23 July 2021
EMA/CVMP/IWP/30398/2019
Committee for Medicinal Products for Veterinary Use (CVMP)

# Overview of comments received on 'Guideline on the use of adjuvanted veterinary vaccines' (EMA/CVMP/IWP/315887/2017)

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

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1. | Professor Anders Miki Bojesen, University of Copenhagen, Denmark |
| 2. | AnimalhealthEurope |
| 3. | Phibro Animal Health |

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# 1. General comments – overview

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| 1. | Overall, the document is easy to follow and understand. To provide an overview for persons less familiar with the application process I suggest that a flow chart depicting the major steps and including references to associated guidelines and directives. | The comment is noted. A flowchart on the application process is not useful in this context. References to associated guidelines and directives are included in the guideline. |
| 2. | Considering that the current guideline is rather old for a topic where science is progressing rapidly, AnimalhealthEurope welcomes an update of this guideline. Overall, the impression is that the focus of the new guideline relies on several aspects now: quality including stability, mechanism of action and MRL, sometimes with a too academic viewpoint or overly high requirements.<br><br>Increase in requirements does not appear to be linked to well-identified problems with existing adjuvants in currently registered vaccines and therefore appears:<br><br>1. not justified for existing adjuvants<br><br>2. a potential additional obstacle to the introduction of innovative adjuvants and vaccines.<br><br>In our opinion a clear distinction should be made between Regulatory requirements for Quality, Safety and Efficacy (the “must have”) and scientific knowledge (the “good to know”).<br><br>Also, the proposed title for the Guideline can be read as recommendations for use of adjuvanted vaccines in animals, what it is | Agreed. The comment is considered. Respective parts were shortened or deleted.<br><br>The comment is considered, and the guideline is revised accordingly. New aspects are now included.<br>The applicant can support the choice of the adjuvant making reference to other vaccines marketed in the EU containing the same or similar adjuvant<br><br>Title of GL was revised. |

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| | definitely not. “Guideline on the data requirements for adjuvants in veterinary vaccines” would appear more suitable and self-explanatory should the content be kept in the same spirit. | |
| 2. | The demands for the quality part have increased drastically, which may have implications on the research animal health companies can do. The burden of additional experiments may increase to such an extent that it is no longer feasible for a pharmaceutical company to invest into innovative veterinary vaccines or adjuvants. With this in mind, it would be good to have some flexibility and to consider that this is a guideline and not a “must comply with”. Additionally, it would be very beneficial, if well-known adjuvants would be listed as already accepted without the need for any further justification for sake of predictability. | The comment is considered, and the guideline is revised accordingly. New aspects based on the scientific development have been included.<br><br>Regarding well-known adjuvants (already used in approved veterinary vaccines) special facilities are described in several chapters of the GL. See comment above. |
| 2. | With all the described requirements for an adjuvant, it seems that it is being treated as an active substance, which it is not scientifically sound and not according to the current EU Legislation either, as its main purpose is to enhance the effect of the actual active ingredient(s). This should be considered during the process of this revision.<br><br>Related to the role of the adjuvant, while Industry is welcoming the intent of addressing the situation of immunomodulators, AnimalhealthEurope is of the opinion that immunomodulators and adjuvants should not be addressed within the same document, and | Requirements outlined are in line with Regulation (EU) 2019/6.<br><br>Immunomodulators are not in the scope of this GL. The revised version of the GL does not contain the term immunmodulator. |

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| | that for the following reasons:<br>- Adjuvants are associated with specific antigens in order to induce a specific immune response while immunomodulators are usually not intended to induce an immune response against a specific antigen and can be standalone products;<br>- (Most) adjuvants used in veterinary vaccines are well-established and studied ingredients while immunomodulators, especially those with targeted specific activity are an emerging area for Veterinary science for which scientific knowledge remains limited and experience/expertise among Regulators and Industry is so far rather limited.<br>AnimalhealthEurope is therefore recommending to remove immunomodulators from the scope of this guideline and to address this important topic as a separate Note for Guidance from IWP. | |
| 2. | Throughout the new guideline reference is often made to the manufacturing processes of the adjuvant and the blending process of the adjuvant(s) and the vaccine active substances and excipients.<br>These are two distinctively different processes and should be described separately.<br>More importantly, many pharmaceutical companies buy adjuvant(s) from third party suppliers and are thus not involved with the manufacturing process. Usually the adjuvant is received with a CoA | The comment is considered, and the description is now separate.<br>Paragraph was reworded. Content was specified and comments were taken into consideration. CoA is included. |

