EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 July 2013
EMA/CVMP/IWP/441123/2013
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)', (EMA/CVMP/IWP/594618/2010)

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

Stakeholder no.	Name of organisation or individual
1	IFAH Europe
2	PHARMAQ AS

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	IFAH-Europe welcomes the opportunity to comment on the second draft of this guideline. It is acknowledged that this version is improved compared to the previous draft. In particular, the ability to mention trade names in the SmPC, as well as the acceptance of manufacturing differences between vaccines and the flexibility with the safety of 10-doses is welcomed. Nevertheless, 3 major issues remain that will have a major impact for applicants: a demanding level of requirements leading to a systematic full clinical re-development, underdeveloped approaches for the reduction of animal use and lack of consideration for alternative approaches. These are explained in more detail below. 1. Requirements remain very demanding, with the potential for severe impacts when incremental innovations on existing products are considered (*i.e.* re-demonstration of a 3 year DOI, update of strains, inclusion in the SmPC of field use habits). Moreover, if the requirements concerning the injections in different sites remain more or less the equivalent of full development, companies will be reluctant to perform compatibility studies, leading to a situation where the users/practitioners will implement association (or worse, mixing) without any control/frame and knowledge of the consequences. Thus the development of alternative approaches is necessary, particularly to avoid the EU market being placed at a disadvantage compared to other regions. 2. The Directive 2010/63 is often cited but only a few arrangements are proposed to concretely apply the reduction of animal use. For instance, a serological marker can be used only if the demonstration of the correlation with the protection is established with a threshold. This totally disregards	These general comments are a repetition of comments provided during the first consultation phase and have been partially addressed. There is a recognition by CVMP that the impact of this guideline may be difficult to predict and the CVMP has therefore agreed the effect of this guideline will be assessed by the Agency two years after it coming into effect. This report on the effects of the guideline will involve a consultation of the interested parties which provided comments on this guideline.

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	the rarity of this case. In most cases, the full re-demonstration of safety and efficacy will have to be performed (to ensure acceptance in a predictable manner). Indeed, the demonstration of such protective thresholds requires a large number of animals, often many more than is required for the OOI and DOI, this rises further if there are multiple claims based on special studies (including field trials). To avoid any waste and limit the use of animals, it would be appreciated if the authorities provide examples of acceptable protocols to demonstrate such thresholds as well as a list of diseases where an acceptable threshold exists (specifying the marker and its threshold). For other cases, alternative approaches to avoid challenges and limit the use of animals should be considered as detailed in the next point. 3. Cases where applicants have extensive knowledge of a strain included in various vaccines over a long time should be considered. Serological parameter follow-up, combined with a demonstrated robustness of the safety and efficacy of the strain whatever the environment, should be accepted. In that configuration, serological results should be consistent in a comparative study (contemporary or retrospective if the serological test is identical), even if this parameter has not been fully demonstrated as correlated to protection. The use of new immune tools, increasingly developed by companies, should also be considered. Thus in a comparative study, aimed at demonstrating the absence of an impact of the combination compared to the stand alone vaccine, a similar immune response covering several humoral and cellular parameters should be accepted. The applicant should justify the tools and parameters used. The underlying principle here is based on immune response: if in different situations many immunological responses remain unchanged, this shows absence of interference and therefore the same response yielding the same result (in terms of protection). Introducing these possibilities, which are scientifically based would lead to real improvements in terms of both innovation and reduction of animal use.	

