14 June 2012
EMA/CVMP/IWP/913310/2011
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on requirements for the production and control of immunological veterinary medicinal products' (EMA/CVMP/IWP/206555/2010)

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

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EDQM welcomes EMA's efforts to simplify all the EMA guidance documents on requirements for the production and control of IVMPs (11 guidance documents merged in only 1 guideline). Nevertheless, we have the following comments and proposals.	
2	PHARMAQ welcomes a revision and updating of the general guidelines for production and control of veterinary vaccines in order to give a better overview of the current requirements. PHARMAQ AS is the world's leading pharmaceutical company supplying the aquaculture industry, and our comments will focus on issues relevant for fish vaccines.	
3	IFAH-Europe would like to commend the IWP for taking this step to replace great part of Eudralex Volume 7B, as this should avoid duplication and confusion between guidance documents for IVMPs. Originally, the existing EU guidelines were 1:1 copy-pasted into Ph. Eur. general chapters and (general) monographs, but gradually these guidelines tended to grow apart. At this moment the situation is even more complex. There are three (often not aligned) pillars to take into consideration: Directive 2009/9/EC, VICH guidelines and Ph. Eur. Resolution of these discrepancies by the IWP, representing the competent EU authorities, is therefore necessary indeed. The two major subjects right now are 1) the number of inactivation control tests required and 2) the Ph. Eur. proposal to omit the target animal batch safety test for veterinary vaccines, which would not be in line with Directive 2009/9/EC. We hope that the IWP will be able to solve the second issue as elegantly as the first one.	The outcome of the decision of the commission of Ph.Eur. on TABST is awaited in November. This GL will then be discussed again by IWP.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Some parts of the proposed guideline seem to have been set based on a collection of points of disagreement in various procedures. In our view, the implementation of the proposed draft as it is would cause additional burden where there is no need: it will not provide additional clarification on risks and it will not increase benefit as the final quality will not change. Contrary to the quality parts, the content of the safety and efficacy sections of this draft guideline only repeat what is already detailed in the Annex I to Directive 2001/82 and/or European Pharmacopoeia. It would be more appropriate that when very specific texts are needed these are developed separately (as it is the case for the guideline on fish vaccines). We propose therefore to leave these sections out of the guideline and to focus only on the quality aspects of IVMP development. In case the safety and efficacy sections are kept in this guideline, it would be useful to include a section clarifying the general requirements for labelling, as this would help to 1) harmonise approaches and 2) make numbering of this guideline matching the usual split of a dossier (part 2=Quality, part 3=safety and part 4=efficacy). Finally, we would also suggest that the guidance for production and control of immunoserum is dealt with in a separate guideline. This would provide opportunity for more detailed guidance on immunoserum in a specific document. Please note that since new requirements were set in 1992 for immunoserum, such developments are no longer envisaged by industry due to complexity, cost and risks. If one wishes to redefine requirements for marketing authorisation for immunoserum, very specific approaches need to be set.	This GL intends to clarify the points of disagreement seen during the procedures and should therefore be helpful. The section on safety and efficacy tests is short and contains only the requirements that are not covered by other texts. It cannot be deleted. The numbering was amended. As mentioned by IFAH Europe there was no development of this type of products during the last decades and therefore there is no need to waste time on this subject.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
80	1	Comment: a reference to the General monograph on Vaccines for veterinary use (0062) could be given. The aim of the revision was to remove from the guideline provisions that are also given in European Pharmacopoeia monographs. The removed text was replaced by a reference to the relevant Ph. Eur. text. This could be clearly stated in the introduction. Proposed change (if any): The guideline is intended to supplement Directive 2001/82/EC as amended, the relevant texts of the European Pharmacopoeia (Ph. Eur.), in particular Ph. Eur. monograph 0062 Vaccines for Veterinary Use, and must also be read in conjunction with the principles of the GMP Directive (91/412/EC) and the related GMP guidelines. This guideline intends to clarify the requirements that are not covered by the previous texts.	Agreed.
124	1	Comment: please provide the exact reference for this table. Proposed change (if any): the table of extraneous agents (reference …) should be taken into account.	The reference added is Volume 7, 7BIm10a and annex in 7BIm9a which are still valid until the content of the new table of extraneous agents is adopted.
185	1	Comment: Please note that the tests for inactivation are currently under discussion in Group 15V. The guideline includes the same wording as Annex I (which is in line with current Ph. Eur. requirements), and adds the EMA point of view (need for only 1 inactivation test in most cases), which as you know, is not in line with Annex I/ current Ph. Eur. requirements. Proposed change (if any):	Noted.