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| | ensuring quality/consistency and very limited other information about its manufacture. This approach was considered acceptable up to now. Additionally, not all adjuvants are manufactured, i.e. mixed, in particular if you consider aluminum salts. Overall, it is not obvious how the knowledge of this manufacturing process contributes to the safety and efficacy of the vaccine.<br><br>In our view, it should be possible to continue using current well-known adjuvants, whether these are emulsions/ mixtures or single component systems that are in use in products in the market and have shown to be safe in use without any additional laboratory work or testing or further justification.<br><br>We suggest either deleting the references to the manufacture of the adjuvant in the sections as specified in the table below (2. Specific comments on text), or to be more specific with regard to the guidance about the use of singles source material, in-house material, material supplied by a 3rd party manufacturer and the manufacturing process (keeping in mind this may create overload in variation management later on, and therefore should be avoided). Here it would be advantageous to classify the adjuvants. | See comment above. |
| 2. | The chapter regarding data requirements for Part 2 (Point 4.1) includes a paragraph about Product Development. This, however, describes information about safety and efficacy. To a certain extent there is also an overlap of the information in this part with the description of Parts | |

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| | 3 & 4. | |
| | For clarity reasons, there should be a clear distinction between Quality, Safety and Efficacy (considering also that QSE is typically assessed with the adjuvanted vaccine, not with the adjuvant alone). In order to avoid repetition of information, we suggest incorporating the paragraph about Product Development into Parts 3 and 4 as appropriate. | Chapter was reconstructed and shortened taking the comments into consideration. References to Parts 3 and 4 underline the choice of adjuvant. |
| | The guideline includes unnecessary repetitions from the current legislation (and other guidelines), such as the need for 3 vaccine consistency batches or the need to have a positive-risk benefit balance for the product. Sometimes the suggested requirements seem to go beyond the current legislation. For example, the requirement to provide extensive information on the mechanism of action of the **adjuvant** whereas the current EU Legislation refers to the following "**If possible,** the immune mechanism (cell-mediated/humoral, local/general classes of immunoglobulin) which is initiated after the administration **of the immunological veterinary medicinal product** to target animals by the recommended route of administration shall be specified and documented". To AnimalhealthEurope's understanding, the EU legislation does not require to understand (in detail) the mechanism of action of the adjuvant itself. Another example is the requirement to provide as a "standard requirement" 3 vaccine consistency batches. Even at (manufacturing) scale for emulsion-adjuvanted vaccines". AnimalhealthEurope is concerned that this deviates from the widely accepted approach to provide two 10% scale | The comment is noted. Reference to the 3 consistency batches is included for completeness. |

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| | batches and one full-scale batch for consistency. This requirement also negates the requirement for MUMS ("two pilot R&D batches" followed by one full-scale batch as post-authorization commitment). | |
| 2. | The original Note for Guidance on the use of adjuvanted veterinary vaccines included recommendations on assessment of local reactions. While such guidance is not specifically related to adjuvanted vaccines, Industry considers it quite useful, especially as no such guidance is given anywhere else in EU requirements and guidance documents, AnimalhealthEurope would therefore welcome the introduction of this guidance into, as a suggestion, the "Guideline on requirements for the production and control of immunological veterinary medicinal products" at next revision opportunity. | Noted. |
| 3. | The technical update of the guideline is clear and understandable for non-commercial adjuvants and substances. More flexibility in the requirements for documentation should be ensured for the well-established "proven" adjuvants that are already on the market and in use for many years – e.g. when a well-known adjuvant is included in a new vaccine or with a new vaccine strain. It is important that the concerns related to commercial adjuvant concepts, as described in the requirements of the draft guideline, do not cause un-intended and un-necessary hurdles for well-functioning, existing adjuvant concepts, e.g., oil-emulsions or polymer-based.<br>In the EU, there are many veterinary vaccines, where the adjuvant is supplied as a proprietary, branded product to the vaccine manufacturer as a ready-to-use or combine-with-antigen adjuvant. These adjuvants are the result of many years of research and | The comment is considered, and this aspect is reflected now in the GL. |

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| | continued development, and consequently highly commercially sensitive for the adjuvant producer. The adjuvant producer can therefore not disclose to the vaccine manufacturer the exact content, concentrations, sourcing, etc. of the adjuvant for open inclusion in the application dossier without risking his entire business. The adjuvant producer makes all necessary information on limits, tests, etc. available to the vaccine manufacturer, so it fulfils its obligations. However, the exact content and production details of the adjuvant have for confidentiality reasons always been provided by the adjuvant manufacturers directly to regulatory authorities on request. It is of utmost importance that this option is maintained and clearly reflected in the updated guideline to keep such adjuvanted veterinary vaccines available on the EU market. | |