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2	PHARMAQ commented on the previous draft guideline also, and we appreciate the opportunity to repeat and explain in some more detail one of our previous proposals that not was taken into account.	
2	Aquaculture is a dynamic industry that develops rapidly. New diseases are identified and new products are developed continuously. The diseases also vary between regions and it is not possible to have standard combined vaccines for all situations. The fish will therefore sometimes have to be vaccinated with more than one IVMP. The currently available injection vaccines for fish are all administered by intraperitoneal (i.p.) injection, and for the reasons explained below repeated injections at different times should be avoided if possible. It is therefore our opinion that simultaneous i.p. injection of two vaccines should be possible when documented.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
60-76 76-onwards	2	Comment: Injection vaccines for fish are usually administered as combined vaccines in a single intraperitoneal injection. However, injection of two or more IVMP's at the same time and at the same site is relevant in cases where the fish need more than one IVMP to be protected. Re-vaccination of fish (at different times) is time and resource demanding and from a fish welfare point of view not optimal because vaccination and handling is stressful for the fish and may lead to reduced ongrowth for a period of time. Injection of two or more IVMP's at the same time but at different sites is not a solution to this, as the fish are typically only 25-50g when vaccinated and injection of oil-based vaccines in another site, i.e. muscle is not an alternative since this will induce melanisation in the muscle and thus reduce the quality of the filet when the fish is slaughtered. We therefore propose that administration of two or more IVMPs at the same time at the same administration site should be included as an option in the guideline. Provided that the quality, safety and efficacy requirements of Directive 2001/82/EC are fulfilled, the most important aspect is to secure correct dosage of each IVMP. This secured, the same possible associations between two or more IVMPs must be expected independent of whether the mixing of the IVMPs occurs before or just after administration. Proposed change (if any): (iiiv) administration of two or more IVMPs at the same time at the same administration site	The comments and proposals could not be accepted, as they would have created a separate guidance for fish vaccines. According to current legislation and guidance this was regarded as not being possible. Nevertheless, there is recognition of the special requirements for fish and this is reflected under the point of associations on line 71 and 72 where it is now stated that in the special case of intra-peritoneal injections of two or more IVMPs in fish at the same time the requirements for point (i) apply.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 90-94	1	*"The following legal limitations apply to the types of association of IVMPs:* - *an association achieved by the mixing of individual products from separate applicants cannot be authorized* - *associations of products from different applicants (other than mixing of IVMPs) are possible providing that there is consent and agreement between the applicants."* Comment: The legal background to exclude the possibility of mixing products from different MAHs if they are in agreement is not fully understood. Proposed change (if any): "The following legal limitation~~s apply~~ to the ~~types of~~ association of IVMPs **applies**: - ~~an association achieved by the mixing of individual products from separate applicants cannot be authorised.~~ - associations of products from different applicants ~~(other than mixing of IVMPs)~~ are possible providing that there is consent and agreement between the applicants."	Not accepted. The proposal describes quite the contrary approach as the one intended by the GL and the current legal provisions. This non-acceptance is based on legal interpretation of current legislation.
Lines 104-105	1	*"Changes of one product will lead to discontinuation of the association claim unless new data supporting the continuation of the association are available. These changes will be subject to variation procedures."* Comment: This paragraph was added since the last version. Minor changes not	Not accepted. The restriction to major changes does not reflect the sum of

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		affecting the final composition of the product should not lead to the discontinuation of the association claim. The decision to remove the claim should be based on case by case assessment. Proposed change (if any): "**Significant** changes **to the composition (*e.g.*, adding a new strain to vaccine) or manufacturing process (*e.g.*, adding a purification step)** of ~~one~~ **either** product **covered by the association** ~~will~~ **may** lead to discontinuation of the association claim~~ unless new data supporting the continuation of the association are available~~. ~~This~~ **These** changes **will need to be assessed on a case by case basis and if discontinuation of an association is needed**, this will be subject to variation procedures."	minor changes which may lead to a major negative impact in the individual products and the associations. In addition no proposal was made, which significant changes are envisaged.
107-108	1	Comment: The sentence commencing "*Based on historical….*" is not clear . Proposed change (if any): **Based on the historical development of IVMPs ~~and~~ their proof of safety and especially efficacy was mainly performed by challenges.**	The comment is accepted. The wording was changed.
108-111	1	Comment: Unless proprietary, more information on the development of serological markers should be provided by the authorities in this document and shared. This will greatly help with the implementation of Directive 2010/63 and the acceptance of this data in a predictable manner. Proposed change (if any): Consider placing this information in an annex to the guideline, which would permit a more rapid updating of the information without the need to reopen the entire guideline.	The introduction of a more detailed description of serological markers is regarded as too specific for the general GL. There, the wording was changed, but the general formulation was maintained.
Lines 121-125	1	*"Data from laboratory and/or field safety studies carried out on a combined*	Accepted

