24 June 2022
EMA/CVMP/IWP/157851/2022
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on requirements for the production and control of immunological veterinary medicinal products' (EMA/CVMP/IWP/206555/2010-Rev.2)

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

Stakeholder no.	Name of organisation or individual
1	European Manufacturers of Autogenous vaccines and Sera - EMAV
2	Dr Sam Saunders, on behalf of Cruelty Free Europe
3	Access VetMed
4	AnimalhealthEurope

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	EMAV, the association of the European Manufacturers of Autogenous Vaccines and Sera, welcome the draft of the Guideline on requirements for the production and control of immunological veterinary medicinal products to clarify important items related to the quality, safety and efficacy parts of the marketing authorisation dossier that are not sufficiently defined in the requirements of Annex I of Regulation (EU) 2019/6 on veterinary medicinal products and in the Commission Delegated Regulation (EU) 2021/805 amending Annex II to Regulation (EU) 2019/6 repealing Directive 2001/82/EC and in the European Pharmacopoeia (Ph. Eur.). The draft of the Guideline published for public consultation reflects this intention in general concurrently. Following recital 70 of reg. 2019/6 detailed guidelines of good manufacturing practice should specifically be prepared for inactivated immunological veterinary medicinal products which are manufactured from pathogens and antigens obtained from an animal or animals in an epidemiological unit and used for the treatment of that animal or those animals in the same epidemiological unit or for the treatment of an animal or animals in a unit having a confirmed epidemiological link. These inactivated immunological veterinary medicinal products should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially	Not accepted. This guideline is not applicable to autogenous vaccine. As indicated in Regulation 2019/6, although inactivated immunological veterinary medicinal products referred to in Article 2(3) should be manufactured in accordance with the principles of good manufacturing practice, detailed guidelines of good manufacturing practice should specifically be prepared for those products since they are manufactured in a way that is different from industrially prepared products.

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	prepared products. That would preserve their quality without hindering their manufacturing and availability. **Therefore EMAV is proposing to exclude explicitly all aspects referring to the manufacturing of these non-licensed so called Autogenous vaccines from the scope of this Guideline and to develop a specific Guideline dedicated to products referred to Article 2(3) of Reg. 2019/6!** This approach would complete the portfolio of immunological veterinary medicinal products in the Guideline on the one hand but underline the need for a separate workflow for the development of a guideline for products referred to Article 2(3) of Reg. 2019/6 too. **EMAV is interested to learn when EMA would start the development of a specific Guideline dedicated to Autogenous vaccines and the expected timeline for preparation of the document.** EMAV has developed a proposal for a dedicated "EU-GMP-Annex for Autogenous vaccines", published at https://www.emav.be/position-papers in March 2021, to support the development of a specific GMP guidance for products referred to Article 2(3) of Reg. 2019/6. This EMAV position paper was implemented in the scientific discourse at the IABS conference about "Autogenous Vaccines: Quality of production and movement in a common market" in September 2021 in Munich. The congress report drafted by Kornelia Grein, Carmen Jungbaeck and Vaughn Kubiak was published in BIOLOGICALS, see at Elsevier https://authors.elsevier.com/sd/article/S1045-1056(22)00003-3 as well as in the contents lists at ScienceDirect. Additional information are published at the IABS congress website at https://autogenous-vaccines-munich-2021.iabs.org/index.php too.	

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	To share further information and support the process of the development of specific GMP guidance for products referred to Article 2(3) of Reg. 2019/6 **EMAV would like to offer a personal consultation with EMA and the GMP/GDP Inspectors Working Group as a next step!** Your interest in this stakeholder consultation would really be welcome! EMAV – European Manufacturers of Autogenous Vaccines and Sera - is representing actually 18 recognised manufacturers of Autogenous vaccines and antisera for animals from 10 EC member states and from the United Kingdom (www.emav.be). EMAV combines the interests of manufacturers of specific vaccines and sera for livestock, pets and exotic animals, to promote the European harmonization process. EMAV is listed at EC Transparency Register, ID nb. 224469535841-56 and registered as EMA/HMA stakeholder. For more information contact Dr. Klaus-Peter Behr (Chairman, at behr@anicon.eu) or Dr. Gerfried Zeller (Managing Director, at gerfried.zeller@outlook.de).	
2	Cruelty Free Europe welcomes this update to the Guideline on requirements for the production and control of immunological veterinary medicinal products. Our suggestions below highlight areas in which the guideline can be further strengthened with regard to the 3Rs.	
4	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. The revision of this guideline provides an opportunity to clarify its (essential) purpose. To our opinion, this should be a guideline to clarify relevant requirements, focusing on manufacturing, needed to develop and register a vaccine.	