221-222	1	Comment: Please note that the paragraph “The Ph. Eur. monograph 0062 Vaccines for Veterinary Use and the Directive 2001/82/EC as amended request that an overdose safety test is performed on the finished product” is subject to change in the context of the general revision of Ph. Eur. monographs on vaccines for veterinary use following publication of VICH GL 41 and 44 (see proposals in Pharmeuropa 23.1). Proposed change (if any): We would recommend awaiting the outcome of the discussions if you want to keep this statement, or to refer to the Ph. Eur. monograph without specifying the wording.	The GL will not be ready before the discussion of this point at the Ph. Eur. Commission in November. This GL will then be discussed again by IWP. Furthermore, even if the Ph. Eur. is modified the Directive will still request this test.
223-225	1	Comment: “The pass criteria of this safety test for inactivated vaccines will be based on the results of the batch safety tests performed with the 3 consecutive batches produced to demonstrate batch-to-batch consistency.” We note that, since the overdose safety test for inactivated vaccines is no longer required via VICH GL, it is now requested to base acceptance criteria on 3 consecutive batches. This is new and would be a possibility if the TABST was kept. But this might not be the case. So it might be premature to have this statement included in the guideline. Proposed change (if any):	The GL will not be ready before the discussion of this point at the Ph. Eur. Commission in November. This GL will then be discussed again by IWP.
226-228	1	Comment: Could you clarify the reason for introducing this paragraph? If needed, this could instead be introduced in the General monograph on Vaccines for veterinary use (0062). Proposed change (if any):	
226	1	Comment: Furthermore, it was decided during the IWP	Not agreed.

		meetings that the guideline would specify that the General monograph on Vaccines for veterinary use (0062) also applies when there is no specific monograph. This was said in a general way, and not only for live avian vaccines. Proposed change (if any): Where no specific monograph exists ~~for a live avian vaccine, if the vaccine is intended to be administered by spray or drinking water in the field, it shall be given by eye-drop in the batch safety test to ensure that a full dose is administered~~, Ph. Eur. monograph 0062 Vaccines for Veterinary Use applies.	This requirement comes from the GL of avian vaccines and is not covered by the Ph. Eur. monographs.
249	1	Comment: "The number of animals in the vaccinated and control groups should be sufficient to obtain statistically significant and clinically reliable results." It is proposed to delete this sentence in the interest of animal welfare. Proposed change (if any): ~~The number of animals in the vaccinated and control groups should be sufficient to obtain statistically significant and clinically reliable results~~.	Not agreed. Animal welfare is an important matter that is acknowledged by the IVMP and introduced in this GL under II Safety and efficacy. Nevertheless the validity of a trial is also an important point and the statistical analysis is necessary to demonstrate it.
106-119	2	Comment: 1. Devices Devices for administration of fish vaccines Fish vaccines are administered using either manual- or automatic injection. Several types of devices produced by various manufacturers exist for both vaccination methods. Examples of manual vaccination syringes used in aquaculture are Kaycee Fishjector (Kaycee Veterinary products LTD, West Sussex, England), Socorex pistol grip syringe (Socorex ISBA S.A, Switzerland) and AquaJector (Matsco/Europharma, Norway). The two former syringes are operated by hand force while the latter is pneumatic (air driven). Machines used for automatic vaccination are Lumic (Lumic AS, Norway), NFT-10	

		(Nordic Fish Tech AB, Sweden) and Maskon (Maskon, Norway). Both manual and automatic devices may differ significantly in both construction and operation, and the devices are occasionally subject to technical modifications and improvement by the manufacturers. The method of vaccination is chosen by the fish farmer in cooperation with the prescribing fish health service. Trained operators perform manual vaccination and control vaccination machines under supervision of fish health personnel. Instructions for storage and handling of the vaccine container, localization of injection site and injection volume is provided by the vaccine manufacturer in the Product Information and Package Leaflet. As the range of equipment used for vaccination of fish in aquaculture is comprehensive and the technology frequently improves, documentation of application of all available devices in safety- and efficacy trials (lab and field) is an impossible task for manufacturers of fish vaccines. Vaccination machines are unsuitable for small-scale vaccination due to their size, operation and costs, and manual vaccination will thus be the method of choice in laboratory trials. In field trials however, one should if possible, aim to include sites using various devices.	
To be inserted after 119	2	Proposed change (if any): When devices not supplied by the manufacturer of the IVMP are used for administration (e.g. manual- or automatic devices for commercial scale vaccination of fish), relevant and general recommendations regarding the handling and administration of the IVMP should be provided.	The following sentence was added: “To avoid the use of inappropriate devices not evaluated in the safety and efficacy trials, the product information should indicate the type of device that should be used when administering the IVMP, and describe the physical and biological prerequisites and specifications of the device

