12 April 2017
EMA/CVMP/IWP/506137/2016
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species (MUMS)/limited market' (EMA/CVMP/IWP/123243/2006-Rev.3)

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

Stakeholder no.	Name of organisation or individual
1	PHARMAQ AS, part of Zoetis
2	IFAH-Europe

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	PHARMAQ welcomes the opportunity to comment on this draft guideline which is very important for the development of new fish vaccines. The fish farming industry is under continuous development including new species and new regions, and there is a constant need for new vaccines either for minor use in Atlantic salmon or for other species defined as minor. In order to extend the availability of safe and efficacious products and through this increase the sustainability of the industry, it is important not to increase the regulatory burden on MUMS products. We are concerned that rather than stimulate the development of new vaccines for MUMS, this update of the guideline will lead to increased time and costs for development and thus reduce the incentive for bringing new fish vaccines to market.	The comment is noted. Comments received during the public consultation were considered in the revised guideline. It is considered that the revised Guideline does not increase data requirements except for introducing the requirement of a Detailed and Critical Summary (DACS). This is a legislative requirement and, to address this requirement, it is proposed that only one DACS is provided to cover quality, safety and efficacy. In addition to this being a legislative requirement, the CVMP is of the view that for MUMS applications in particular, it is in the interests of the applicant to have the application dossier subject to expert critique prior to submission of a marketing authorisation application. In doing so, the data package can be reviewed vis-a-vis legislative requirements/relevant guidelines, deficiencies identified and actions taken to address the gaps/deficiencies either by generation of additional data or robust scientific argument. This, in turn, is expected to facilitate the assessment/authorisation procedure. In some areas of the guideline, expansion of the text is included for clarification but there is no substantive increase in data requirements. For example, reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing process of industrial

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		scale batches. In some areas there are reductions in data requirements such as the deletion of DOI studies for new MA applications (previously this was restricted to line extension applications), with DOI established as a post-authorisation commitment.
2	IFAH-Europe welcomes the opportunity to comment on this draft revised guidance. The revised guideline provides some useful clarifications (e.g., on extent of data reduction for GMOs and DNA vaccines). There is, however, generally an increase in requirements over the previous version or reduced flexibility. Whilst we appreciate the intent of the CVMP to provide a guidance that is more helpful to industry within the legal constraints of Directive 2001/82, we feel that in some places opportunities were missed. For instance the option to not provide all translations for centralised products but just for those countries in which the product will be marketed (see specific comment on the table). The removal of the list of diseases was disappointing, although we understand the desire to make it clear that diseases outside the list could qualify for MUMS. However, the list provided certainty for those diseases on the list and provided a useful example of the thinking at CVMP on what qualified. We would strongly urge the CVMP to reinstate the list with a clear rider that the list is given as guidance but should not be considered exhaustive and other diseases may qualify if justified. Additionally there is a major concern that the regulatory requirements actually increase (such as the addition of a requirement for Detailed and Critical Summaries and revision of “R&D batches” into “pilot batches” for consistency and stability), which contradicts	The concerns on the removal of the list are noted. The former list represented the needs for MUMS/limited market vaccines which were considered of value according to information available to authorities at that time. Originally it was not considered useful to distinguish between minor or major species, but to identify the species and disease combination that represent a minor use/limited market. This list is now outdated. Furthermore, there is an ongoing EMA/CVMP initiative to update the guidance on MUMS classification. The purpose of this work is to reconsider the MUMS classification criteria and, in doing so, to give more predictability for diseases and indications that would be subject to the policy. It is considered that the revised Guideline does not increase data requirements except for introducing the requirement of a Detailed and Critical Summary (DACS). This is a legislative requirement and, to address this requirement, it is proposed that only one DACS is provided to cover quality, safety and efficacy. In addition to this being a legislative requirement, the CVMP is of the view that for MUMS applications in particular, it is in the interests of the applicant to have the application dossier subject to expert

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	the general principle of favouring (acceptable) data reduction for MA applications in order to increase the availability of products. The provision of free scientific advice for all MUMS applications would be a beneficial incentive given the emphasis on requesting scientific advice through this guidance particularly for those small companies which have outgrown SME status.	critique prior to submission of a marketing authorisation application. In doing so, the data package can be reviewed vis-a-vis legislative requirements/relevant guidelines, deficiencies identified and actions taken to address the gaps/deficiencies either by generation of additional data or robust scientific argument. This, in turn, is expected to facilitate the assessment/authorisation procedure. In some areas of the guideline, expansion of the text is included for clarification but there is no substantive increase in data requirements. For example, reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing process of industrial scale batches. In some areas there are reductions in data requirements such as the deletion of DOI studies for new MA applications (previously this was restricted to line extension applications), with DOI established as a post-authorisation commitment.