## 2. Specific comments on text

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| 4-5 | 2. | Comments:<br>The proposed title for the Guideline can be read as recommendations for use of adjuvanted vaccines in animals, which it is definitely not.<br><br>Proposed change (if any):<br>Replace by "Guideline on the requirements for adjuvants in veterinary vaccines". | Partly accepted. Agreed to change title of GL.<br>Proposal: Guideline on the data requirements for adjuvants in vaccines for veterinary use. |
| 8 | 2. | Comments:<br>An incorrect date is given for the current "Note for Guidance on the Use of Adjuvanted Veterinary Vaccines" – It is stated that it was adopted in 1996.<br><br>Proposed change (if any):<br>The date should read 1998. | Accepted. |
| 36 | 2. | Comments:<br>Adjuvants frequently consist of several components.<br><br>Proposed change (if any):<br>It is recommended to talk about "substances or combination of substances". | Accepted. |
| 51-64 | 2. | Comments:<br>Overall, the introduction includes a definition of an adjuvant and ensures that every reader has the same understanding.<br>It is assumed that the description of the different | Not accepted. The description of the different mode of actions for the various groups of adjuvants was deleted. |

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| | | mode of actions for the various groups of adjuvants can be used as a reference in future applications even if coming from one publication and mainly in human research area (this highlights risk of very detailed data that veterinary may not be able to afford).<br><br>Proposed change (if any):<br>If there is any further known mode of action, we suggest including it as well as specifying some (categories) adjuvants as examples for the different modes of action. | |
| 51-70 | 2. | Comments:<br>Different types of adjuvants are detailed. The purpose of such detail is not clearly understood as the list is not exhaustive (e.g. carbomers are missing).<br><br>Proposed change (if any):<br>start line 51 with "typical examples of adjuvants are" | Not accepted.<br>Examples were deleted in the text. See explanation above. |
| 71-74<br>& 158-161 | 2. | Comments:<br>In the introduction it is stated that an adjuvant's activity is the result of multiple factors and active substances vary in their physical, biological and immunogenic properties, thus the modulation of the immune response obtained with one active substance – adjuvant combination cannot as a rule be extrapolated to other active substance – adjuvant combinations.<br>However, later on (lines 158-161), it is stated that to support the choice of adjuvant, reference can be made | Accepted. The paragraph was rearranged for clarity. |

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| | | to other vaccines marketed in the EU containing the same or similar adjuvant(s) and / or adjuvant components as well as similar concentration ranges. References to published literature can also be made. It should be kept in mind that by putting a lot of emphasis (for example, the current wording on the need to demonstrate that an "optimal" type of immune response needs to be elicited, as opposed to a "suitable" immune response) on this, a lot of expectations from assessors (and also developers) are created, triggering a huge amount of studies (in-vitro but also in-vivo) to validate the choices. Very often this is neither affordable for animal health industry nor desirable from a 3R principle standpoint. In this context, it is worth to remind that, in contrast to Human Health industry, Animal Health industry has the opportunity to fully validate its vaccine (adjuvant-antigen combination) efficacy in the target species, by challenge experiments. Accordingly, whereas theoretical mode-of-action considerations take place when selecting potential adjuvants during the research phase on new vaccines, it is not unusual for animal health companies to select the best adjuvant-antigen combination (out of several candidates) by side-by-side comparisons of the efficacy of the different vaccine formulations against challenge experiments. To our opinion, this information is certainly relevant and in turn reduces the need for a (complete) understanding of the mode of action of the adjuvant. | |

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| | | In our view well-established adjuvants used in products in the market should therefore be used through ways of extrapolation. Additionally, extrapolation would also contribute significantly to the support the 3R Principles (i.e. no studies required).<br><br>Proposed change (if any):<br>"As adjuvant activity is a result of multiple factors and active substances vary in their physical, biological and immunogenic properties, these parameters should be taken into account when using knowledge on the modulation of the immune response obtained with one active substance (adjuvant combination) cannot as a rule be extrapolated to another active substance (adjuvant combinations)." | |
| 75-76 | 2. | Comments:<br>The requirements of both optimal immune response and minimal adverse effects could require extensive testing and seem unrealistic in the framework of development of veterinary vaccines. Moreover, veterinary vaccines are developed on the principle of a benefit/risk balance. A balance needs to be found between the induction of a relevant immune response while. keeping a satisfactory safety profile<br><br>Proposed change (if any):<br>Adjuvants should be chosen based on the type of immune response desired and should be formulated with the active substance(s) of the vaccine in such a | Partly accepted.<br>In general, proposal was accepted to adapt text on the current conditions as described. For clarity "the optimal type of" was deleted. |