			(e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc..)."
123-124	2	2. Starting materials Comment: 2.1 Absence of extraneous agents Reference is made to the table of extraneous agents, but according to page 1 (line number 22-23) this guidance document will no longer be valid. Proposed change (if any): When the Directive 2001/82/EC as amended and the Ph. Eur. refer to the testing of potential contaminants, the table of extraneous agents should be taken into account. the diseases occurring in the country of origin should be taken into account.	The reference added is Volume 7, 7BIm10a and annex in 7BIm9a which are still valid until the content of the new table of extraneous agents is adopted.
128-131	2	Comment: 2.2 Antibiotics It should preferably be clarified that an MRL for the antibiotic not necessarily will have to be established for the species that the vaccine is indicated for, but merely has to be listed in table 1 (allowed substances) of the annex to the regulation. It should also be possible to use other antibiotics if not included in table 2 of the annex (prohibited substances).	Agreed and amended
128-131	2	Proposed change (if any): Only antibiotics with established MRLs and listed in table 1 of the annex to Regulation 37/2010 can be used if the vaccine is intended for any food producing species. Other antibiotics may	Agreed in general but different wording

		also be used if only very small or negligible traces are remaining in the final product as long as the antibiotic not is included in table 2 of the annex to the regulation. The number of antibiotics used has to be justified. The maximum amount of antibiotics used during the production should be defined and the remaining content at the level of the finished product should be indicated.	
197-198	2	Comment: 2.7. Samples The stock of Master Seeds which has been in use for a long time may be very limited, and it should not be necessary to provide samples of seed materials for new product applications based on established Master Seeds already in use and approved in an authorised product.	
197-198	2	Proposed change (if any): Samples of all seed materials not already in use in authorised veterinary vaccines, reagents, in-process materials and finished product shall be supplied to the competent authorities, on request.	The sentence is : “Representative samples of all seed materials (e.g. subsequent passages), reagents, in-process materials and finished product shall be supplied to the competent authorities, on request.”
220-228	2	Control on the finished product Comment: 3.3 Safety tests Draft revisions of the Ph. Eur. monographs concerning veterinary vaccines have recently been out for comments. These draft revisions propose to remove the batch safety test, and this guideline should be harmonised with the revised Ph. Eur. Monographs. Section 3.3 should be deleted (if the proposed Ph. Eur. revision goes through).	The GL will not be ready before the discussion of this point at the Ph. Eur. Commission in November. This GL will then be discussed again by IWP.

220-228	2	Proposed change (if any): 3.3 Safety tests The Ph. Eur. monograph 0062 Vaccines for Veterinary Use and the Directive 2001/82/EC as amended request that an overdose safety test is performed on the finished product. The pass criteria of this safety test for inactivated vaccines will be based on the results of the batch safety tests performed with the 3 consecutive batches produced to demonstrate batch-to-batch consistency. Where no specific monograph exists for a live avian vaccine, if the vaccine is intended to be administered by spray or drinking water in the field, it shall be given by eye-drop in the batch safety test to ensure that a full dose is administered.	
236-237	2	Comment: 4. Stability tests When standard container/closure systems intended for sterile medicinal products are used, it should not be necessary to provide sterility data at the end of the shelf life. One container of fish vaccines may contain up to 10 000 doses and storage of extra samples for stability testing will in addition to testing resources also add unnecessary product costs.	The sterility is a key parameter that is tested on the finished product and that should also be tested at the end of the shelf life.
236-237	2	Proposed change (if any): The sterility of the vaccine has to be proven at the end of the shelf life. This can be achieved by sterility testing or alternatives (e.g. test for container/closure integrity).	
22	3	Comment: The guideline replaces 7BIm9a, whereas a new draft guideline has been recently published also to replace this	Not agreed. This guideline presents the quality