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	For example: safety and efficacy should be mentioned only where there are links to Part 2 (establishment of minimum guaranteed titre/potency till the end of shelf life or of minimum release titre…) Also, we would strongly prefer that all the 'paraphrasing' (or copy-pasting) of the listed regulation / guideline / monographs should be avoided as this may cause confusion, and in addition every time a cited text is modified this may lead to discrepancy between the corresponding documents. Only a precise reference of the relevant part of the text should be made. Otherwise, the reader is not certain if the text of this guideline is 100% following the original text, or whether it is an explanation of the requirements. Obviously, explanations given to help understanding specific parts of the referenced guidelines/monographs are sometimes very useful and welcome (for example explanations given by authorities before they issue a new requirement, or a new version of a given requirement. But we would suggest to not copy-paste exact wording (and in those occasions, only cite the relevant reference). Annex 2 on monograph 5.2.5. is a good example.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 16-20	4	**Comment:** The reference to Annex II of Reg. (EU) 2019/6 is misleading because it does not contain the current technical data set requirements or section IIIb as mentioned here. Therefore, it should be amended as follows: **Proposed change:** "Annex II of Regulation (EU) 2019/6 **amended by the Commission Delegated Regulation (EU) 2021/805** provides details on the technical data to be provided by the applicants for marketing authorisations of veterinary medicinal products."	Partly accepted. Addition of an explanation in 'Executive summary'
Lines 34-35	4	**Comment:** The referred version number and title belong to the version released for public consultation. It should be replaced by the finalised version. **Proposed change:** ~~"Guideline on data requirements for authorisation of immunological veterinary medicinal products under exceptional circumstances" (EMA/CVMP/IWP/299554/2021)~~ "**Guideline on data requirements for authorisation of immunological veterinary medicinal products in exceptional circumstances" (EMA/CVMP/IWP/251947/2021)**	Not accepted. The reference to the guideline is deleted.
Lines 42-43	4	**Comment:** Typo. **Proposed change:** The approach to demonstrate freedom from extraneous agents as part of the	Accepted.

		production and control of IVMPs ~~for IVMPs~~ is attached as Annex 2 to this guideline.	
Line 46	4	**Comment:** Version number is not correct. **Proposed change:** ~~EMA/CVMP/IWP/206555/2010~~ **EMA/CVMP/IWP/314550/2010**	Not accepted. The reference to the guideline is deleted
Lines 50-51	4	**Comment:** The cited section originates from the **amending** Annex II section IIIb.2A1(2) (adopted on21.05.2021). **Proposed change:** "**The amending** Annex II of Regulation (EU) 2019/6, Section IIIb, Part 2A, 1. Qualitative and quantitative composition states that:"	Partly accepted. Addition of an explanation in 'Executive summary'
Lines 84-85	4	**Comment:** This sentence is copied from Ph. Eur. 0062 without change and additional guidance. A simple reference to the monograph seems sufficient to avoid deviations generated by future amendments. **Proposed change:** ~~The addition of antibiotics during the manufacturing process is normally restricted to cell culture fluids and other media, egg inocula and material harvested from tissues and embryonated eggs.~~	Accepted.
Line 98	4	**Comment:** At this point all the related requirements should be referred for the sake of completeness. **Proposed change:** Please add references to *Ph. Eur. 0062* (2-2-2) and *Guideline on data requirements to support in-use stability claims for veterinary vaccines* (EMA/CVMP/IWP/250147/2008)	Accepted.
Lines 120, 155, 177	4	**Comment:** For the sake of accuracy the references should be amended. **Proposed change:** "**The amending** Annex II of Regulation (EU) 2019/6, Section I, I.2.2.(7) states that:"	Partly accepted. Addition of an explanation in 'Executive summary'.