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| | | way that the optimal type of an appropriate immune response with minimal adverse effects is obtained, while ensuring the safety of the dose chosen. | |
| 81 | 3. | Comments:<br>For well-established, branded and proprietary adjuvants, it is necessary for the adjuvant producer to be allowed to not disclose the commercially sensitive details of the adjuvant production to the customer, the vaccine manufacturer, while still being fully transparent to the regulatory authority. This must be reflected in the updated guideline to avoid loss of continuous development of adjuvant science.<br><br>Proposed change (if any):<br>Please add after "…assay of adjuvant'.: Where the adjuvant is commercially available, the trade name, amount, and other non-confidential information is submitted, while any additional commercially sensitive data can be requested during the assessment phase, where necessary and provided directly by the adjuvant company to the Regulatory Authority. | Partly accepted.<br><br>These concerns are covered in the chapter for part 2. |
| 83-84 | 2. | Comments:<br>The efficacy of the final product is already addressed by requirements in the cited directive 2001/82/EC, and also in Ph. Eur. Monograph 5.2.7. This addition in the guideline seems unnecessary.<br><br>Proposed change (if any):<br>Please remove the sentence. | Not accepted.<br>However, the chapter was partly reworded. |

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| 120-121 | 2. | Comments:<br>AnimalhealthEurope cannot agree with the proposal to provide systematically the tradename of the adjuvant when it is available. AnimalhealthEurope does not believe this is more helpful for Pharmacovigilance tracking than providing a comprehensive biological/chemical name. Including adjuvant trade names in composition tables and SPCs would be an unnecessary burden to Industry when the supplier of well-defined adjuvants is being changed (examples: aluminium salts) as this would require both Regulatory variations and change of SPC/PI/PL. Moreover, tradenames may be "masking" the actual composition.<br><br>Proposed change (if any):<br>Please remove the sentence, thereby retaining the current situation. | Not accepted.<br>It refers to adjuvants where there is more than one adjuvant and / or the adjuvant(s) consists of a number of constituents. In such cases the trade name could be useful for PhV purposes. |
| 124 | 3. | Comments:<br>The proprietary adjuvants, including the specific ingredients, exact content and concentrations, the sourcing of materials, blending and all manufacture and control assays, are the result of many years of development and testing. These data are highly commercially sensitive and comprise the core of the proprietary adjuvant business. We have never revealed these data to our customers – the vaccine manufacturers – but have sent the required data directly to the Regulatory Authorities.<br>Over the years, the European authorities have | Accepted.<br>Sentence was added in the next chapter. |

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| | | demonstrated a widely based understanding of the delicate situation of confidential data in the manufacture and control of a proprietary adjuvant by accepting submission of a separate file of data.<br>The guideline currently does not specify that confidential data regarding a proprietary adjuvant in a vaccine can be submitted directly to Regulatory Authorities to keep the commercially confidential details of the adjuvant separated from the marketing authorization applicant (MAA). It is of utmost importance to maintain this situation and not to lose the proven and well-established proprietary adjuvants that are included in a variety of existing veterinary vaccines. We would like to maintain that this is an option open to all manufacturers of proprietary adjuvants, of which there are several in the world, who share this concern.<br><br>Proposed change (if any):<br>Please add: "For commercially available and proprietary adjuvants, the commercially confidential data required for the dossier may be submitted separately by the adjuvant producer upon agreement with the Regulatory Authority." | |
| 125-135 | 2. | Comments:<br>The current description on commercially sensitive information about the adjuvant as mentioned in the draft Guideline is understood by Industry as follows:<br>There is the awareness within the CVMP that some | Partly accepted.<br>It was proposed to include a separate "SPC" chapter to reflect product information issues. The chapter was shortened.<br>Guidance regarding the handling of commercially sensitive |

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| | | information is sensitive and does not need to be part of documents, which are made publicly available. This is followed by the information that the notice of applicant describes that the adjuvant should be stated where the knowledge is essential for the safe administration. On the basis of this, information about the adjuvants composition should be stated in Section 2 of the SPC for components responsible to the immune modulatory effect. Additionally, all other components without such effect should be listed in section 6.1.<br>In our view there is no clear guidance regarding commercially sensitive data and how to deal with it, so that all parties involved are satisfied. Some companies have an internal policy to not make this information public. As long as it has shown to be safe and information can be exchanged between the authority and the company, then this should be sufficient – for the animal, the user and the consumer.<br>There is still too much uncertainty about how to handle established and available ready-to-use adjuvants. This is very often subject to IP from the manufacturer and thus not all information will be available for the vaccine manufacturer.<br><br>Proposed change (if any):<br>We propose that the focus should be on the component(s) of the adjuvant, which has/have an impact of the immune response towards the antigen. If | data was included. See also comment before. |