		document. Proposed change: Please delete this reference from the list of documents to be replaced by the proposed guideline.	requirements for fish IVMPs also. The section "II Safety and efficacy tests" applies to fish IVMPs.
81-83	3	Comment: GMP aspects are dealt with by Inspectorate at national level and are not part of the marketing authorisation aspects. Stating that the guideline should be read in conjunction with GMP principles as setup in Directive 91/412/EC will certainly lead to unjustified request for GMP information within the registration scope. Reference to relevant VICH guidelines should also be made here. Proposed change: "The guideline is intended to supplement Directive 2001/82/EC as amended, the texts of the European Pharmacopoeia (Ph. Eur.) and relevant VICH guidelines. and must also be read in conjunction with the This guideline intends to clarify the requirements that are not covered by the previous texts. pPrinciples of the GMP are covered by specific guidance and by Directive 91/412/EC and the related GMP guidelines and are out of the scope of this guideline. This guideline intends to clarify the requirements that are not covered by the previous texts."	Agreed. Proposal: "The guideline is intended to supplement Directive 2001/82/EC as amended, the texts of the European Pharmacopoeia (Ph. Eur.) and relevant VICH guidelines. This guideline intends to clarify the requirements that are not covered by the previous texts. Principles of GMP are covered by specific guidance and by Directive 91/412/EC and are out of the scope of this guideline but they should be kept in mind in order to understand the rationale behind the requirements of this guideline."
89	3	Comment: Please consider that there may be cases where a specific reduction of requirements is justified even if the product is not intended for MUMS (e.g. absence of field trials when vaccination is not allowed in EU). Proposed change: "Reductions in the requirements that may be acceptable are provided in a specific guideline "Guideline on data requirements for immunological veterinary medicinal	Agreed.

		products intended for minor use or minor species/limited markets". When appropriately justified, reduced requirements may be also acceptable for products not intended for MUMS."	
92-93	3	Comment: Please refer to our General comment regarding inclusion of guidance on production of immunosera. A separate guideline would be more appropriate. Proposed change: "Specific requirements for the production and control of immunosera and colostrum substitutes are attached as Annex 1 to this provided in a separate guideline."	Not agreed. As mentioned by IFAH there was no development of this type of products during the last decades and therefore there is no need to waste time on this subject.
100	3	Proposed change: "Directive 2001/82/EC as amended by Directive 2009/9/EC, Annex I, Title II, Part 12.A, 1. Qualitative particulars..."	Agreed.
109-113	3	Comment: Providing information on particulars of well-known devices (e.g. device for spray, intranasal, or classical syringe) would not be justifiable. In accordance with the text of the Directive ("...where necessary for the assessment of the product."), there is no need to provide a detailed description of sterilisation, disinfection and handling of standard devices (because this falls under Good Veterinary Practice) nor the sources accessible in each Member State (because marketing information is never required in product dossiers). Since it is the IVMP that is under assessment, a clear differentiation should be made between those proprietary devices delivered together with the IVMP and therefore part of the MA application and those devices that are not. For those devices that are not, appropriate recommendations for use in combination with the IVMP should be included in the PIL that fall under Good Veterinary Practices rather than under the assessment of the IVMP. Providing information on the	Proposal: 1.2. Data requirements As the use of a device can have an impact on the safety and efficacy of the IVMP, all the necessary data should be provided: - A precise description of the device including an analysis of the possible influence on safety and efficacy of the IVMP. - A detailed description of the sterilisation or disinfection of the device.. - A detailed description of the handling of the device. - A clear statement of whether the device is delivered together with the IVMP or not.

		administration specifications of the product is needed for safety and efficacy aspects, but a request for detailed information on a device would be justifiable only for specific/unique devices and/or for devices distributed with the product. Proposed change: “The amount of information to be provided depends on the nature of the devices and the relevance of any details (such as droplet size, needle length, delivered dose volume, etc.). Technical details on the design of the device are not essential, only what it is capable of doing. Hence, the data requirements listed below are the maximum data that might be requested in case of non-standard devices. For devices delivered together with the product and/or non-standard devices, the following information should be provided: A precise description of the device including... A detailed description of the sterilisation or disinfection... A detailed description of the handling...”	- A clear indication of the sources accessible in each Member state if the device is not delivered with the immunological veterinary medicinal product. accessible in each Member State To avoid the use of inappropriate devices not evaluated in the safety and efficacy trials, the product information should indicate the type of device that should be used when administering the IVMP, and describe the physical and biological prerequisites and specifications of the device (e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc.)
114-116	3	Comment: Including in the dossier a clear statement on whether the product is delivered with or without a device will only add to administrative burden and complicate the lifecycle of the product through increased number of variations. The source of device may vary from country to country and should not be managed in a registration procedure. If the same device is provided with the product in all concerned MSs, a statement can be included in the SPC and/or leaflet, together with a short explanation if necessary. Proposed change: “A clear statement of whether the device is	Not agreed. The Directive clearly states that the details of devices which will be delivered with the medicinal product shall be provided. There should be no difference with the containers.

