9 September 2021
EMA/CVMP/147910/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6' (EMA/CVMP/59531/2020)

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

Stakeholder no.	Name of organisation or individual
1	European Group for Generic Veterinary Products (EGGVP)
2	Animal Health Europe

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EGGVP welcomes this guideline and the opportunity to comment. Efforts to increase availability for MUMS and limited markets is clearly set and acknowledged. The new provisions are seen as great opportunity for smaller companies in particular those more flexible to cope with specific needs of customers regarding species, or fill smaller geographical areas.	The comment is noted. Comments received during the public consultation were considered in the revised guideline.
	EGGVP notes that applications for Art. 23 (limited market status) will undergo a scientific advice, with subsequent increased resource efforts for applicants (and this may be a limiting factor for some MAHs, SMEs in particular, which have proved to be great contributors to availability for limited markets in the past). EGGVP suggests the inclusion of possible reduction for scientific advice fees for limited market products to be applied. It is also noted that decisions will be taken on a case-by-case basis. This on the one had offers flexibility which is welcome, but it also involves a higher degree of uncertainty and lower predictability to the applicant, which are critical aspects for R&D plans and decision making for MAHs.	The comment is noted. It is mentioned in the guideline on data requirements that Scientific Advice is available upon request to confirm precise requirements for a specific application. Fees are not in the scope of this guideline. Noted. This is part of the classification of a product as intended for a limited market and/or confirmation of eligibility for authorisation according to Article 23 (Applications for limited markets). As indicated in the guideline, not all scenarios can be foreseen and addressed in a general guidance document. The requirements and data reductions will depend on the type of the product (active substance, mode of action) and the availability of information (published literature, data in

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		other species, other indications). Therefore, Scientific Advice is available upon request to confirm precise requirements for a specific application.
	Question has been raised about VMPs that do not comply with the eligibility criteria for an Art.23 application (already authorized as MUMS/limited market status under current guidelines or VMPs which shall fall under Art. 4(29) limited market status but not complying with eligibility criteria). It is not clear if the contents of the existing technical guidances on reduced data requirements (including those on quality data requirements) will still apply to these; or if a review and update of these existing guidances is to be expected. EGGVP suggests that options for these VMPs not fitting all criteria in Art 23 are clearly stated. For these, it may be critical to elaborate process allowing deviations from full annex II dossier (complementary guideline for VMPs for limited markets not falling under Art 23) as an incentive for MAHs towards minor use/species/limited markets development. In order help readers with scope and terminology, EGGVP suggests that the guideline is revised so as to provide the necessary clarity on that.	Noted. This is under further discussion in connection with the reflection paper on classification of a product as intended for a limited market and/or confirmation of eligibility for authorisation according to Article 23 (Applications for limited markets). Please note that the current *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) will cease to apply as of 28 January 2022 and will be replaced by the present guideline (EMA/CVMP/59531/2020). Please refer to the document 'Overview of comments received on 'Reflection paper on classification of a product as intended for a limited market and/or eligibility for authorisation according to Article 23 (Applications for limited markets)' (EMA/CVMP/235292/2020)'. The scope of the present guideline is clearly stated (applications for VMPs intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6. No further amendments are considered necessary.
	Overall, EGGVP is in the opinion that withdrawing the existing guideline on quality requirements is not in line with the objective of	Noted. Is under discussion.

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	Regulation (2019/6) to improve the availability of safe and effective VMPs for MUMS/Limited market. EGGVP insists to propose a revision of the above instead of a drastic withdrawal. The draft guidelines prepared by CVMP (safety and efficacy of IVMPs and non-IVMPs) lead to softer and beneficial provisions to MAHs in matters (e.g. Process Validation, batch analysis data, and finished product stability). Thus, the EGGVP would really appreciate if the CVMP could re-consider the decision to fully withdraw (EMEA/CVMP/QWP/128710/2004-Rev.1, and consider instead a revision that could not potentially compromise the availability of certain minor species, minor use/limited market products. Main concern is that the reduction of data requirements for part 1 (single DACS for parts 2, 3, 4) and for part 2 (quality) of the dossier has been completely excluded in the proposed guidelines due to wording in Article 23 of regulation 2019/6. EGGVP suggests that exceptions from Annex II for limited market products can be made also for parts 1 & 2. To be more specific, this would refer to: - having 1 DACS (quality/safety/efficacy) instead of 3 separate ones - using two pilot/R&D batches which for demonstrating process validation and consistency - batches not necessarily under GMP but representative of the production process	Please note that quality data requirements are not within the scope of this guideline. Please also refer to the document 'Overview of comments received on 'Reflection paper on classification of a product as intended for a limited market and/or eligibility for authorisation according to Article 23 (Applications for limited markets)' (EMA/CVMP/235292/2020)'. Noted. The legislation does not provide for exceptions from Annex II requirements for parts 1 & 2 for limited market products; therefore, deviations from basic Annex II requirements cannot be accepted.

