15 March 2010
EMA/614258/2009
Committee for medicinal products for veterinary use (CVMP)

Overview of comments on 'Reflection paper on the demonstration of a possible impact of maternally derived antibodies on vaccine efficacy in young animals' (EMEA/CVMP/IWP/439467/2007-CONSULTATION)

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

Name of organisation or individual
IFAH-Europe

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	IFAH-Europe acknowledges the development of this reflection paper for the provision of guidance during veterinary vaccine development. IFAH-Europe appreciate that published literature may be used to support the extent and duration of passively acquired immunity. However, Industry faces considerable difficulties in finding publications to support certain claims. The general principles laid down in this paper are already applied by manufacturers since long time, and thereforethis document to a large extent supports existing practice. The large number of different species and products involved in this subject forces this reflection paper to remain very general, with the disadvantage that it may not match all possible situations. As this is the only document that provides guidance on impact of Maternally Derived Antibodies (MDA), there is a risk that due to the high diversity of situations, it will be used with significantly different interpretations. In that sense, vaccine manufacturers have concerns that some aspects (e.g. study general design) are too precise and will create the need for each deviation to be justified. The strict application of this document would jeopardise the availability of vaccines for young animals due to the amount of data that has to be generated. In addition, it is not clear how manufacturers and assessors should link the MDA study to the product claims when criteria followed are not strictly identical to those used in other efficacy studies. IFAH-Europe believes that more flexibility on the study	It should be mentioned that, with regard to MDA induced interference to vaccine efficacy and age of vaccination, much discussion exists during the assessment of dossiers. In an attempt to avoid many of those discussions as much as possible, this reflection paper may be of help to all parties. It is a reflection paper, not a guideline! Indeed, data on MDA are not always available to the extent that companies or assessors would like, but also at the present, if absence of interference by MDA is (or should be) demonstrated, such data must be given or values need to be taken into account. This is little different to the existing situation. Flexibility has been introduced in the document; line 60: "*this reflection paper gives an example of data*...." Indeed, an example of data that are required for allowing a good assessment but it is an example and therefore does not exclude other approaches! and line 109-110 mentions: "*a study similar to that described below, but modified as necessary to take account of the particular circumstances, can be performed*" allows for much flexibility in the approach but, of course, reliable data have to be provided.

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	design principles proposed would be beneficial. The design given in this reflection paper should be presented only as an example, to be adapted on a case by case basis if needed. Finally, we would like to emphasise the importance of a non-retrospective approach on the application of this document, and also not at marketing authorisation renewal. **Proposal:** (Lines 60-61) *"This reflection paper presents data that ~~should~~ may be provided when a vaccine is intended to be used in young…"*	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
line 43		Comment: The wording *"… depending on the level of MDAs and the potential of a vaccine to break through the MDA barrier."* is not accurate. Proposed change (if any): *"… depending on the level of MDAs and the potential of a vaccine to ~~break through the~~ immunise and confer subsequent protection despite presence of MDA ~~barrier~~."*	Accepted
lines 69-70		Please correct: *part ~~3~~ 4- efficacy*, according to Commission Directive 2009/9/EC amending Directive 2002/82/EC.	Accepted
line 104		*"… such data can generally be gathered from scientific publications…"* Experience shows that even for a well-known disease like rabies, it was impossible to find publications to support the absence of MDA at 3 months of age. IFAH-Europe would like to suggest the development of a list collecting common scientific knowledge per specific disease in order to facilitate a common ground for assessment.	While it would be advantageous to have a list CVMP is not in a position to produce such a list. Also, prior to this reflection paper, data often had to be gathered by vaccine manufacturers when absence of interference needed to be demonstrated
line 114		Comment: *"The MDA titre found should be representative of the titre of animals of the same age to be vaccinated under field circumstances."* From a practical point of view it is very difficult to sample a	This comment is not entirely clear. Also at present, when the vaccine manufacturer wants to set forward an age at which the vaccine is advised to be administered and at which MDA may still be present, the MDA's at that age need to be determined; now, it is asked to

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		statistically significant number of "representative" young animals in the field, particularly pets. It is also not evident what is meant by *"representative"* and therefore assessors tend to use the worst case scenario based on old literature. Furthermore, in particular cases where the purpose is to vaccinate the part of the progeny population that is not adequately protected by maternal antibodies (e.g. some bovine vaccines against newborn diarrhoea), the average level of MDA in the population is not representative of the target. Although animals used to perform laboratory studies on MDA interferences have to be representative of the situation in the field (line 114), it is also stated that animals in laboratory studies can be used to determine the MDA kinetics and expected level of MDA (lines 103-105) i.e. of what is representative. These requirements are an endless loop, whereas they do not provide for any clarity of what is *"representative"*. Proposed change (if any): Please clarify how we should obtain "representative" animals with MDA.	make sure to take animals with MDA titres or -values representative (averaging) for those present in the field at that age. This seems logical! The target is another point; In the example given, evaluation f efficacy of vaccination in newborns may have to be done by challenge and the titre of MDA is less important but still, an average at the age to be vaccinated (=representative) can easily be taken.
line 118		Comment: "*The recommended vaccination schedule, using a vaccine with minimum titre or potency, should be applied to ….*" This requirement is not in line with Directive 2009/9/EC, i.e. the new Annex I to Directive 2001/82/EC, as amended by 2004/28/EC. We propose to use the same text as included in the new Annex I:	Accepted