		delivered together with the IVMP or not should can be provided on the SPC and/or leaflet. If not delivered with the immunological veterinary medicinal product a clear indication of the sources accessible in each Member State should be provided."	
117-119	3	Comment: The requirement in this sentence incorporates two different businesses (vaccine and device) that work independently. It is assumed that device manufacturers properly validate the use of new devices. It is not a responsibility of the applicant to refer to brand names and other commercially defined aspects of devices that are not of his property. The requirement should be to describe the physical and biological prerequisites and specifications of the appropriate device (e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc.) Proposed change: "To avoid the use of similar inappropriate devices not evaluated in the safety and efficacy trials, the product information should include a statement of the relevant sources of appropriate devices that should be used when administering the IVMP, and such as a description of delivered volume, droplet size, etc. the device and its handling."	Agreed. Proposed sentence: "To avoid the use of inappropriate devices not evaluated in the safety and efficacy trials, the product information should indicate the type of device that should be used when administering the IVMP, and describe the physical and biological prerequisites and specifications of the device (e.g. volume of the delivered dose, pattern of distribution in skin, location of administration (intracutaneous, subcutaneous, and intradermal), pressure of the device, droplet size, etc.)
122-124	3	Comment: Please consider appropriate reference to the table of extraneous agents, since this draft GL is supposed to also replace 7BIm10a.	The reference added is Volume 7, 7BIm10a and annex in 7BIm9a which are still valid until the content of the new table of extraneous agents is adopted.
126	3	Comment: Please note that according to current practice and PhEur the use of antibiotics in finished product is generally not	Agreed.

		acceptable (PhEur 62, §2.1.2: 'The addition of antibiotics during the manufacturing process is normally restricted to cell culture fluids and other media, egg inocula and material harvested from skin or other tissues' and PhEur 62 §2.2.5 'Addition of antibiotics as antimicrobial preservative is generally not acceptable'). Proposed change: "Antibiotics used during the production of a vaccine (in process steps or in the finished product) should..."	
128-129	3	Comment: The proposed requirement that only antibiotics with established MRLs listed in Table 1 of the annex to Regulation 37/2010 can be used in the antigen production phase (e.g. cell culture) if the vaccine is intended for food producing species, has serious and unacceptable consequences. Whereas for years penicillin and streptomycin could not be used because its use was prohibited by GRLMV and GRIMV and polymyxin has been used widely, in the future use of penicillin and streptomycin (included in MRL list) would be allowed and use of polymyxin B (not included in MRL list) would be forbidden. This would require a change of the antibiotics (mixture) used for and a re-evaluation of a large number of antigen production processes, followed by an even larger array of variation procedures. This does not seem justified, since only traces of antibiotics added to media appear in the final product and they have no pharmacological activity in the dose applied. Proposed change: "Antibiotics used during the production of a vaccine (in process steps or in the finished product) should be used under the provision of the Ph. Eur. monograph 0062 Vaccines for Veterinary Use.	Agreed but different wording