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	Otherwise the requirements will aggravate development of new products with limited market value because of the low or late return on investment	
2	AnimalhealthEurope welcomes the opportunity to provide written comments on this important guideline. In general, the Guideline is definitely welcome and provides appropriate clarity on data reductions related to parts 3 and 4. However, there are also several major comments that we are willing to make on the draft guideline, as follows: • The current GL focuses on the reduction for safety/efficacy data requirements only. In the previous guideline on data requirements for MUMS/limited market for immunological veterinary medicinal products, reductions on requirements for part 1, and (more importantly) part 2 were also possible (e.g. validation studies, extent of Master seed testing, 2 consistency batches versus 3 required, acceptability of R&D batches, reduction of requirements on finished product control testing and stability), despite absence of a formal legislation/regulation basis. Now, despite the fact that the New Vet Regulation explicitly foresees facilitating the registration of veterinary medicinal products (VMPs) for limited markets, it is stated that the full Annex II of Regulation (EU) 2019/6 applies to parts 1 and 2 for limited markets. Not incorporating some reduction of quality-related requirements into the present guideline would be a significantly-missed opportunity for incentive and availability of veterinary vaccines. This also appears to be in	The comments are noted. Comments received during the public consultation were considered in the revised guideline. Comment on the quality requirements is noted. However, the legislation does not provide for exceptions from Annex II to Regulation (EU) 2019/6, requirements for parts 1 & 2 for limited market products; therefore, deviations from basic Annex II requirements cannot be accepted. The issue on quality requirements is under further discussion in connection with the reflection paper on classification of a product as intended for a limited market and/or confirmation of eligibility for authorisation according to Article 23 (Applications for limited markets).

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	contradiction with the objectives announced in lines 114-116, i.e. to facilitate the authorisation of veterinary medicinal products intended for limited markets. The reduction of requirements may take different forms: this could be for example the possible extrapolation of relevant data from other similar products (as explicitly allowed by annex II and CVMP guidelines for non-limited market IVMPs as well), reduction of batches at submission time with possible commitments, etc. These options would provide additional incentive on investing in this area (this is cost and time sensitive).	
	• IVMPs and especially vaccines intended for limited markets should be considered as products for which by definition the benefit of their availability on the market outweighs the risk inherent in the fact that certain documentation has not been provided. We would highly welcome if this would be clarified in the text of this guideline (or elsewhere). This would provide predictability and incentives to the development of such products (as opposed to multiple, uncertain, procedures). Please also see AnimalhealthEuropes comments on the concept paper on limited market product classification.	The legislation requires that in order for a product to be considered for authorisation in accordance with Article 23 the applicant is required to show that the benefit of availability outweighs the risk of certain documentation not being provided. This is a condition that has to be satisfied and should not be assumed. Therefore, all product types should follow the same two-step procedure for determining eligibility for Article 23.
	• In addition to a list based on animal species, we believe that there is high value in re-introducing in the guideline a list of diseases/indications against which the development and authorization of limited market vaccines would be beneficial. This concept would provide additional predictability and further incentivise developing such "niche products".	The concerns on the removal of the list in the past are noted and understood. However, CVMP is not in favour of re-introducing and including a list of diseases/indications. Regulation (EU) 2019/6 contains now a definition for 'limited market'.

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	• A transition period keeping previous quality considerations for projects started before implementation of this Guideline would be welcome (if it is decided to not include data reductions on quality in the present guideline). In the text it is not mentioned that this new guideline will replace guideline EMEA/CVMP/IWP/123243/2006 Rev 3. Also, no indications are given on Guidance on the classification of veterinary medicinal products indicated for minor use minor species (MUMS) / limited market EMA/CVMP/388694/2014-Rev.2 Corr. Will this guidance remain valid in the future?	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
131	1	Comment: It is not clear in which format this "benefit" should this be assessed: - Is this a separate document submitted by the applicant - Is this a document on 'justification' of the limited market product or a 'benefit-risk' document where all the scientific and literature data is assessed and prevalence of the benefit is explained EGGVP would also welcome explanation about where (which part of the application/dossier) this document should be located.	Not accepted. This document is not within the scope of the guideline, but part of the LM classification procedure (EMA).
146	1	Comment: please refer to general comment on quality waivers - no details for reductions for parts 1 and 2 – quality deviations from Annex II	Comment on the quality requirements is noted and is under further discussion in connection with the reflection paper on classification of a product as intended for a limited market and/or confirmation of eligibility for authorisation according to Article 23 of Regulation 2019/6 (Applications for limited markets).
170-171	1	Comment: This is not clear. If the data for the product in question were already generated then there would be no need for literature data. Proposed change: Could this be explained a bit further?	Accepted. Explained further.