2. Specific comments on text

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
34	2	**Comment:** the executive summary should be explicit that the objective is to increase the availability of (immunological) VMPs. **Proposed change:** (…) and leading to an overall positive benefit-risk balance for ~~the~~ **such** product**s, and lead to an increased availability of immunological veterinary medicinal products.**	Accepted
61	2	**Comment:** the regulatory requirements and the market conditions, have a major impact on a product's availability. **Proposed change:** (…) that would otherwise not be developed in the current market conditions **or state of regulatory requirements.**	Not accepted. The regulatory requirements have an impact on the development of product development. But reduction of requirements is possible within the current legislation.
67-68	2	**Comment:** "*with the aim of **updating** the acceptable data requirements in light of **experience** gained and clarifying, where appropriate, the **applicability***" From the IFAH-Europe point of view we did not see great support of the MUMS system. The 'experience' is mentioned to support this new update but we do not see clearly what 'experience' was used (and was used to better define the scope –i.e. when one cannot use the table- than increasing situations where data can actually be reduced.	The regulatory requirements in legislation were reviewed and the GL updated to reflect the opportunities for reduced data requirements. The experience gained from the assessment of IVMP applications authorised under the MUMS policy was used to determine how the existing GL is used in practice and to clarify data requirements, where applicable.

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77-78	2	**Comment:** This is clearly wording from pharmaceutical guidance. This does not give impression that this guideline was specifically adapted to Vaccines. **Proposed change:** already for a major species or major use ~~or an MRL~~ has been established for a major species~~, or if a product concerns an active substance belonging to a well-known class of substances~~.	Accepted – the whole paragraph has been deleted.
78-81	2	**Comment:** The idea of a MUMS GL is to stimulate development of new products for minor uses or minor species/limited market. In that respect it is important to stimulate the use of new active substances, novel therapy products or products being the first in class. The benefit of a MUMS GL limiting its use to existing actives and known therapies is becoming very small. Additionally please introduce abbreviations at first occurrence. **Proposed change:** ~~However, for products ….are likely to be limited. Similarly, f~~**F**or products presenting a specific risk, e.g. for products containing an antimicrobial or vaccines containing genetically modified organisms (GMOs), …	Accepted – the whole paragraph has been deleted. The revised MUMS GL applies to all IVMPs except those products with indications for FMD, BTV and AI for which specific GLs apply.
80-81	2	**Comment:** Regarding this sentence “Similarly, for products presenting a specific risk, e.g. for products	Accepted, the whole paragraph has been deleted.

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		containing an antimicrobial or vaccines containing GMOs…" The quantity of antimicrobial in an immunological is usually very low, often without pharmacological activity so the risk is quasi-inexistent. Moreover, many GMOs veterinary vaccines are on the market for years and did not prove to be "product at risk". **Proposed change**: Similarly, for products ~~presenting a specific risk~~ **requiring specific attention**, e.g. for products containing an antimicrobial or vaccines containing GMOs, the possibility for reducing data requirements ~~will~~ **may** be ~~severely~~ limited in the area related to addressing ~~the risk~~**specific requirements**, i.e. adequate data…	
81-83	2	**Comment:** Once the safety for the environment and for human health has been established for a live GMO vaccine (Directive 2001/18/EC), the quality, safety and efficacy requirements (Directive 2001/82/EC) should be the same for a live GMO vaccine as for a conventional live vaccine. Likewise, reduction of these requirements in case of MUMS/limited markets should also be the same. **Proposed change:** …i.e. adequate data to justify the indication and establish the appropriate dosage regimen or data to ensure **safety with regard to**	Partially accepted, the whole paragraph has been deleted. The GL reflects that the quality and efficacy data requirements are the same for live GMO vaccines as other IVMPs; however, this is not the case for the safety requirements. For IVMPs containing a GMO the Guideline is only applicable for quality and efficacy requirements. In addition to requirements of Directive 2001/18/EC, the full set of safety data as required in Directive 2001/82/EC should be provided. Nevertheless it is acceptable for an applicant to submit data which has been generated for similar GMO constructs already authorised to fulfil part of the requirements for quality and