		Only antibiotics with established MRLs and listed in table 1 of the annex to Regulation 37/2010 can be used if the vaccine is intended for food producing species."	
130-131	3	Comment: It is not clear whether "maximum amount of antibiotics" means 'maximum number' or 'maximum concentration level'. In any case, we assume this information should only be provided for information in Part 2 of the dossier. We expect that the remaining content of antibiotics should be an estimation based on calculation rather than an analysis. However, the requirement to indicate the antibiotics content at the level of the finished product is of little practical relevance and the proposal sharply contrasts with the current practice that antibiotics are seen as "remnants of production" and do not have to be listed in SPC section 6.1. The restrictions to the use of antibiotics during production set by Ph. Eur. general monograph 0062 (normally only in culture media, egg inocula, etc. and not in the excipient of the finished product), the concentrations at which antibiotics are used for these purposes and the loss of activity occurring during the production process amply warrant that MRL levels or otherwise pharmaceutically relevant levels will not be reached at the IVMP injection site. It is appreciated that the IWP will consider the number of antibiotics used as presented by the applicant, since the limitation as per old guidance (i.e. maximum 3) caused issues in the past where by multiplying antigens in multivalent vaccines the final number at vaccine level was more than 3. Nevertheless, in order to keep alignment with the requirements in other regions, we propose setting-up a limit	The maximum amount means the maximum concentration level. The text is amended. No analysis is requested to control the amount of antibiotics in the finished product and the remaining content of antibiotics could be an estimation based on calculation. The text is amended. The antibiotics as remnants of production have not to be mentioned under 6.1. in the SPC. Not agreed. The IWP doesn't want to be prescriptive if not necessary. The requirements set in other regions can be followed by the applicant as long as he provides a justification for the number of antibiotics used.

		of no more than 3 antibiotics for the preparation of the same active ingredient. Additionally, we would suggest keeping the restriction to the use of Penicillin and Streptomycin for vaccines used by parenteral or aerosol (oronasal) application. Proposed change: “The maximum amount of antibiotics used during the production should be defined and the remaining content at the level of the finished product should be indicated. For the preparation of the same active ingredient no more than 3 antibiotics may be used, unless justified. The use of Penicillin and Streptomycin are not allowed for preparation of vaccines with parenteral or aerosol (oronasal) administration.”	
133-149	3	Validation of preservative effect has been always difficult and therefore called for a specific limit in PhEur 62 reducing requirements of general test 5.1.3. When all classical microorganisms recommended by PhEur are employed, a justification for the range of microorganisms should not be required. The long description of prerequisites for selecting a preservative provided in this draft guideline may lead to different interpretations across MSs. In order to avoid unnecessary discussions, we propose including of a statement that long term experience and well-established use of preservatives (e.g. thiomersal, formaldehyde) are sound justifications for choice of the preservative. Proposed change: Please insert after line 142: “Long term experience with the use of the preservative in numerous similar products (e.g. thiomersal, formaldehyde) can be	Agreed.

		regarded as sufficient justification." (Lines 144-149) "The range of microorganisms chosen for the testing should reflect the potential risk. As the Ph. Eur. allows some flexibility in the experimental conditions and range of microorganisms, the materials and methods for testing, if different from the ones listed in Ph. Eur. 5.1.3, should be described in appropriate detail by the applicant, who must in particular also validate the method to "ensure that any residual antimicrobial activity of the product is eliminated by dilution, filtration or by the use of a specific inactivator" in the recovery operation."	
150-151	3	Comment: Demonstration of efficacy throughout period of validity requires a complex study design. Please consider that demonstration of quantity of preservative throughout period of validity is also acceptable. Proposed change: "The maintenance of preservative efficacy (or quantity if justified) throughout the period of the immunological veterinary medicinal product shelf life should be demonstrated."	Agreed.
168	3	Comment: In order to avoid unnecessary testing, it should be allowed to show virucidal/bactericidal activity of a diluent using one representative vaccinal strain, e.g. one of the viruses involved with the particular diluent. As the current guidelines for avian vaccines will be replaced by this draft, there will be no longer a description of the test for virucidal/bactericidal effect that provides a basis for a common approach. Proposed change: Please add: "Virucidal/bactericidal effect on	Not agreed. If the diluent is provided with the vaccine, it should be tested for virucidal/bactericidal activity with this vaccine. The test of virucidal/bactericidal activity