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201	1	Comment: Table, section 3.A - *"For inactivated IVMPs, use of standard batches in safety studies is allowed".* EGGVP wonders if pilot/R&D batches for studies would be allowed.	Accepted. Added: The use of pilot/R&D batches is possible.
201	1	Comment: Omission of studies such as duration of immunity (DoI) and effect of maternally derived antibodies (MDA) are acceptable if reflected in the SPC. For the sake of predictability applicants would need to know if, in the case a similar product (same indication, same target specie) is already authorised with complete DoI or MDA data, these data would also be required for the product under development?	Accepted. If a product is classified as eligible for Article 23 authorisation, omission of these studies is acceptable.
45	2	**Comment:** it should be noted that the incentive given by a positive list of possible disease targets that was existing in the first version of the Guideline disappeared in the second version reduced Industry's willingness to invest in the development of limited market IVMPs. Re-introducing a list would facilitate focusing on needed targets.	Not accepted. The concerns on the removal of the list in the past are noted and understood. However, CVMP is not in favour of re-introducing and including a list of diseases/indications. Regulation (EU) 2019/6 contains now a definition for 'limited market'.
65/76/129/ 146/151…	2	**Comment:** Data requirement across the text is limited to safety/efficacy only. **Proposal:** Quality should also be addressed with clear guidance (including potential collaboration with inspectorate specific to GMP requirements and	Not accepted. Comment on the quality requirements is noted. However, the legislation does not provide for exceptions from Annex II to Regulation (EU) 2019/6 requirements for

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		timelines for those, independent of MA dossier requirements).	parts 1 & 2 for limited market products; therefore, deviations from basic Annex II requirements cannot be accepted. The issue on quality requirements is under further discussion in connection with the reflection paper on classification of a product as intended for a limited market and/or confirmation of eligibility for authorisation according to Article 23 of Regulation 2019/6 (Applications for limited markets).
125-134	2	**Comment**: IVMPs and especially vaccines intended for limited markets should be considered as products for which by definition the benefit of their availability on the market outweighs the risk inherent in the fact that certain documentation has not been provided. For those products, it is proposed that all products fitting the Limited Market definition as stated in Article 4 (29) *"limited market' means a market for one of the following medicinal product types:* *(a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas;* *(b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats;"* can be automatically eligible for the data reductions listed in the GL without having to justify compliance with Article 23(a) "*the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided;"* **Proposal:** This aspect would best be further reflected upon and introduced explicitly in the present	Not accepted. The legislation requires that in order for a product to be considered for authorisation in accordance with Article 23 the applicant is required to show that the benefit of availability outweighs the risk of certain documentation not being provided. This is a condition that has to be satisfied and should not be assumed. Therefore, all product types should follow the same two-step procedure for determining eligibility for Article 23.

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		guideline. We believe that this proposal is in line with the spirit of the New Veterinary Regulation (as commented above), and in close alignment with the Veterinary Vaccine availability EU initiative. As also mentioned above, re-introducing the concept of disease list where there is a clear need for vaccine, would ease (and incentivise) developing such targets.	The concerns on the removal of the list in the past are noted and understood. However, CVMP is not in favour of re-introducing and including a list of diseases/indications. Regulation (EU) 2019/6. 2019/6 contains now a definition for 'limited market'.
135-138	2	*2. Where a veterinary medicinal product has been granted a marketing authorisation in accordance with this Article, the summary of product characteristics shall clearly state that* ***only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data****."* **Comment**: (as mentioned under lines 186-188 of the Guideline), the Guideline should mention the exact sentence to be included in the SPC as mentioned in the Regulation 2019/6 (or refer to the QRD Template). This wording should be included in all SPC of products authorised in accordance with this article and should be sufficient to address the difference of data package submitted. Mentioning every individual gap on the SPC will lead to an increase of complexity for the end-user. This would also be contradictory with the goal of limited market approach and increased vaccination. The data omitted will be explained and justified in the EPAR. **Proposal** :	Partly accepted. Line 135-138 is the original text from the Regulation 2019/6 and is included here as legal basis. Deletion is not supported. The proposed sentence is on the SPC statement is already included in section 6. It was agreed to mention specific gaps in data in the public assessment report. Added in section 6