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		vaccine may be acceptable to demonstrate the safety of a vaccine containing one of the active substances or smaller combinations of the active substances providing the components (antigens, composition of excipients and/or adjuvants) are identical in each case and it is only the number of active substances which is changed. Minor differences could be accepted if already agreed by the competent authorities." Comment: The acceptance of minor differences is welcomed; however it is not clear how these minor differences could already have been agreed by the competent authorities. Proposed change (if any): "Minor differences could be accepted if ~~already agreed by the competent authorities~~ **suitable justification is provided**."	
Line 129-132	1	Comment: Does this mean that the 10 doses safety study per strain will exist as a stand-alone study? Proposed change (if any): Please clarify	The text is modified to clarify the requirement
Lines 146-147	1	*"The onset of immunity and the duration of immunity should be established for each active substance of the combined vaccine."* Comment: The requirement to demonstrate the onset of immunity and duration of	Accepted

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		immunity for **each active substance** is questionable for a combination vaccine. Provided evidence is given that at a single time point protection of **all** the active substances occurs, there is limited benefit to demonstrating protection of the individual actives at other time points i.e., if protection of one active occurs faster than another, normally only the longest time should be relevant on the label recommended immunisation period. However there may be benefit in listing more rapid OOI for certain strains, particularly for emergency use situations. Proposed change: *"The onset of immunity* **that infers protection of all of the active substances in the combination** ~~*and the duration of immunity*~~ *should be established* ~~*for each active substance of the combined vaccine*~~*.* **Duration of immunity may be supported by field trial data in place of laboratory studies**.*"*	
Lines 147-148	1	*"If appropriate, the influence of passively acquired and maternally derived antibodies on the immunity shall be adequately evaluated."* Comment: The data on the effect of maternally derived antibodies should also be accepted from the individual vaccines if available. Proposed change (if any): *If appropriate, the influence of passively acquired and maternally derived antibodies on the immunity shall be adequately evaluated* **or this data may be supplied on the individual IVMPs if available.**	Accepted. The wording is modified

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Lines 152-153	1	*"Minor differences could be accepted if already agreed by the competent authorities."* Comment: The acceptance of minor differences is welcomed; however it is not clear how these minor differences could already have been agreed by the competent authorities. Proposed change (if any): "Minor differences could be accepted if ~~already agreed by the competent authorities~~ **suitable justification is provided**."	Accepted
Lines 154-155	1	*"potential interactions of the active substances in the larger combination on the induction of protection in the vaccinated animal are taken into account."* Comment: How is it envisaged that this could be achieved, a similar level of antibodies? Proposed change (if any): Please outline acceptable evidence.	The current formulation allows a case by case decision on the data. Antibody levels alone may create a hurdle. Reduction of clinical signs could also be a tool.
Lines 193-194	1	*"The basis for association of IVMPs should be a demonstration of acceptable safety and absence of serious interference between the IVMPs involved."* Comment: IFAH-Europe supports this well written statement. We regret, however,	No comment here

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		that this sound principle is not applied further on in the GL, e.g. in lines 240 - 243, where the lack of interference is required to be shown for each category of each target species by all recommended routes of administration.	
Lines 201-202	1	*"It should also be noted that changes that have an impact on the production or composition of any of the concerned IVMPs will also require re-evaluation of the compatibility of the association."* Comment: Minor changes not affecting the final composition of the product should not lead to the discontinuation of the association claim. The decision to remove the claim should be based on case by case assessment. It is suggested to use the wording already proposed: lines 104-105 Proposed change (if any): "It should also be noted that **significant** changes ~~that have an impact on the production or composition of any of the concerned IVMPs will also require re-evaluation of the compatibility of the association~~ **to the composition (eg, adding a new strain to vaccine) or manufacturing process (eg, adding a purification step) of either product covered by the association may lead to discontinuation of the association claim. These changes will need to be assessed on a case by case basis and if discontinuation of an association is needed, this will be subject to variation procedures**."	Not accepted. The explanation, what is understood as significant change is missing
Lines 219-220	1	*"If justified the studies may be reduced to tests in the most sensitive category of each target species using the most sensitive route of*	The comment is not understood. The wording appears to be clear enough.