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		environment and human health ~~and efficacious use~~ of such a vaccine will need to be established, ...	safety.
90-91	2	**Comment:** Applicants are advised to request scientific advice on their individual data package to confirm the precise requirements for their specific application. As applicants are advised throughout the guidance to seek scientific advice regarding the MUMS dossier data reductions advice for MUMS applications should be free of charge.	Not accepted. The scientific advice procedure, and related fees, are not within the scope of the guideline.
93	2	**Comment:** Please amend the scope to accurately reflect the title of the guidance. **Proposed change:** The objective of this guideline is to clarify the **data** requirements for the following applications	Accepted.
100-102	2	**Comment:** Since IVMP are the main scope of the guideline (see line 95, and formal guideline), why should immunological products other than vaccines and immunosera seek for a specific scientific advice if they are not GMO or DNA vaccines. **Proposed change:** delete lines 100-102: ~~However, other immunological products may fall under the MUMS/limited market policy and reduction in data requirements may apply but for such products specific scientific advice should be sought.~~	Accepted. GL updated to include IVMPs within scope except products subject to European Union control such as BT, FMD, CSF and AI, and in some cases specific guidelines.
102-103		**Comment:** For several minor species it could be	Deleted from the scope. GLP requirements can be lifted

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		difficult or impossible to find a CRO working under GLP conditions to perform the laboratory studies. Since this guideline mentions that the GLP requirements could be lifted if appropriately justified (see line 172), we propose to maintain this possibility also for GMO and DNA vaccines for which this guideline is only applicable for efficacy requirements. **Proposed change:** For GMO and DNA vaccines this guideline is only applicable for efficacy requirements. If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC, the full set of data with regard to Directive 2001/18/EC should be provided. **However, for safety laboratory trials, the GLP requirements could be lifted, if justified.**	provided the protocols and reports allow a satisfactory assessment of the trials.
102-103	2	**Comment:** GMO are shown as a risky product. This should be avoided. Both quality and efficacy can be reduced as any other products. Only safety is managed specifically according to directive 2001/18 still with use of existing data (in that case reorganisation of text is needed by putting line 108-109 closer). We do not see reason for having DNA out of MUMS reduction. **Proposed change:** ~~For GMO and DNA vaccines this guideline is only applicable for efficacy requirements. If the vaccine contains a genetically modified organism (GMO) according to Directive 2001/18/EC, the full set~~	Accepted – moved from section 2 to section 5.

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		~~of data with regard to Directive 2001/18/EC should be provided.~~ For ~~all other~~ vaccines **that do not contain a genetically modified organism (GMO)** it is acceptable to submit data generated for other vaccines containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the quality, safety and efficacy data requirements of Annex I to 2001/82/EC. **For GMO vaccines this guideline is only applicable for quality and efficacy requirements as, according to Directive 2001/18/EC, the full set of data with regard to Directive 2001/18/EC should be provided. Nevertheless,** it is acceptable for an applicant to submit data which has been gained with similar GMO constructs already authorised to fulfil part of the requirements for quality and safety.	
Line 103	2	**Comment:** See comment to line 100-102 **Proposed change:** If the ~~vaccine~~ **IVMP** contains a genetically…	Accepted.
Line 106	2	**Comment:** See comment to line 100-102 **Proposed change:** For all other ~~vaccines~~ **IVMP** it is acceptable to submit data generated for other ~~vaccines~~ **IVMP**…	Accepted.

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106-108	2	**Comment:** The current text reads as follows: "For all other vaccines it is acceptable to submit data generated for other vaccines containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the quality, safety and efficacy data requirements of Annex I to 2001/82/EC". The current text is too vague and clarification is needed, especially on the extent of possible extrapolation of efficacy demonstrated for multivalent vaccines to less valent vaccines containing the "MUMS product". **Proposed change:** Please add rows in the safety and efficacy sections in Table 1 to clarify that safety and efficacy trials carried out with vaccines containing the same active ingredient(s) and adjuvant(s) (such as combined vaccines containing "the MUMS product" and differing only by the number of active ingredients) are acceptable to demonstrate the safety and the efficacy of "the MUMS product" without further data or justifications.	Accepted. Table revised to include the following wording: For safety and efficacy studies: Data from larger combinations are acceptable.
111-112	2	**Comment:** Horses are minor species and even if very specific case seems to be 'a big market' and to support availability of medicines, no exceptions to the rule should exist. In addition the EIV example may not be appropriate as there is already a monograph and a	Accepted. Specific reference to horses removed from the GL on data requirements.