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| | | more information is needed about the other components of the adjuvant, CoAs or EP declarations are submitted. If there are any additional questions, then this could be handled in a closed exchange between authority and manufacturer in case of sensitive IP data.<br>Generally, it should be made clear that well established adjuvants do not need extensive further laboratory work, firstly as these are well established and secondly to avoid double work at all costs (including unnecessary use of animals). | |
| 133 | 3. | Comments:<br>For commercially confidential details of the adjuvant, it should be adequate to use high-level terms such as "mineral oil" or "oil-in-water emulsion" or "polymer" instead of specific details on which mineral oil, concentrations - details that are not to be disclosed to commercial competitors. The information necessary for safe administration of the product is not linked to specific details of the composition, but to the high-level property of e.g. mineral oil or a specific polymer such as a Carbomer.<br><br>Proposed change (if any):<br>Please add after "… modulatory effect": e.g. Brand-name, oil-in-water xx ml/dose." | Not accepted.<br><br>For SPC issues an own chapter was introduced. The addition is not necessary in this context. |
| 135 | 3. | Comments:<br>Since decades, branded adjuvants with commercially confidential details have appeared with the brand | Partly accepted.<br>For SPC issues an own chapter was introduced. The |

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| | | name and amount on the SPC of authorised veterinary vaccines. There is no reason to change this, no safety issues that cannot be handled, no need for the end-user to acquire the exact components and concentrations included in the branded, composed adjuvant. On the contrary, requirements for publication of the components will hamper any further separate scientific development of adjuvants, because the innovations cannot be protected as trade secrets by the innovating company. Please maintain the current situation where the registered trade name is used as identifier.<br><br>Proposed change (if any):<br>Please add (new text in italics):<br>A qualitative listing of all the components of the adjuvant, or the registered trade name, should be given in SPC Section 6.1. | amendments were included there. |
| 139-152<br>& 259-261 | 2. | Comments:<br>In the draft guideline it is recommended that the mechanism of action of the adjuvant in combination with the active substance in the target species with the desired administration route should be described in as much detail as possible:<br>1. In what manner the adjuvant or the individual component of the adjuvant does exert its effect on the active (optimizing uptake, protection from degradation, etc);<br>2. Type of immune system triggered (innate/ adaptive, | Partly accepted.<br><br>Chapter was shortened. Details were deleted.<br>First proposal is partly added: "the following information may be provided if available."<br>Second proposal was not added as this aspect is already described similarly in this chapter. |

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| | | humoral/ cell-mediated, etc);<br>3. Type of interaction/ binding adjuvant – active (ionic, adsorption, encapsulating etc.).<br>Although these are scientifically very interesting questions, it is questionable how important this is to know for a vaccine, especially when the vast majority of adjuvants present in veterinary vaccines (including those vaccines that were registered in the recent years) have been in use for 30 or 50 years. This without talking about the fact that in some cases – aluminium hydroxide – mode of action remains essentially not know despite 50 years of scientific investigations.<br>Additionally, it should be kept in mind that the Animal Health industry is not as big as the Human Pharma industry, consequently there is less investment. The above desired information triggers a huge burden of laboratory and animal tests that may make it not feasible for a company to start a new vaccine development (see l.71-74 comments above). Many veterinary pharmaceutical companies simply can't afford to perform that level of laboratory investigations. This does not support the development of innovative solutions, nor does it take consideration into animal welfare. As a reminder, MRL regulation already slowed down new adjuvant entry in development (mainly for cost reason). This GL as currently written may increase this trend for some categories of products (where economically sensitive). | |

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| | | It is not clear to what extent this information would contribute and improve the safety and efficacy of the vaccine. In particular since the efficacy studies that have to be performed already demonstrate that the vaccine as a whole is efficacious (typically by challenge experiments).<br>Finally, the vast majority of research studies requires in vivo testing, and this is on laboratory animals. Extrapolation to other species is not as straightforward. The demonstration will be limited by target species knowledge on adjuvants mode of action and the lack of tools for immune response monitoring (blocking the investigations).<br><br>Proposed change (if any):<br>Either delete the paragraph or add the following:<br>"In order to understand the mode of action of the product, the following information may be provided if available.<br>…<br>Reference to already licensed veterinary vaccines containing the same adjuvant(s) and used under similar conditions as well as to public literature is acceptable." | |
| 151-152 | 3. | Comments:<br>The example given is not fully adequate; "For example, tests for phase separation during storage are important for vaccines containing emulsion adjuvants."<br>The emulsion adjuvants supplied by Phibro are "ready- | Not accepted.<br>Reference is incorrect. Belongs to chapter Stability. Sentence is deleted. |