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		administration." Comment: Whilst this statement gives the opportunity to reduce the use of animals, without clearer guidance on when this would be accepted, or re-written conversely to permit it with stated exceptions; we face a continuation of the current position of different MS adopting very different approaches on what is acceptable. This will lead to all tests being performed to ensure a predictable and timely outcome. Proposed change (if any): Please consider re-wording to take into account the concerns expressed.	
Lines 220-222	1	*"If different minimum ages are approved for the individual IVMP, the safety of the association should be established for the youngest age of vaccination (worst case scenario)"* Comment: The study aiming at showing the safety of the association defines the youngest age where the associated use is allowed. This will normally be the older of the two "youngest age" involved and not the younger. However the age covered by the association should be the Applicant's choice and will depend among others on epidemiological considerations. Proposed change (if any): *"If different minimum ages are approved for the individual IVMP**, the applicant will need to justify the minimum age recommended for the association**; ~~the~~ safety of the association should be established*	The association will be accepted for the oldest of the minimum ages recommended. The wording is adapted accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		accordingly *~~for the oldest age of vaccination (worst case scenario)~~"*	
Lines 233-236	1	*"The safety of associated use can be supported by adequate safety data from field trials using a standard batches of vaccine without the requirement for additional laboratory trials, provided a satisfactory justification has been given and that the follow up is the same as the ones performed in the safety laboratory studies when the IVMPs are given alone".* Comment: Whilst the concept is welcome; in practice it is very difficult to perform such a detailed follow-up in the field. Proposed change (if any): *provided a satisfactory justification has been given and that ~~the~~* ***a*** *follow up is ~~the same as the ones performed in the safety laboratory studies when the IVMPs are given alone~~* **performed.**	Not accepted. Other parameters as already used will not allow the comparison of data for individual products and the associations.
Lines 240-243	1	*"In most cases the batches being mixed should contain the minimum titre or active content and the mixture should be administered such that a single dose of each of the individual vaccines is administered to each category of each target species, by all the recommended routes of administration."* Comment: For IFAH-Europe, this requirement appears to be in contradiction to the 3Rs principles. For a reasonable comparison IFAH-Europe would like to propose to study efficacy for each target species but not for each category of the target species; or to give the possibility to apply for mixed use in a subset of the categories licensed for the individual IVMPs.	Partly accepted

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		Proposed change (if any): *"In most cases the batches being mixed should contain the minimum titre or active content and the mixture should be administered ~~such that a single dose of each of the individual vaccines is administered to each category of each target species, by all the recommended routes of administration~~* **according to the recommended schedule for the mixed use under conditions most likely to result in interference (most sensitive category of applicable target species, most sensitive route of administration). It will also be possible to show efficacy and apply for mixed use of IVMPs for only a subset of the categories and target species of the individual IVMP.***"*	
Lines 247-251	1	*"Challenge against each of the active substances included in the IVMPs: If a threshold for a marker parameter that is correlated with protection has been established for one or more of the active substances of the individual IVMPs, the challenge against these active substances can be omitted and the follow up of these marker parameters after administration of the mixed IVMPs is acceptable to support the claim for these active substances."* Comment: In this section the marker parameter only refers to immune marker post-vaccination which is a reduced definition when compared to the definition of "marker parameter" given in the glossary. Proposed change (if any): *"Challenge against each of the active substances included in the IVMPs: If a threshold for a* ***immune response to vaccination recognized as a correlate or surrogate of protection (marker parameter)*** *~~marker~~*	Accepted