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		guideline to define what is required including strain replacement. The case by case approach removes incentives and creates uncertainty due to lack of predictability. **Proposed change:** please remove the specified exception in horses: Horses are considered as a minor species~~; however, for some IVMPs, e.g. equine influenza vaccines, where the use is normally not minor or considered a limited market, the reduced data requirements according to this guideline may not be applicable~~	
111-118	2	**Comment:** This guideline is on data requirements, whether or not a product can be regarded as intended for MUMS/limited market is to be detailed in the Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) /limited market (EMA/CVMP/388694/2014)**.** **Proposed change:** Please delete lines 111-118 and include a reference to EMA/CVMP/388694/2014	Partly accepted. Exclusion of IVMPs for diseases subject to European Union control, where vaccination is only allowed under emergency conditions, is further included in the scope. Reference to EMA/CVMP/388694/2014 is already included.
~~118-119~~ 119-120	2	**Comment: "**As a general principle, the CVMP and VICH guidelines concerning immunologicals are applicable to minor use/minor species products." This gives a wrong impression stating all requirements are applicable before listing some are not.	Accepted. Reference to VICH GLs removed. The only reference to VICH is in the reference section.

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		Proposed change: Please rephrase or put in the introduction that existing guidance may not apply totally to “MUMS”.	
121-142	1	**Comment**: The list of "minor uses/limited markets for IVMPs" (table 2 in previous version) is removed form this new version of the guideline and replaced by the definitions listed under section 3. Although referred to elsewhere in the draft, guidance on where to seek advice on classification of an intended product with regard to MUMS status should also be included in section 3. **Proposed change**: A clearer reference to the "Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/CVMP/388694/2014)" should be made. We also suggest that the list of "minor uses/limited markets for IVMPs" is kept as an appendix to the guideline. More details will give the industry better predictability.	Not accepted. Reference to EMA/CVMP/388694/2014) is already included The concerns on the removal of the list are noted and understood. The former list represented the needs for MUMS/limited market vaccines which were considered of value according to information available to authorities at that time. Originally it was not considered useful to distinguish between minor or major species, but to identify the species and disease combinations that represent a minor use/limited market. This list is now outdated. There is an ongoing EMA/CVMP initiative to update the guidance on MUMS classification. The purpose of this work is to reconsider the MUMS classification criteria and, in doing so, to give more predictability for disease and indications that would be subject to the policy.
131	2	**Comment:** Since Salmon referred in this context as Atlantic Salmon (see note 1), it can be indicated directly in the text. (the note regarding other members of salmonidae family needs to be kept). **Proposed change:** ~~Salmon~~ **Atlantic Salmon**	Accepted. Section 3 was shortened. Reference to the revised policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited market (EMA/308411/2014) is included.

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137-142	2	**Comment:** No indication is presented in this text to define with precision the criteria for classification as a minor use. Although the text EMA/308411/2014 indicates this classification is a case by case approach, clarification of the criteria taken into account would be helpful.	Not accepted Reference to EMA/308411/2014) is already included. The former list represented the needs for MUMS/limited market vaccines which were considered of value according to information available to authorities at that time. Originally it was not considered useful to distinguish between minor or major species, but to identify the species and disease combinations that represent a minor use/limited market. This list is now outdated.
168	2	**Comment:** It is stated that for line extensions to add a minor species no additional quality data are required. This sentence is confusing since quality data is normally not required for line extensions to add another species, even for major species. Therefore, as it does not add any useful information and indeed could actually cause confusion this should be deleted. **Proposed change:** Delete the sentence "~~For line extensions to add a minor species no additional quality data are required~~".	Accepted
167-168	2	**Comment:** To make this really work, there should be no room for discussion whether or not a requirement can be lifted. **Proposed change:** ~~However, some r~~**R**eductions in requirements for new marketing authorisations and line extensions ~~could be acceptable and~~ are listed in	Accepted