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| | | to-use" and are blended gently with the antigen. Upon storage, Phibro's adjuvants show layering in vaccines but this has been documented repeatedly to be not deleterious to the vaccine efficacy and safety. The product is re-blended just by movement of the container. This statement in the guideline is targeted to water-in-oil or water-oil-water type emulsion containing vaccines that have to be homogenized with the antigen, and not relevant for all emulsion adjuvants.<br><br>Proposed change (if any):<br>Please add the word "some", i.e. "…containing some emulsion adjuvants." | |
| 154 | 2. | Comments:<br>"…giving due consideration to the mechanism(s) of action of the adjuvant and its components."<br>It is not clear how this contributes to the overall safety profile.<br><br>Proposed change (if any):<br>Delete this part of the sentence. | Partly accepted.<br>Paragraph was reworded to make the context clear. |
| 154-157 | 2. | Comments:<br>This particular part of the guideline describes several aspects, which are as follows:<br>• Safety profile of active-adjuvant combination should be provided,<br><br>-> In our view this is already covered by safety studies | Partly accepted.<br>Paragraph was reworded.<br>The "impurity" part of the sentence was deleted. |

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| | | that have to be performed for Part 3. Additionally, safety warnings are included in the SPC.<br>• The adjuvants effect on the immunogenicity of the active substance should be described<br><br>-> This relates to efficacy described in Part 4.<br>• An evaluation of interactions between adjuvant and active substance with other vaccine impurities that may cause allergic or immune responses.<br><br>-> This relates to Part 2 and 4 and involves a heavy laboratory burden and is not feasible.<br><br>Proposed change (if any):<br>For the sake of clarity for the reader, a clear distinction should be made between, quality, safety and efficacy related topics.<br>This cited part of the guideline should be deleted or partially deleted by removing the last part "…including impurities should be considered." | |
| 157-158 | 2. | Comments:<br>Risk mitigation is part of the SPC and thus already investigated for the product. This is also continuously monitored and evaluated as part of the pharmacovigilance system. | Partly accepted.<br>Paragraph was reworded. |
| 160 | 2. | Comments:<br>The restriction to data evaluated in the EU is not in line with the will of Regulatory harmonisation across the world. Data coming from different sources should be | Accepted.<br>Sentence was reworded. Chapter was re-arranged for clarity. |

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| | | evaluated to facilitate introduction of innovating combinations.<br><br>Proposed change (if any):<br>To support the choice of the adjuvant, its mechanism of action and expected safety profile of the proposed active substance(s) - adjuvant combination reference can be made to other marketed vaccines in the EU containing the same or similar adjuvant(s) and / or adjuvant components and to published literature. | |
| 162-167 | 2. | Comments:<br>The consideration of increased concentration of adjuvant and/or active substance relates mainly to the safety profile of the combination.<br><br>Proposed change (if any):<br>Regarding the safety profile, reference to and reliance on publicly available information may not be adequate where the concentration of the adjuvant and / or active substance(s) is higher than in IVMPs authorised to date […] | Accepted. Chapter was re-arranged (and shortened) for clarity. |
| 168-170 | 2. | Comments:<br>It is proposed to remove this paragraph as this is unnecessary repetition of already existing requirements. | Accepted. |
| 176 | 2. | Comments:<br>As well as exact composition, the manufacturing process of the adjuvant can be proprietary information of the supplier and may not be available to the vaccine | Partly accepted.<br>Paragraph was reworded. The proposal to include a possible third party manufacturer for the adjuvant was taken in consideration. |

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| | | manufacturer. Thus, a detailed description of this process may not be possible.<br>It is therefore proposed to make a distinction between the production of the adjuvant that may or may not be conducted by the vaccine manufacturer and the blending of the adjuvant and the vaccine that is in all cases conducted by the vaccine manufacturer.<br>For the production of the adjuvant, a detailed certificate of analysis (for adjuvant from external suppliers) or a summary of information (for home-made adjuvants) should be provided.<br>For the blending of the adjuvant and the vaccine, description of the critical steps should be provided.<br><br>Proposed change (if any):<br>The critical steps involved in the manufacturing processes of the adjuvant(s) should be described whenever available. Alternatively, when adjuvant is obtained from a third-party manufacturer, an example of a comprehensive certificate of analysis should be provided, together with the corresponding specifications.<br>The critical steps involved in the manufacturing processes of the adjuvant(s) and blending of the adjuvant(s) and the vaccine active substance(s) and excipients should be described.<br>Critical steps / parameters in the production and mixing processes considered important for association of the active substance(s) and the adjuvant(s) and / or | |