		the active ingredient substance by using the diluent to solve the active substance or one representative of the vaccinal strain(s) involved with the particular diluent prior to titration. For avian vaccines, the absence of virucidal/bactericidal effects in the diluent may be carried out by titrating the vaccine (or the most sensitive vaccinal strain in case of multivalent vaccines) immediately after reconstitution and again after 2 hours at room temperature. The loss in titre over 2 hours shall not be more than 50% of the original titre if measured by p.f.u. test and not more than 5 fold decrease or one dilution step (whichever is the less) of the original titre if measured by TCID50 or EID50 tests."	mentioned in the avian GL interferes with the "in use stability" guideline. It is not considered relevant anymore.
171	3	Comment: Compliance with MRL legislation is only necessary for starting materials used for the production of IVMPs for food producing species. Proposed change (if any): "Starting materials used for the production of IVMPs for food producing species should comply with the current MRL legislation."	Agreed.
174	3	Comment: Combined vaccines use vaccine as diluent, possibility of fall-out should be considered here as the diluent may have not been tested as it is (but a larger combination). Proposed change: "Provided the relevant studies are performed with the final product solved in the diluent, no separate studies on the diluent concerning safety and efficacy are required. For the cases in which the diluent is itself a vaccine (e.g. combined vaccines), demonstration of safety and efficacy may be performed with the largest combination and less-valent diluent."	Not agreed. The diluent is not a vaccine and contains no active substance. The definition is amended.

183-184	3	Comment: The maximum bioburden may also be based on a safety study. Proposed change (if any): “The maximum bioburden should be defined by the applicant, based on data from validation and/or safety studies and controlled in each harvest or bulk as an in process control”.	Agreed.
193-195	3	This interpretation of the Annex I and the Ph. Eur texts regarding inactivation control testing is welcome. However, we would expect further guidance from this document with regards to “when detection of any residual live antigen is most likely” and the few cases where a single test would not give complete assurance. From our point of view, the inactivation is fully validated for production of antigen and there is no case where such a test on finished product is to be required. Proposed change: “It is considered that a single test to confirm complete inactivation carried out at the stage after inactivation when detection of any residual live antigen is most likely should give sufficient assurance of complete inactivation and compliance with the pharmacopoeial standard in most cases. If a concentration step is included down-stream of the inactivation or detoxification process, the inactivation control may be performed on the concentrate”.	Partly agreed. The second sentence is not added because the applicant has to show that he performs the control of inactivation at the most appropriate time.
197-198	3	Comment: Availability of samples of master seed materials are restricted and could potentially damage the permanence of the master seed lot. Proposed change: “Representative samples of all seed materials (e.g. subsequent passages), reagents, ...”	Agreed.
210-213	3	Although the key parameters in VICH GL1 and VICH GL2 are	Not agreed.

		relevant in theory, this is not true for the entirety of the document as the guidelines have been developed for pharmaceuticals and therefore the experts on IVMPs were not involved in the discussions at the time. VICH GL2 clearly states the need for different approaches: 'Due to their complex nature, analytical procedures for biological and biotechnological products in some cases may be approached differently than in this document.' The reference to the VICH GL for live vaccines followed by no guidance at all for inactivated vaccines also reduces the convenience of this paragraph. Proposed change: "For a live vaccine, the titration of the active substance shall be validated according to the principles of the VICH GL1 "Guideline on validation of analytical procedures: definition and terminology" and VICH GL 2 "Validation of analytical procedures: methodology" for its linearity (not applicable for end point dilution), repeatability and intermediate precision. An inactivated vaccine shall be shown to be of satisfactory potency using validated methods."	The principles of the VICH guidelines apply to validation in general. Furthermore as mentioned by IFAH the guideline VICH GL2 clearly indicates that in some cases a different approach is possible.
221	3	Since Ph. Eur. is under review to remove the target animal batch safety test (TABST) of veterinary vaccines, this section should be either adapted or a footnote should be inserted as appropriate. We also would like to propose that, in the case that the TABST is not deleted from Ph. Eur., the routine TABST may be waived as early as the MA is granted based on historical available data from e.g. R&D batches and production of 3 consecutive validated batches. Proposed change: "The Ph. Eur. monograph 0062 Vaccines for	Not agreed. The Ph. Eur. monograph 0062 under section 2.3.3. Batch allows the waiving of the TABST.