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		Table 1.	
172	2	**Comment:** Lifting GLP requirements is a small risk compared to a large benefit regarding work load, costs and time. GLP conditions are a major obstacle to the use of safety studies done in regions other than the EU and/or designed as post marketing studies. For MUMS products the GLP requirements should be generally lifted. However, in the draft proposal, it is proposed to restrict the lifting of GLP requirements to appropriately justified circumstances. This raises the question on what is regarded being appropriate. As appropriate is an open formulation, it remains a subjective criterion what is believed to be an appropriate justification to lift GLP requirements. Hence, open to unnecessary discussion. Lifting of GLP requirements remains at risk of the manufacturer. **Proposed change:** For laboratory trials, the GLP requirements ~~could~~ **can** be lifted~~, if appropriately justified.~~	Accepted.
177-179	2	**Comment: "**It is recognised that existing field studies may not always satisfy current GCP requirements. Such studies may..". IFAH-Europe has already given some thought to field efficacy trials for vaccines in general. These should be required only in very specific situation. Here an incentive may be :	Accepted.

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		Proposed change: replace lines 177-179 by **"<u>clinical trial are not required except when no laboratory studies can validate the efficacy. Such studies may not need to be conducted to current GCP requirements</u>"**	
180-183	2	**Comment:** Requiring appropriate statistical methodology and demonstrating statistically significant treatment benefit for IVMPs usually requires study designs that are quite demanding and not in line with the aim to stimulate availability of vaccines. **Proposed change:** ~~The applicant should test for treatment differences using appropriate statistical methodology.~~ It should be possible in all cases to demonstrate a benefit of treatment that is ~~statistically~~ **~~significant~~**<u>**biologically relevant**</u>. ~~However, the practical limitations of data collection for a minor use/limited market product will be taken into consideration.~~	Partly accepted. A simplified statistical analysis is required as, in many cases, it is the only tool to determine a true effect. The wording was amended.
Table 1	2	**Comment:** compared side by side, there is generally increased data quantity needed or reduced flexibility. Where this is not the case the requirements are unchanged. This updated GL does not reduce the requirements. Please see specific table comments below.	The concern is noted. In some areas of the guideline, expansion of the text is included for clarification but there is no substantive increase in data requirements. For example, reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing

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			process of industrial scale batches. In some areas there are reductions in data requirements such as the deletion of DOI studies for new MA applications (previously this was restricted to line extension applications), with DOI established as a post-authorisation commitment.
Administrative Part IB	2	**Comment:** If a MUMs product is registered via the centralised procedure and is intended for limited markets only it does not make sense to provide translations for all the different languages in each EU member state. The administrative burden would be reduced if it was permitted to provide SPC, PI, PL translations for the intended markets only. **Proposed change:** Please add a line in the Table referring to the administrative part IB to include the following: "**SPC, PI, PL translations only for countries where the product is intended to be marketed. If at a later stage the product is intended to be used in additional markets this can facilitated via a type I variation.**"	Not accepted. Administrative issues are not subject of the Guideline.
Table 1. Section 1.C	2	**Comment:** The previous guideline did not refer to the need of expert reports (DACS). The revised guideline does. This is an additional cost and burden that may not bring a significant benefit. This is against the claimed objective to increase product availability. It is appreciated that the revised Guideline refers to the need for a single DACS (versus one for each section);	Partly accepted This comment is noted but the change is unavoidable because of legal advice. See additional justification provided above.

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		however, a full assessment will also be needed by the expert so the reduction compared to DACS for a "normal" product is not straightforward. **Proposed change:** remove the need for DACS, consistent with current situation.	
Table 1, Section 1.C	2	**Comment:** The waiving of DACS was one of the most significant incentives in the previous version of the guideline, especially with regards to lifecycle management of MUMS products. Indeed, a lot of variations for immunologicals are considered as Type II variations, requiring a DACS. Whilst it is appreciated that the current proposal refers to a single common DACS for all parts of the dossier; however, a full assessment will also be needed by the expert so the reduction compared to DACS for a "normal" product is negligible. Additionally for life-cycle management usually only one part of the dossier is impacted by a single variation. The re-inclusion of DACS as a mandatory requirement is not understandable, as it is one of the requirements that can be omitted without a critical impact on the overall quality/safety/efficacy evaluation. **Proposed change:** Please revert to previous version of the guideline and remove the requirement for a DACS.	Partly accepted. This comment is noted but the change is unavoidable because of legal advice. See additional justification provided above.

