at the formulation step."
Page 7 **2nd paragraph**	*The main parameter of efficacy of the vaccine is a prevention in viraemia post-challenge accompanied by the absence of clinical signs (if relevant).* *If it is not possible to achieve this goal the acceptable level of efficacy will be established on a case by case basis taking into account for example reduction of viraemia, reduction of clinical signs, prevention or reduction of transplacental infection.* We wish to emphasise, as indicated in the text above, that prevention of onset of clinical symptoms is not necessarily attached to the prevention of detectable viraemia.	Accepted

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
	The requirement for *prevention or reduction of transplacental infection* is adding even more demand on vaccines whereas this is not believed to be a major contributor to BTV situation today. IFAH-Europe suggests the following changes: *The main parameter of efficacy of the vaccine is a prevention in viraemia post-challenge accompanied by the absence of clinical signs (if relevant).* *If it is not possible to achieve this goal the acceptable level of efficacy will be established on a case by case basis <u>using a risk/benefit approach</u> taking into account for example <u>available data on</u> level of reduction of viraemia of clinical signs, prevention or reduction of transplacental infection.*	
Page 7 **3rd paragraph**	*The methods used to detect the post-challenge viraemia should be validated. The combination of methods such as virus isolation and RT-PCR would normally allow the best follow up.* The *combination of methods* is duplication of requirements. One of these requirements should suffice, as there is insufficient benefit in combining two different tools. IFAH-Europe suggests the following changes: *The methods used to detect the post-challenge viraemia should be validated. ~~The combination of m~~<u>M</u>ethods such as virus isolation and RT-PCR <u>(if possible)</u> would normally allow ~~the best~~ <u>satisfactory</u> follow up.*	Accepted

GUIDELINE SECTION TITLE		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Page 7 – ***Onset of immunity***	*The onset of immunity should be as rapid as possible to allow the use of the vaccine in emergency conditions.* The requirement for an '*as rapid as possible onset of immunity'* does not add value and may guide people to pre-set a timing whereas the most important is to have a vaccine with an associated vaccination plan. IFAH-Europe suggests either deletion of the sentence, or the following change: *The speed of onset of immunity should be ~~as rapid as possible to allow the use of the vaccine in emergency conditions~~ fully taken into account in the benefit/risk assessment in order to allow the use of the vaccine in emergency conditions.*	Accepted
Page 7 – ***Marker vaccine***	In the paragraph 2. S*cope*, the DIVA approach is said to be dealt with in a future revision of this text. In order to avoid misinterpretation the paragraph on *Marker vaccine* should be kept for the coming guideline and withdrawn from this version. IFAH-Europe suggests withdrawal of this paragraph. It is sufficient that DIVA is already mentioned in section 2.	Not accepted. The marker vaccine is mentioned here in order to insist on the necessity to work on this type of vaccine in the future.