		Veterinary Use and the Directive 2001/82/EC as amended request that an overdose safety test is performed on the finished product. This safety test may be waived by the regulatory authority when a sufficient number of consecutive production batches have been produced and found to comply with the test, thus demonstrating consistency of the manufacturing process. This removal can be implemented at registration time when enough batches have been already produced and tested (e.g. R&D batches, the production of 3 consecutive process validation batches)."	
223-225	3	For inactivated vaccines, as the batch safety test is not very representative of product safety one cannot rely only on the 3 consecutive batches to set the criteria, please also take account of data from R&D safety studies, even if these studies have not been done with an overdose. Proposed change: "The pass criteria for inactivated vaccines is to be based on the results of the batch safety tests performed with 3 consecutive produced to demonstrate batch-to-batch consistency and the R&D safety studies."	Agreed. The sentence will be : "The pass criteria for inactivated vaccines is to be based on the results of the batch safety tests performed with 3 consecutive produced to demonstrate batch-to-batch consistency. If available, the results of other studies performed with an overdose of vaccine may be taken into account in addition".
227	3	Comment: A full dose of an avian vaccine can be also administered orally with a syringe in an experiment. Proposed change: "...if the vaccine is intended to be administered by spray or drinking water in the field, the required dose it shall be given by eye-drop manually to each bird in the batch safety test to ensure that a full dose is administered."	Agreed.
230-231	3	Comment: The templates issued by the EC and the EDQM use terms that are only applicable to products with a Marketing Authorisation. For older IVMP batches, protocols cannot	Agreed.

		always be adapted to the newest templates (note that this requirement is more an administrative request than development guidance). Proposed change: “The batch protocols should be based on comply with the templates issued by the European Commission and the European Directorate for the Quality of Medicines (EDQM) at the time the batch was produced.”	
233-235	3	Comment: In order to avoid losing the clarity now provided by GRLMV/GRIMV, please add that the requirement to extend stability studies until 3 months beyond the end of the claimed shelf life exists only for virus titrations, bacterial counts and batch potency tests. Proposed change: Stability testing shall be carried out as specified in the Directive 2001/82/EC as amended and in the European Pharmacopoeia monograph 0062 Vaccines for Veterinary Use on not fewer than 3 representative consecutive batches. For virus titrations, bacterial counts and potency tests, results until 3 months beyond the end of the claimed shelf life are to be provided. The three consecutive production runs may …..”	Not agreed. Covered by section 2.2.6 Stability of Ph. Eur. monograph 0062. All the necessary parameters (moisture, adjuvants, preservatives, pH,...) shall be tested until 3 months beyond the end of the claimed shelf life.
247	3	Comment: Since vaccines for fish benefit from a specific guideline, we would suggest replacing the example in this line.	Agreed.
242-262	3	Comment: In our view this section only provides information that is already described in existing texts. We therefore propose to omit this section completely. If this is not acceptable, please consider the comments to lines 249-252 and 257-259 below.	Not agreed. The IWP considers that the animal welfare is a priority that should be kept in mind when designing studies.
249-252	3	Comment: Please restrict this requirement to efficacy tests	Not agreed.

		only. In the case of safety test, usually a limited number of animals (8 to 10) are required to assess safety. There is no statistical significance required, as this would be counterproductive due to need for use of too many animals depending on the type of difference one wishes to assess. Additionally, when statistical principles are used, comparison between treated and control groups is not used to prove safety. Even for efficacy tests, statistically significant results are not always possible and hence not required. This is particularly true for clinical effects; please refer to Ph. Eur. monographs 1176 and 1177 as examples. Proposed change: "For efficacy tests, the number of animals in the vaccinated and control groups should be sufficient to obtain statistically significant and clinically reliable relevant results, unless justified otherwise. Specific requirements for testing of vaccines for fish are setup in EMA/CVMP/IWP/314550/2010."	A field study will allow to compare groups even for demonstration of safety (e.g. comparison of production parameters)
257-259	3	Comment: Comment: The safety tests referred to in this paragraph are studies performed during product development, i.e. before marketing authorisation. Therefore there is no "batch of diluent with which the IVMP is to be marketed". Additionally, a vaccine is not necessarily marketed together with the diluent. Proposed change: "The batch of vaccine to be tested shall be diluted in the batch of recommended diluent with which it is to be marketed, if appropriate." Note: If this requirement was designed for batch safety, the added value of matching the batch to be sold together as a combination may not be justified on formal, scientific and 3Rs	Agreed.

		reasons: Directive 2009/9/EC indicates: “Diluents may be packed together with the vaccine vials or separately” and hence diluents can be marketed separately from the vaccine. Scientific: if two products are tested for safety independently and if the combination was shown to be safe during development, repeating the test of a specific batch combination will not add knowledge. 3Rs: as diluents are usually used for more than one product and one vaccine may be sold with different diluents and vice versa, a batch-specific testing will add tests and will increase number of used animals without adding knowledge.	
Annex 1	3	As suggested in our ‘General comments’, it would be more appropriate to setup the requirements for immunosera in a separate guideline.	Not agreed. See above.