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Table 1C	1	**Comment**: Introduction of a single DACS to cover both quality, safety and efficacy is new compared to the previous version of the guideline where no DACS was required. Requirement for a DACS represent a further alignment to the requirements for a full MA application. **Proposed change**: The expected requirements for this new DACS should be specified and less comprehensive compared to the DACS's made for full MA applications.	Partly accepted. This comment is noted but the change is unavoidable because of legal advice. See additional justification provided above. Regarding the proposal to specify the expected requirements for the DACS, the following should be noted. The legal requirement is to provide a DACS. While the CVMP is of the view that it is in the interest of the applicant that this be a comprehensive review and critique of available data to facilitate the assessment/authorisation procedure, the precise content of the DACS is a matter for the author of the document.
Table 2B	1	**Comment**: The need for two pilot batches to validate the consistency of production is considered a major extension of the requirements compared to the previous version of the MUMS guideline where the use of R&D batches was acceptable. A requirement for larger batch sizes for documentation of antigen and/or finished product processes will hamper development of new products with limited market value, because the low return on investment. **Proposed change**: Keep the old requirement where R&D batches was allowed and rather expand the requirement to verify consistency by post-authorisation commitment.	Accepted. Reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing process of industrial scale batches.
Table 1: section 2B	2	**Comment:** It is mentioned in this section that the use of 2 pilot batches to validate the consistency of	Accepted. Reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides

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and 2F		production process for the finished product is acceptable. However, in the previous GL the use of R&D batches was allowed. Typically, "pilot batches" are understood by Industry as being batches of reduced size (compared to commercial) but still being manufactured under GMP conditions. In contrast, R&D batches are manufactured in an R&D environment, not necessarily fitting GMP conditions. This is seen as a stricter requirement than that stated in the previous GL. Provided that the experimental batches have been produced according to the manufacturing method described in Part 2B of the application its use should be acceptable. Therefore, it is suggested to leave as it was in the previous GL. **Proposed change:** Use of 2 runs (R&D batches allowed) to validate the consistency of production process for the finished product is acceptable (to be verified with a 3rd batch at industrial scale as a post-authorisation commitment).	the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing process of industrial scale batches.
204: Table 2.c.2.1	2	**Comment:** For clarification. **Proposed change:** "Extraneous agents testing: only for those agents that may occur in the source species **and are expected to infect and/or cause disease in the target species"**	Not accepted. The master seed must be shown to be free of all extraneous agents not only those that might cause disease in the target species. The requirement here is already reduced compared to major products.

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204: Table related to 2.E.7	2	**Comment:** The point related to extraneous agents testing on the final bulk will need clarification as it is not clear to what is referred. For inactivated vaccines no extraneous agents testing is needed, neither on antigen stocks nor on final bulk. This should be reflected in the table. For live vaccines extraneous agents testing should be conducted either on the antigen bulk or on the individual bulk. The manufacturer can decide on a preferred strategy depending on the product. **Proposed change:** Depending on what the intention of this line: Remove the mark for inactivated vaccines and reword to "**Extraneous agents testing: permitted to be done on either final bulk or on the individual antigen bulk**".	Accepted
Table 2F	1	Confer comment under 2B	Accepted.
Table 1: section 2G	2	**Comment:** In line with the comment on sections 2B and 2F, in this section the use of R&D batches should also be allowed. **Proposed change: Results of 1 batch (R&D batches allowed) are acceptable (results of one industrial batch to be provided as a post-authorisation commitment).**	Accepted. Reference to pilot/R&D batches for studies does not increase the requirement to GMP pilot batches but provides the opportunity to generate data with either R&D or pilot batches providing these are representative for the manufacturing process of industrial scale batches.
204 / 2.G 2nd row	2	**Comment:** The largest presentation may not be presentation representing the worst case. Usually, the	Accepted.

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		smaller presentations are considered the worst case and often these are included in stability studies. Asking for the largest one often means an additional stability study to be conducted. Not a reduction. **Proposed change:** stability data on one final container size is acceptable provided the **selected** presentation ~~is the largest one~~ **is justified by the applicant.**	
204 / 2.G 4th row	2	**Comment:** If the in use shelf life can be subject to a post authorisation commitment, what is then for the time being the recommendation for use? Additionally It is not a requirement to demonstrate an in-use shelf-life, especially if it is possible to administer the product in a reasonable timeframe (in which case a suitable warning "once broached use immediately" can apply), and companies are not expected to claim for an in-use shelf-life in absence of suitable data. **Proposed change: When in-use shelf life is necessary, if it** ~~in-use shelf life~~ **can be based on experience with other vaccines, the** data can be subject to a post authorisation commitment.	Accepted. Stability data obtained with combined products can be used for smaller combinations or single products derived thereof as final data.
Table 2G	1	Confer comment under 2B	Accepted.
204 / 3.B	2	**Comment:** Having to justify the maximum titre is an additional requirement to the previous version of this GL.	Not accepted. This point is important and should not have been omitted from the previous version. The maximum titre needs to be