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| | | adjuvant component(s) should be outlined. For example, for oil-based adjuvants, the description of the emulsification process should include details such as the process scale and size and type of equipment used, temperature, duration, speed, pH adjustment and any critical parameters for successful formation of the emulsion. Details of the sterilisation conditions for the adjuvant(s) / adjuvant components should also be provided for each stage of production to the final product. | |
| 185-189 | 2. | Comments:<br>It is proposed to remove this paragraph as this is unnecessary repetition of already existing requirements. | Accepted. |
| 191-192 | 2. | Comments:<br>In many cases the detailed composition of adjuvants is not known. It is therefore recommended to focus on those materials that may be of concern, typically animal origin materials. In addition, this is already part of normal requirements for materials used in manufacturing.<br><br>Proposed change (if any):<br>Delete this sentence or replace by the following:<br>„Details of the source of the adjuvant(s) and each of the adjuvant components where relevant (e.g. of chemical or biological origin) should be given whenever possible, when of animal origin. “ | Partly accepted.<br>Paragraph was reworded. Content was specified and comment was taken into consideration. |

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| 193-196 | 2. | Comments:<br>In general, all excipients, which are in the final product or are used during the manufacturing process, have according to the European Pharmacopoeia to be tested and be compliant with requirements. This is routinely done and the manufacturer documents this in CoAs (and COPs, if necessary). Thus, there should not be the need for justification. Moreover, some parameters proposed can be completely irrelevant (example: adsorptive properties of adjuvants when in the case of many veterinary vaccines unpurified antigens are being used).<br>With this extended demand for detailed information, a lot more detail has to be registered. Additionally, adding this amount of detail will eventually create more variations, which we currently observe to be and become even more a heavy administrative burden.<br><br>Proposed change (if any):<br>Please delete this paragraph. | Accepted. |
| 207-210 | 2. | Comments:<br>This part of the guideline states "A description of the tests applied as controls for the critical steps/parameters in the production of the adjuvant(s) and /or mixing with the active substance(s) and excipients to guarantee the consistency and integrity of the adjuvant in routine vaccine batches should be given."<br>Proposed change (if any): | Accepted. |

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| | | We would like to exchange the wording "integrity" as this leaves too much room for interpretation and to use "quality" instead:<br>A description of the tests applied as controls for the critical steps/parameters in the production blending of the adjuvant(s) and /or mixing with the active substance(s) and excipients to guarantee the consistency and integrity quality of the adjuvant in routine vaccine batches should be given." | |
| 211-213 | 2. | See comments above in section 1 regarding the manufacturing processes of the adjuvant and the blending process of the adjuvant(s) and/ or the vaccine active substances and excipients. | Accepted.<br>Paragraph was deleted. |
| 220-225 | 2. | Comments:<br>In AnimalhealthEurope's opinion, it is not really the purpose of the adjuvants GL to discuss 3Rs. It should be clarified that replacing in-vivo methods by in-vitro ones is only possible once in-vitro methods are available for both the active ingredient(s) and the adjuvant.<br>Moreover, the principles of 3Rs do not exclude the possibility to use alternative in vivo testing, at the condition that they contribute to the reduction or refinement of existing tests. Furthermore, the status of serology is not clear in this statement. Indeed, the use of serology often constitutes a good alternative to existing in-vivo potency tests conducted by challenge.<br><br>Proposed change (if any): | Partly accepted.<br>Paragraph was reworded. |

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| | | … the continued use of in-vivo potency tests simply on the basis that they support the performance of the active ingredient–adjuvant combination is no longer considered an adequate justification for not developing either alternative in-vitro tests for IVMPs (when alternative methods can be developed for both the adjuvant and the active ingredient(s)), or improved in vivo or serological tests. | |
| 226-231 | 2. | Comments:<br>Interferences from other components is not the only reason why quantification of the adjuvant cannot be achieved, the same applies when the adjuvant is present in low concentrations in the vaccine.<br>Moreover, situations where it is difficult to quantify the adjuvant and/or its components in the vaccine formulation due to interference from other components are not exceptional in veterinary vaccines.<br><br>Proposed change (if any):<br>"It is recognised that there may be situations where it is difficult to quantify the adjuvant and / or its components in the vaccine formulation due to interference from other components of the vaccine formulation or to the low concentration of the adjuvant in the formulation. In exceptional circumstances, and only When a suitable justification can be given, alternative approaches may be acceptable e.g. quantification of the adjuvant(s) and / or its components in the solution prior to addition to the | Partly accepted.<br>Paragraph was reworded. The additional aspect was included. |