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		~~*parameter that is correlated with protection*~~ *has been established for one or more of the active substances of the individual IVMPs, the challenge against these active substances can be omitted and the follow up of these marker parameters after administration of the mixed IVMPs is acceptable to support the claim for these active substances."*	
Lines 257-260	1	*"Whenever challenge studies are carried out the results must be similar and support all the efficacy claims of the individual IVMPs. If a follow up of marker parameters has been used, it should be demonstrated that the results obtained with the mixed IVMPs are at least equal to the threshold established for each individual IVMP."* Comment: For IFAH-Europe, testing the association for all the efficacy claim is in contradiction to the 3Rs principles. Furthermore, some claims can only be demonstrated under field conditions. Finally the use of a marker parameter is made possible, however it is not clear how such parameter could be used to support all efficacy claims. According to IFAH-Europe, if the marker parameter at the primary response (onset of immunity) shows the same quantitative and qualitative response in the associated product when compared to the individual IVMPs, absence of interference is sufficiently demonstrated. Consequently, it could reasonably be assumed, that all claims approved for each of the individual IVMPs are also valid for the association. Proposed change (if any): ***"In the case where no immune marker parameter post-vaccination is available,*** *challenge studies must be* ~~*are*~~ *carried out.* ~~*the results must*~~	Partly accepted. The text was reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~*be similar and support all the efficacy claims of the individual IVMPs. If a follow up of marker parameters has been used,*~~ *it should be demonstrated that the results obtained* ***for the marker of efficacy post challenge*** *with the mixed IVMPs* ***is*** ~~*are*~~ *at least equal to the threshold established for each individual IVMP (some level of interference is allowed if acceptably justified; cf. section 5.1).* ***The study will focus on the primary response only (onset of immunity). If the primary response is not impacted, all claims of the individual IVMPs will be extrapolated to the associated IVMPs.*** *" Where a threshold has not been clearly established, but the parameter is known to be relevant, then a lack of inferiority study comparing vaccine responses is acceptable.*	
Lines 261-262	1	*"If different minimum ages are approved for the individual IVMP, the efficacy of the association should be established for the youngest age of vaccination (worst case scenario)."* Comment: Testing the efficacy at the youngest age of vaccination approved for the individual IVMP implies that the applicant would need to generate compatibility claim including efficacy aspects for which the Applicant might know nothing for at least one component. Furthermore the age covered by the association should be the Applicant's choice and will depend among others on epidemiological considerations. Proposed change (if any): *"If different minimum ages are approved for the individual IVMP****, the applicant will need to justify the minimum age recommended for the association****;* ~~*the*~~ *efficacy of the association should be established*	The text is reworded.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		accordingly *~~for the oldest age of vaccination (worst case scenario)~~"*	
Lines 272-274	1	*"Instructions on administration should be provided in the SPCs for each individual IVMP and instructions on how to mix them should be provided in the section dealing with posology (amounts to be administered, administration route)."* Comment: Instructions on administration should also be included in the SPC sections on posology. Proposed change (if any): *"Instructions on administration ~~should be provided in the SPCs for each individual IVMP~~ and instructions on how to mix* **the IVMP** *~~them~~ should be provided in the* **SPC for each individual IVMP *in the*** *section dealing with posology (amounts to be administered, administration route)."*	Accepted
Line 279	1	Comment: This sentence should either read "for **the** mixture" or "for mixture**s**"	Accepted
Line 284	1	Comment: Section on quality is missing.	A general crossreference to Dir. 2001/82 is inserted.
Line 296-298	1	*"In some cases the possibility of recombination or genetic reassortment of related viral strains due to administration of the IVMPs at the same time or within a time interval which may result in recombination or genetic reassortment should be subjected to a risk analysis."* Comment: In order to allow predictability a given time interval should be specified. Proposed change (if any):	Not accepted. The time interval must be defined on a case by case basis, reflecting the characteristics of the antigens involved.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please replace "time interval" with a specified time period (*e.g.* 7 days, 14 days)	
Lines 300-301	1	*"If different minimum ages are approved for the individual IVMP, the safety of the association should be established for the youngest age of vaccination (worst case scenario)"* Comment: The study aiming at showing the safety of the association defines the youngest age where the associated use is allowed. This will normally be the older of the two "youngest age" involved and not the younger. However the age covered by the association should be the Applicant's choice and will depend among others on epidemiological considerations. Proposed change (if any): *"If different minimum ages are approved for the individual IVMP**, the applicant will need to justify the minimum age recommended for the association**; ~~the~~ safety of the association should be established **accordingly** ~~for the oldest age of vaccination (worst case scenario)~~"*	Not accepted. See comment above
Lines 311-315	1	*"Challenge against each of the active substances included in the IVMP: If a threshold for a marker parameter that is correlated with protection has been established for one or more of the actives of the individual IVMPs, the challenge against each of these actives can be omitted and the follow up of these parameters after administration of the associated IVMPs is acceptable to support the claim for these active substances."* Comment: In this section the marker parameter only refers to immune marker post-vaccination which is a reduced definition when compared to the definition	Accepted