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Please delete this requirement.	justified otherwise it cannot be concluded that the full range specified is safe.
204 / 3.B.1, 3.B.4 and 5	2	**Comment:** These are not a MUMS specific requirement but are valid for all live IVMPs **Proposed change**:	Partly accepted The text serves to remind applicants that these studies can be omitted if appropriate.
3.C.	2	**Comment:** Additional clarity would be beneficial as to how it can be justified that laboratory safety studies are representative of safety under field conditions. Please see also the comment to lines 177-179. **Proposed change: "**If laboratory studies adequately demonstrate the absence of a**n acceptable target animal** safety risk, field studies are not required. It should be adequately ~~demonstrated~~ **justified** that the data from the laboratory studies are representative for safety under field conditions. **Appropriate justification includes the use of representative animals (versus field conditions in the EU), body weight or lactating yield (where relevant).** Safety data from the field may still be required as a post-authorisation commitment."	Accepted.
3.B & 3.C	2	**Proposed change:** Please add row(s) to clarify that safety trials carried out with vaccines containing the same active ingredient(s) and adjuvant(s) (such as combined vaccines containing "the MUMS product" and differing only by the number of active ingredients) are acceptable to demonstrate the efficacy of "the MUMS	Accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		product" without further data or justification. **Proposed change**:	
Table 1: section 4B	2	**Comment:** A mention is made in this section that for line extensions the omission of studies such as duration of immunity, effect of MDA, is acceptable provided that it is made clear in the SPC that the data are not available. This option should also be valid for new applications for MUMs/limited markets. DOI studies represent a great effort for companies in terms of time, resources and economically. Relevant warning in the SPC should be accepted or the option to perform them as a post-authorisation commitment study should be clearly stated. **Proposed change: <u>The omission of studies such as duration of immunity, effect of MDA, is acceptable, provided that it is made clear in the SPC that the data are not available.</u>**	Partly accepted. Acceptable for MDA effect. Acceptable for DOI only if relevant warning in the SPC and the applicant made a commitment to perform the DOI study post-authorisation.
Table 1: section 4C	2	In this section two options are given: either you can carry out laboratory efficacy studies if these are representative of the efficacy under field conditions" or "field efficacy studies may replace laboratory efficacy studies, if adequately justified". However, these two options are not given for safety studies in section 3C and this is considered confusing. If it is possible to demonstrate efficacy with field studies, it would make sense also to demonstrate the safety of the vaccine only in field studies.	Not accepted. General omitting the requirement for laboratory safety studies cannot be accepted.

Line no.	Stakeholder no. *(To be completed by the Agency)*	Comment and rationale; proposed changes	Outcome *(To be completed by the Agency)*
		Proposed change: Add in section 3C: **Field safety studies may replace laboratory safety studies.**	
4.C	2	**Comment:** additional clarity would be beneficial as to how it can be justified that laboratory safety studies are representative of safety under field conditions. **Proposed change: "**Field studies are not required if **it is justified that** the laboratory efficacy studies ~~adequately demonstrate that the studies~~ are representative of efficacy under field conditions. **Appropriate justification includes the use of a laboratory challenge model relevant to EU field situation and reproducing relevant clinical signs and/or microbiological outcomes".**	Accepted. Revised wording: If laboratory studies adequately demonstrate the absence of a significant target animal safety risk, field studies are not required. It should be adequately justified that the data from the laboratory studies are representative for safety under field conditions. Appropriate justification includes the use of animals representative for the target population in the EU, e.g. body weight, physiological status and reproduction performance. Safety data from the field may still be required as a post-authorisation commitment. Data from larger combinations are acceptable.
4.B & 4.C	2	**Proposed change:** Please add row(s) to clarify that efficacy trials carried out with vaccines containing the same active ingredient(s) and adjuvant(s) (such as combined vaccines containing "the MUMS product" and differing only by the number of active ingredients) are acceptable to demonstrate the efficacy of "the MUMS product" without further data or justifications.	Accepted. Data from larger combinations are acceptable if justified.