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| | | active substance(s) during blending to confirm that the correct amount of adjuvant is added to the vaccine blend." | |
| 239 | 2. | Comments:<br>Comparability between routine and clinical trial batches is not specific to adjuvant(s) and is already addressed in existing requirements.<br><br>Proposed change (if any):<br>Please delete the paragraph. | Accepted.<br>Whole paragraph was deleted. |
| 249-252 | 2. | Comments:<br>It is described in the guideline that the stability of the adjuvant should be monitored throughout the shelf-life of the vaccine. Overall, this is a reasonable proposal and many tests are already performed and are typically part of the dossier – to the extent that is possible. The current text of the draft guideline should be changed, in line with comments made above (1. On the possibility to continue using in vivo testing where appropriately justified, 2. On the wording "integrity" of the adjuvant, and 3. On the need to focus on the components responsible for the adjuvant effect, as opposed to components that may be included in the adjuvant composition, but that are not likely to display an adjuvant effect, such as emulsifiers, stabilizers, …).<br><br>Proposed change (if any):<br>As the investigated stability is regarding quantity and | Accepted. |

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| | | quality, we propose to change as follows:<br>"During the stability studies on the vaccine, appropriate qualitative and / or quantitative tests, preferably in-vitro tests should be performed to support the integrity of the adjuvant…"<br>to<br>"During the stability studies on the vaccine, appropriate qualitative and/ or quantitative tests, preferably in-vitro tests should be performed to support the integrity for the adjuvant and its components throughout the shelf life of the vaccine."<br>As commented above this would be in line with the current testing with sufficient testing of the adjuvant ensuring its desired effect. | |
| 259-261 | 2. | Comments:<br>Requirements for safety studies for veterinary vaccines are well defined and addressed in current guidelines and legislation. Taking into account the mode of action of the adjuvant is not considered relevant (in addition to the current requirements) for the design (monitoring) of the safety studies. The current wording opens the door to uncertain outcome in the assessment and should be avoided. What is more relevant is to take into account any known issues (clearly) associated with a known adjuvant (in case the same adjuvant is to be used) in the design of the safety studies. This is more the exception than a general rule, and the text should reflect this (if the paragraph is kept). | Accepted.<br>Last sentence was slightly shortened. |

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| | | Proposed change (if any):<br>It is suggested to remove this paragraph, or alternatively to reword as follows: "Ph. Eur. 5.2.6 requires the animals used in the safety studies to be examined 'for signs of local and systemic reactions' when the vaccine is given by 'each of the recommended routes of administration'. The safety of the adjuvanted vaccine in the target animals should be addressed in line with the relevant target animal safety guideline (VICH GL44). Exceptionally, where relevant, the adverse reactions follow-up criteria monitored in the vaccine target animal safety studies should be adjusted to take into consideration potential safety concerns previously associated with the adjuvant. the mechanism of action of the adjuvant and its interaction with other vaccine components as discussed in the Product Development section of the dossier. | |
| 265-284 (MRL) | 2. | Comments:<br>Regarding vaccines for food producing animals, user safety has become more a focal point and thus it seems like a natural consequence that MRL requirements are of increasing importance.<br>From the description in the guideline, it is understood that if an adjuvant has a no MRL requirement classification or is on the list of "out of scope" substances, then there is no need to file/ disclose more data/ information. The same is valid, if it can be shown that the substance has no pharmacodynamic activity at the dosage used in the final product. If this can be | Partly accepted.<br>The paragraph containing Lines 283-284 was deleted.<br><br>The proposed short and to-the-point message was not accepted. It was considered necessary to give some more information in the text regarding the MRL status, but the chapter was shortened in general. |

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| | | shown, then it should be sufficient evidence without having to consult with an authority, which also is combined with a time and cost burden.<br>Adjuvants that are a component in already established products should explicitly be exempted as these have been shown to be safe for animal, user and consumer.<br>It seems a long-detailed text for describing what is already done and existing as normal management of MRL and substances. This duplication of place where it is described creates a feeling of additional needs due to the nature of the adjuvant, which should not be.<br><br>Proposed change (if any):<br>Delete l. 283-284<br>and include a short and to-the-point message:<br>If an adjuvant has a no MRL requirement classification, is on the list of "out of scope" substances or has no pharmacodynamic activity at the dosage used in the final product, then no further actions need to be taken. Additionally, there is no need to file an MRL application or submit additional data for established adjuvants that have been used in already marketed products. | |
| | | Comments:<br>As a final remark we would like to suggest the following:<br>If there is this demand for more information about the adjuvant's quality (one component systems and mixtures), then it could be considered to ask the manufacturer to provide information in a Certification | Accepted.<br>Further consideration. Not relevant for the current GL. |

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| | | procedure similar to the Certification of Suitability with the EDQM. Hereby adequate information about quality and impurity could be determined (e.g. manufacturing process, tests performed on raw materials and in-process controls) between the EDQM and the manufacturer and hereby avoiding the risk of exposing IP and also further testing by the vaccine manufacturer. It would save time and resources. | |
| 306-310 | 2. | Comments:<br>See General comments section<br>Proposed change (if any):<br>Please remove the definition of immunomodulator. | Accepted. Deleted. |