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		of "marker parameter" given in the glossary. Proposed change (if any): *"Challenge against each of the active substances included in the IVMPs: If a threshold for a* ***immune response to vaccination recognized as a correlate or surrogate of protection (marker parameter)*** ~~*marker parameter that is correlated with protection*~~ *has been established for one or more of the active substances of the individual IVMPs, the challenge against against each of these actives can be omitted the follow up of these parameters after administration of the associated IVMPs is acceptable to support the claim for these active substances."*	
Lines 320-324	1	*"Results must be similar and support all the efficacy claims of the individual IVMPs. If a follow up of marker parameters has been used, it should be demonstrated that the results obtained with the associated IVMPs are at least equal to the threshold established for each individual IVMP.* *It should be demonstrated that the association of IVMPs should not negatively affect the onset and duration of immunity as established for the individual IVMPs. "* Comment: To IFAH-Europe, testing the association for all the efficacy claim is in contradiction to the 3Rs principles. Furthermore, some claims can only be demonstrated under field conditions. Finally the use of a marker parameter is made possible, however it is not clear how such parameter could be used to support all efficacy claims.	The text is reworded

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		According to IFAH-Europe, if the marker parameter at the primary response (onset of immunity) shows the same quantitative and qualitative response in the associated product when compared to the individual IVMPs, absence of interference is sufficiently demonstrated. Consequently, it could reasonably be assumed, that all claims approved for each of the individual IVMPs are also valid for the association. Proposed change (if any): *"Results must be similar ~~and support all the efficacy claims of~~* ***to those obtained for*** *the individual IVMPs. If a follow up of marker parameters has been used, it should be demonstrated that the results obtained* ***at the primary response (onset of immunity)*** *with the associated IVMPs are at least equal to the threshold established for each individual IVMP (some level of interference is allowed if acceptably justified; cf. section 5.1).* ***If the primary response is not impacted, the duration of immunity and all claims of the individual IVMPs can be extrapolated to the associated IVMPs. Where a threshold has not been clearly established, but the parameter is known to be relevant, then a lack of inferiority study comparing vaccine responses is acceptable.*** *~~It should be demonstrated that the association of IVMPs should not negatively affect the onset and duration of immunity as established for the individual IVMPs.~~ "*	
Lines 332-333	1	*"a natural challenge against all of the relevant pathogens may not occur under field conditions and therefore the results of the trial may not be*	No comment possible

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		sufficient to support the claims" Comment: This is interesting, but an example of what can be designed to improve acceptability may be better, otherwise, such a field trial will never be tried for the majority of diseases. This approach is positive for the 3Rs but for it to be utilised regularly a way needs to be found to reduce costs and improve predictability.	
Lines 334-336	1	Proposed change (if any): *"(b) a marker of protection should be established which can be followed during the trials and the results obtained with the associated IVMPs should be at least equal to the threshold or limits established for each individual IVMP (some level of interference is allowed if acceptably justified; cf. section 5.1)"*	Not accepted. Se comment above
Lines 337-338	1	*"If different minimum ages are approved for the individual IVMP, the minimum age recommended for the administration of the associations should be the worst case scenario."* Comment: The age covered by the association should be the Applicant's choice and will depend among others on epidemiological considerations. Proposed change (if any): *"If different minimum ages are approved for the individual IVMP**, the applicant will need to justify the minimum age recommended for the association***; ~~*the minimum age recommended for the administration of the associations should be the worst case scenario."*~~	Not accepted, see comment above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
367-onwards	2	Comment: See comment above Proposed change (if any): • administration of two or more IVMPs at the same time at the same administration site (relevant for fish vaccines)	See outcome above
377-onwards	2	Comment: Extra definition according to comments above Proposed change (if any): **Same site:** Application of IVMPs separately but so close that mixing of products may occur in the animal, though without impairing safety and efficacy requirements for each IVMP	See outcome above
Lines 385-386	1	*"Immune responses to vaccination identified by serological tests that can be correlated with efficacy (immune response that is responsible for and statistically interrelated with protection). "* Comment: A strict correlation to protection is now required to any immunologic marker used. This simplified approach neither takes the complexity of the immune system nor the complexity of the immune response to a vaccine into account, a complexity that was acknowledged in previous texts. Proposed change (if any): *"Immune responses to vaccination identified by serological tests that can be correlate~~d~~ ~~with efficacy~~* ***of protection*** *(immune response that is responsible for and statistically interrelated with protection)* ***or surrogate of protection (immune response that substitutes for the true***	Not accepted

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		immunological correlate of protection, which may be unknown or not easily measurable) *."*	