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		2. Where a veterinary medicinal product has been granted a marketing authorisation in accordance with this Article, the summary of product characteristics shall clearly state ~~that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data~~." ***"marketing authorisation granted for a limited market and therefore assessment based on customised requirements for documentation"***. It would be best completed by *"Specific gaps in data will be mentioned and addressed in the EPAR".*	
155-156-157	2	*"Possible reductions in requirements for new marketing authorisations and relevant variations (i.e. variations to add new target species) are listed in Table1."* **Comment**: It is not clear whether the relevant variations will be restricted to the addition of new target species and the scope should be clearly defined and extended to other relevant variations. **Proposal:** *Possible reductions in requirements for new marketing authorisations and relevant variations (**such as** variations to add new target species for example) are listed in Table 1.*	Accepted.
158-160	2	*"For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the safety and efficacy data requirements of Annex II to Regulation 2019/6."*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Comment: additional clarification would be welcome in this paragraph, specific to the possibility for an Applicant to refer to data generated in the same target species versus other target species (For example, data generated in sheep to support goat for instance, or data generated in dogs to support ferret). Doing so would provide clarity (and additional incentives). In contrast, not allowing extrapolations (pending appropriate justifications), could unnecessarily restrict development of vaccines for limited market-species. Also note that the reference to annex II in this paragraph may be (unintentionally) perceived as if extrapolation from existing vaccines are restricted to newest vaccines (whereas it should be possible to use data from vaccines authorized before the Annex II comes into force). **Proposal:** *For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs which are already authorised* ***in the EU for the same target species and which*** *contain~~ing~~ the same active ingredient(s) and adjuvant(s).* ~~*to fulfil relevant parts of the safety and efficacy data requirements of Annex II to Regulation 2019/6.*~~ ***Extrapolation of data from one target species (approved for vaccines authorized in the EU and which contain the same active ingredient(s) and adjuvant(s)) to another target species is also acceptable, pending appropriate justifications****."*	

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161-165	2	"*For IVMPs containing a GMO, this guideline is only applicable for efficacy requirements. In addition to requirements of Directive 2001/18/EC, the full set of safety data as required in Annex II to Regulation 2019/6 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 safety.*" **Comment:** The first sentence is too definitive and not appropriate for limited market; it also seems to be in contradiction with the sentences that appear later in the paragraph. It would be a disincentive considering potential new technology approaches for those limited markets. The dossier should fully comply with annex of 2001/18 but may still benefit from waiver for the other part of the Annex II (GMO is assessed through data set that may not be only with master seeds, or not GxP or not the final formulation to fill 2001/18 requirements). By introducing negative sentences for GMO increases mis-perception of the value of these products. Regarding safety, where the GMO approach may be the reason to develop affordable vaccines for those "limited markets" (*e.g*. if a vector has been already characterised for its spread), this information is useful for a new construct using the same vector as well and in line with the directive 2001/18. In this case, only some possible safety concern for the limited market vaccine may still be kept compulsory (such as, target animal safety of 1 dose/1 overdose), but there is no reason to safety has no reason to be complete for such categories. **Proposal:**	Accepted.

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		"For IVMPs containing a GMO, this guideline is ~~only~~ ***fully*** *applicable for efficacy requirements.* ***For safety,*** *~~In addition to~~* ***the*** *requirements of Directive 2001/18/EC* ***must be met****~~., the full set of safety data as required in Annex II to Regulation 2019/6 should be provided~~. ~~Nevertheless,~~* ***In line with the latter Directive,*** *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 safety."*	
201 (headers of the table)	2	**Comment and proposal**: the title of the column "Applications for new Marketing Authorisations and relevant variations" may best be completed by "***and line extensions***" (if addition of production animal as target species is still a line extension in the new veterinary regulation)	Not accepted. Line extensions are not foreseen in Regulation 2019/6. There is only a distinction between variations requiring assessment and not requiring assessment.
201 3A	2	**Comment**: The sentence *"Data from larger combinations are acceptable if justified."* has been removed from Table 1 in this revision of the Guideline. The use of data from larger combinations is considered as a worst case for the demonstration of safety and follows the mindset of the requirements from the 3Rs. This possibility should be maintained in Table 1 for clarity since it is mentioned in section *5. Requirements for IVMPs for limited markets* of the Guideline: *"For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the safety and efficacy data requirements of Annex II to Regulation 2019/6."*	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposal Please add in Table 1 (3A): ***"For both live and inactivated IVMPs, data from larger combinations are acceptable, if justified."***	
201 (3A and 4B)	2	*For inactivated IVMPs, use of standard batches in safety studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study.* **Comment:** The term "standard" should be made more precise; it should mean 'batch made according to the future commercial target'. Moreover, it is typically acceptable to use the same batch of vaccine for the safety and efficacy tests only if the vaccine is formulated to a set/fixed formulation target. We suggest for this to be clarified in the text. **Proposal:** *For inactivated IVMPs,* ***it is allowed for safety studies, to use batches produced following the set formulation target for commercial production*** ~~*use of standard batches in safety studies is allowed*~~***. In this case,*** *The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study,* ***using the same batch(es) of vaccine.***	Partly accepted. Clarification is added.