Lines 174-175	3	Comment: With regards with the terminology, we would welcome a definition of scope for 'in process materials', as it can cover from materials that are used for in process tests (i.e. cell culture used for microbial contamination test during viral vaccine production) or aliquots of product samples, i.e. harvest or virus suspension, etc. Because normally in process samples are used for analytic purposes only, without being archived. So in case the assessment of an in process sample would be requested, that sample would probably have to be provided from some future production batch upon receiving the request.	Accepted. According to CMDv document "Product samples: national requirements for submitting samples for visual and/or laboratory control (https://www.hma.eu/fileadmin/dateien/Veterinary_medicines/Miscellaneous/CMDv_GUI-30_Speciments___samples_24.10.12_EMA-CMDv-394596-2012.pdf) samples of active substances, non-active substances, reference materials, finished product may be required in some countries.
Lines 189-190	2	Comment: To support the 3Rs, text could be included to remind IVMP developers of their obligation under Directive 2010/63/EU to use a non-animal method where possible. Proposed change (if any): "An inactivated IVMP shall be shown to be of satisfactory potency using validated methods. In accordance with Directive 2010/63/EU, methods entailing the use of live animals must not be used if another method or testing strategy for obtaining the result sought is available."	Accepted.
Lines 198-199	4	**Comment:** It is not obvious if this paragraph is pertaining to the batch protocols of the commercial and/or the R&D batches presented in the dossier. In the frame of OBPR/OCABR procedures referred to in Article 128 of Regulation (EU) 2019/6 only the batch protocols of commercial batches are evaluated,	Partly accepted. The batch protocols of commercial batches should be based on the templates issued by the European Commission and the European Directorate for the Quality of Medicines (EDQM) at the time the batch was produced.

		and their format is precisely defined in the (product specific) guidelines developed by VBRN (in collaboration with the Commission of the EU the Veterinary Pharmaceutical Committee and industry). It should not be required to present similar information for R&D batches as for commercial batches. This is because, by their very nature, R&D batches typically start to be manufactured early in development, and not all test methods may be developed or validated at the time those batches are tested. The key (for the respective studies to be considered relevant) is that those batches are representative of the future commercial manufacturing process and that those batches are tested for critical (but definitively not all routine batch release) parameters (the critical parameters are typically titre or potency and sterility or bioburden). To AnimalhealthEurope knowledge, this practice has been consistently accepted until now. Therefore, we suggest that this paragraph is deleted. **Proposed change:** Please delete paragraph 3.3. Batch protocols	
Lines 201-204	4	**Comment:** The draft Guidance is asking for 3 consecutive batches for stability purposes and cites the annex II and the Ph. Eur 0062 for that purpose. This should be revised: the requirement for consecutive batches is not included in annex II; likewise, the Ph. Eur 0062 is under revision and, during the consultation process, AnimalhealthEurope has recommended that the same requirement is not included in the latter Ph. Eur. From a technical	Partly accepted. As Ph. Eur. 0062 and annex II are still discrepant, the reference to "consecutive batches" is removed.

		stability standpoint, the requirement for consecutive batches does not make sense (whereas it makes a lot of sense from a consistency standpoint) and makes it more difficult for Companies to generate (relevant) stability data upfront (*id est*, ahead of the consistency batches). Please note that, although Companies may frequently decide to investigate stability on the same batches that are produced for consistency purposes, it is not an actual requirement to follow stability on those consistency batches (or to attribute a shelf-life based on the stability of the consistency batches), and it should be allowed to assess stability on non-consecutive batches (provided they are representative of the commercial production process). Doing this typically allows more flexibility to generate stability data earlier in development projects and also submit MA dossiers earlier (and ultimately to accelerate availability of veterinary vaccines in the field). Alternatively, as mentioned above, simply citing annex II and Ph. Eur 0062 could be appropriate. **Proposed change:** Stability testing shall be carried out as specified in Regulation ~~/~~**(**EU) 2019/6 and in the Ph. Eur. 0062 Vaccines for veterinary use on not fewer than three representative ~~consecutive~~ batches. The three ~~consecutive~~ production runs may be carried out on a pilot scale, providing this mimics the full-scale production described in the application. **The three batches do not need to be consecutive production runs.**	
Line 208	4	**Comment:** Nomenclature should be consistent with the Regulation 2019/6 and Annex II	Accepted.