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		Proposed change (if any): "*For live vaccines, batches containing the minimum titre or potency shall be used unless justified. For other products, batches containing the minimum active content shall be used unless otherwise justified. The recommended vaccination schedule, ~~using a vaccine with minimum titre or potency,~~ should be applied to ….*"	
lines 126-134		Comment: Case a) is very restrictive as it concerns exclusively antigens for which there is not only a correlation between antibody and protection but also a "protective threshold" has been established *(line 131: "induced an antibody titre which is protective").* This is far from being the classical situation, and if there is a correlation between serology and protection, comparing antibody titre kinetics in groups 2 and 3 should be sufficient. Furthermore, correlation between antibody titre and protection is too limited for certain diseases which have other parameters that have been demonstrated to be correlated with protection. Proposed change (if any): *"If the applicant has previously demonstrated that there is a direct correlation between a parameter (e.g. the antibody titre) and the protection against the disease, a ~~serological~~ follow up of this protection-related parameter will be adequate and group 1 is not needed."*	Accepted

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line 133		*"… the non vaccinated group (group 3), intended to follow the decay of MDAs, would also serve to exclude that field infections have occurred."* For animal welfare reasons, we may not be in a position to have negative controls in the field, which again reduces applicability of this document.	This group is, however, from a scientific point of view, necessary to follow the decay of MDA's allowing to set the time to evaluate the protection related parameter and to exclude field infections. If not included, the protocol is worthless. If impossible for welfare reasons, than the experiment has not to be performed in the field
lines 141-146		Comment: *"… and it should be shown that the efficacy of the vaccine in animals vaccinated in the presence of MDAs is, notwithstanding normal biological variation, similar to that obtained in animals of the same age…* *If the results of the study indicate that the MDAs interfere with vaccine efficacy, this point should be indicated in the SPC…"* We have strong objections to the term 'similar' here. According to the Ph. Eur. monographs for veterinary vaccines, primary efficacy ('Immunogenicity' or 'Potency') should be shown in animals not having antibodies against the agent to which the vaccine provides protection. The efficacy of the same vaccine in animals with antibodies against the vaccine agent does not necessarily have to be identical to the requirements set for the Immunogenicity/ Potency test included in the relevant Ph. Eur. monograph. An example to illustrate this is some of the live respiratory virus vaccines for poultry, administered by the oronasal route. An influence of MDAs may be seen, but since the route of administration is rather insensitive to the influence of MDAs, the vaccines may be highly effective even when applied to day-old chickens with	"level of protection is significant and clinically/biologically relevant" is considered as leaving a too wide margin for all kinds of interpretations. What is relevant for whom? It is agreed that a significant difference with the challenge results obtained in group 3 compared to the target group 2 might be too far reaching. For this reason, it was proposed that the challenge results in the target group 2 should be **similar** to those of group 1 and this allows some flexibility. In the example given in day old chickens, the protection may be similar (not the same!!!) if vaccination was efficacious; Similarity with regard to e.g. protection against clinical disease is possible Group 1 is essential for a scientifically justified protocol to allow evaluation of "similarity" within and during the same experiment. Group 3 is equally essential , as mentioned in the

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		high levels of MDA. The requirement should be only that the level of protection is significant and clinically/biologically relevant. In our view, this point should be included in the SPC only when there is a considerable interference of MDAs in the efficacy of the vaccine. Furthermore, the efficacy of the product should not necessarily be demonstrated in MDA-negative and in MDA-positive animals. If protection is sufficient in MDA-positive animals, a study in MDA-negative animals does not seem necessary (provided a monograph prescribing such study does not exist for the product). A manufacturer may choose to indicate that the vaccine is only to be administered at an age when MDAs have waned. In some cases (e.g. inactivated equine influenza vaccine) this is also the only possibility, as it has been shown that vaccination in the presence of MDAs may induce tolerance. At the other end of the spectrum, repeated vaccinations may have to be prescribed in order to meet situations where MDA levels are highly variable and animals are at high risk of infection as soon as the MDAs have waned (e.g. in case of live cat or dog vaccines). Finally, for some products the measurement of antibody levels may be a good indicator for the right time of vaccination. Proposed change (if any): *"One or more parameters to demonstrate protection from challenge should be evaluated (e.g. clinical, pathological, virological, bacteriological criteria)~~. and it should be shown that t~~The efficacy of the vaccine in animals vaccinated in the presence of MDAs ~~is, notwithstanding normal biological variation, similar, to that obtained in animals of the same age but vaccinated in the absence of MDAs,~~ should be significant and clinically/biologically relevant.* *If the results of the study indicate that the MDAs interfere*	text, to define the time of endpoint for challenge, to check for absence for intercurrent infections and to evaluate the challenge results in the MDA+ but non vaccinated animals(possibility that waning MDA is still present at challenge). Without these control groups, the protocol is scientifically of no value.

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		with vaccine efficacy to a large extent, this point should be indicated in the SPC and the applicant should define the adapted schedule of vaccination that will ensure protection of vaccinated animals~~, both with and without MDAs~~ under the circumstances claimed in the SPC and leaflet text. ”	