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201 (3.B.3)	2	**Comment**: clarification of requirements for safety of the repeated administration of one dose is welcome, it is clearer than in previous version and clearly allows demonstration of safety and efficacy in a single study.	Noted.
201 (3.B.4)	2	*"Studies for the examination of reproductive performance may be omitted. If such studies are not performed, relevant warnings should be given in the SPC"* **Comment**: the word "warning" raises unnecessary negative perception and may be counter-productive (*i.e.,* lead misperception by the vet/user). We suggest replacing "relevant warnings" by "relevant information" **Proposal:** *"Studies for the examination of reproductive performance may be omitted. If such studies are not performed, relevant **information** ~~warnings~~ should be given in the SPC"*	Not accepted. It was agreed to keep the term "warning" for consistency.
201 (3.B.5)	2	*Studies for the examination of immunological functions may be omitted. If necessary, relevant warnings should be given in the SPC.* **Comment**: the word "warning" raises unnecessary negative perception and may be counter-productive (*i.e.*, lead misperception by the vet/user). We suggest replacing "relevant warnings" by "relevant information" **Proposal:** *"Studies for the examination of immunological functions may be omitted. If necessary, relevant **information** ~~warnings~~ should be given in the SPC."*	Not accepted. It was agreed to keep the terms "warning" for consistency.

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201 (4A)	2	**Comment**: The sentence *"Data from larger combinations are acceptable if justified."* has been removed from Table 1 in this revision of the Guideline. The use of data from larger combinations where justified follows the mindset of the requirements from the 3Rs. This possibility should be maintained in Table 1 for clarity since it is mentioned in section *5. Requirements for IVMPs for limited markets* of the Guideline: *"For IVMPs that do not contain a GMO, it is acceptable to submit data generated for other IVMPs containing the same active ingredient(s) and adjuvant(s) which are already authorised to fulfil relevant parts of the safety and efficacy data requirements of Annex II to Regulation 2019/6."* **Proposal** Please add in Table 1 (4A): ***"For both live and inactivated IVMPs, data from larger combinations are acceptable, if justified."***	Accepted.
201 (4B)	2	*For immunosera an immunological action should be demonstrated.* **Comment**: This sentence should be clarified as it does not describe a reduction of data requirements. This is requested for all immunosera.	Accepted. Clarification is added.
201 (4B)	2	*For inactivated IVMPs, use of standard batches in efficacy studies is allowed. The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study.* **Comment:** The term "standard" should be made more precise; it should mean 'batch made according to the future	Partly accepted. Clarification is added.

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		commercial target'. Moreover, it is typically acceptable to use the same batch of vaccine for the safety and efficacy tests only if the vaccine is formulated to a set/fixed formulation target. We suggest for this to be clarified in the text. **PROPOSAL** *For inactivated IVMPs,* ***it is allowed for efficacy studies, to use batches produced following the set formulation target for commercial production*** ~~*use of standard batches in efficacy studies is allowed*~~***. In this case,*** *The safety and efficacy studies may be combined in the same pre-clinical (laboratory) study,* ***using the same batch(es) of vaccine.***	
201 4C	2	*Clinical (field) efficacy studies may replace pre-clinical (laboratory) efficacy studies, if adequately justified.* **Comment:** It should be clearer under which situations field efficacy can replace pre-clinical efficacy studies; it is typically when there are no satisfactory laboratory challenge model. See annex II paragraph IIIb.4C: *Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable.* In this case 'MUMS' IVMPs are not in a different case and this recommendation of the annex II applies.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposal: For clarity, we propose to replace the text by the corresponding text of annex II: ***"~~Clinical (field) efficacy studies may replace pre-clinical (laboratory) efficacy studies, if adequately justified.~~ Where laboratory trials cannot be supportive of efficacy, the performance of field trials alone may be acceptable."***	