		Proposed change: III. Safety and efficacy ~~tests~~ **studies**	
Lines 208-221	2	Comment: The "III. Safety and efficacy tests" section could be strengthened, including to better reflect that untreated control animals may be excluded from efficacy trials on animal welfare grounds under Annex II of Regulation 2019/6 as amended by Delegated Regulation 2021/805. Additionally, text reminding IVMP developers of their obligation under Directive 2010/63/EU to use a non-animal method where possible could be included. Proposed change (if any): "- The number of animals in the vaccinated and control groups should be ~~sufficient~~ the minimum required to obtain statistically significant and clinically reliable results. However, for efficacy trials (including vaccination-challenge studies), ~~the possibility of reducing the number of~~ untreated control ~~non-vaccinated~~ animals should be omitted from the study if efficacy can be otherwise demonstrated, ~~investigated~~ as these animals will suffer disease and associated distress. - Methods entailing the use of live animals must not be used if another method or testing strategy for obtaining the result sought is available."	Partly accepted. In case of vaccination-challenge studies, the absence of control animals would not allow to conclude on the efficacy of the vaccine. For IVMPs, the use of target species is requested in safety and efficacy studies as indicated Annex II of Regulation (EU) 2019/6. Currently, there is no possibility to avoid the use of live animals. Nevertheless, the number of animals to be used must be restricted to the minimum necessary to demonstrate safety and efficacy.
Line 246	2	Comment: To support the 3Rs, text could be included to remind IVMP developers of their responsibility under Directive 2010/63/EU to use a non-animal method where possible.	Accepted.

		Proposed change (if any): "In accordance with Directive 2010/63/EU, the use of donor animals must be replaced, reduced and refined wherever possible. Donor animals should comply with the Ph. Eur. 0030 Immunosera for veterinary use."	
Lines 289-291	4	**Comment:** There is an important contradiction between the Ph. Eur. 5.2.4 and 5.2.5 regarding the substrates for production (*e.g.,* cells, eggs, animals). Ph. Eur. 5.2.5 states that "…**any substrate (after processing, if relevant) found to contain any extraneous agent shall be discarded or *used only in exceptional and justified circumstances*"**. Whilst Ph. Eur. 5.2.4 requires that **"*The cells must not be contaminated by viruses*.** " Since it can't be guaranteed that no new adventitious viruses (apathogenic) are found even in well-known and widely used cell lines at any time, this contradiction should be resolved by providing guidance on those circumstances when the use of contaminated cell lines is deemed acceptable. **Proposed change:** Cell seeds must not be contaminated by viruses (EP 5.2.4.) and should be discarded **unless it is demonstrated in accordance with the principles of Ph. Eur. 5.2.5. that the absence of risk of the extraneous agent is ensured in the final product.**	Not accepted. The probability that new adventitious viruses (apathogenic) are found in well-known and widely used cell lines cannot be excluded but if it happens this situation will be dealt with on a case-by-case basis following a risk assessment approach, as described in Ph. Eur. 5.2.5.
Lines 348-349	2	Comment: The language here could be revised to better reflect Directive 2010/63/EU and encompass non-animal methods beyond *in vitro* methods.	Accepted.

		Proposed change (if any): "~~*In vitro* methods have~~A scientifically satisfactory method or testing strategy, not entailing the use of live animals, has to be used, if available."	
Line 361	4	**Comment:** The requirements for suitable methods are described in lines 350-355 (*e.g.,* adequate sensitivity). The reference to "highly sensitive methods" in line 361 sounds either contradictory or an additional requirement. **Proposed change:** ~~Highly sensitive methods are preferred.~~	Not accepted. It is not an additional requirement. It means that if two methods are available, the method with the higher sensitivity is the most appropriate.
Line 371	4	**Comment:** The second bracket is missing. **Proposed change:** "…are used, e.g., NAT (2.6.21**)**."	Accepted.