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Position paper

18 October 2019

AnimalhealthEurope comments to the Scientific recommendation on the revision of Annex II to Regulation (EU) 2019/6 on veterinary medicinal products

EMA Advice on implementing measures under Article 146(2) of Regulation (EU) 2019/6 on veterinary medicinal products

1. General Comments

AnimalhealthEurope welcomes the opportunity to provide comments on the EMA advice. There are significant changes advised that the industry welcomes, such as the potential to expand the multi-strain dossier concept, the inclusion of the concept of "vaccine platform technology" and the expanded guidance on the VAMF.

We do have concerns on some other points, and these are discussed below.

Save the details for the guidelines

AnimalhealthEurope strongly supports the approach not to put detailed technical regulatory requirements in this Annex especially for novel therapies. The annex should contain high level guidance on ensuring Quality, Safety and Efficacy and details should be reserved for more adaptable texts (e.g. Q&A or guidelines from the EMA).

Whilst an annex in a delegated act can be updated more easily than the text of Regulation itself, such updates are not done often, and the need for such updates should be avoided if possible. With the current rate of evolution in techniques and novel therapies having too much detail in this annex may create possible hurdles or barriers in the future. This does not appear to be fully aligned with introductory remarks on page 3 (article 146 and recital 92).

Fitness check for impact on the objectives

Two objectives of the new regulation were to reduce administrative burden and to promote innovation, and an assessment should be made of the impact of all proposals on these objectives. Unfortunately, we believe that some of the proposed changes to the annex will either increase administrative burden, unnecessarily increase requirements or inadvertently block innovation due to the wording used. This is explained further in our specific comments below.

Novel therapies

We appreciate the effort made by the EMA to provide some predictably for novel therapies whilst maintaining the necessary flexibility for such an innovative area. But we believe that it is too early to include the detailed requirements present in the EMA advice for some

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of the categories of novel therapies. There is not yet sufficient experience to assess the relevance or need in the veterinary sector.

Although more experience is available in the human sector it is important to remember that whilst there are a lot of similarities there are also significant differences. Not all requirements on the human side will be applicable or proportionate to the veterinary side. Within AnimalhealthEurope an early proposal was prepared in this spirit (attached).

Therefore, we would urge that detailed information is not included in the Annex II, as proposed by the EMA advice, and this detail is left for the development of Q&As by the ADVENT group in the first instance and then EMA/CVMP guidelines when the veterinary sector experience has become sufficient.

European Pharmacopoeia risk-based approach

The European Pharmacopoeia is moving towards a risk-based approach to demonstrate the absence of extraneous agents, but this is not fully reflected in the Annex proposed in the EMA advice.

In general, we believe it is a better approach to reference European Pharmacopoeia monographs and general chapters and not repeat the requirements in Annex II.

Consistent terminology

Throughout the document, harmonised terms should be used: the Regulation defines "studies", and thus this term should be used rather than "trials" or "tests" or "experiments".

Reference to specific guidelines

In the various sections of the safety file reference is made to VICH guidelines. As a consequence, these guidelines become part of the Regulation and must be strictly followed. The VICH guidelines are adopted and published by the CVMP. In the INTRODUCTION AND GENERAL PRINCIPLES on page 12, paragraph 2, it already states

"In assembling the dossier for application for marketing authorisation, applicants shall also take into account the current state of veterinary medicinal knowledge and the scientific guidelines relating to the quality, safety and efficacy of veterinary medicinal products published by the Agency and the other pharmaceutical Union guidelines published by the Commission in different volumes of The rules governing medicinal products in the European Union."

Therefore reference to the specific VICH guidelines is not necessary in this high-level document. This level of detail can be reserved for the Notice to Applicants.

VNees structure

Finally, the structure of the new annex creates different numbering which impacts the VNees structure; with the very rigid approach imposed by the IT automated checker this will create issues when working on existing dossiers or the use of existing documentation. This adds significantly to the administrative burden. We request that the existing structure and numbering is retained.

2. Specific comments

In the table below the original text from the EMA advice is shown in blue-italic font.

Page Number	Comment
12	*Introduction, point 1* Reference to Eudralex Notice to Applicants Volume 6B is made. It is acknowledged that on page 4, it is stated that the existing NtA will need to be revised. During that revision, it should be aimed at making Eudralex Volume 6B a document of additional help for applicants. The current version is an exact copy of the text of Directive 2009/9.
12	*All information which is relevant to the evaluation of the veterinary medicinal product concerned shall be included in the application, whether favourable or unfavourable to the product. In particular, all relevant details shall be given of any incomplete or abandoned test or trial relating to the veterinary medicinal product.* Having to provide all data (e.g. invalidated studies, early development studies) would greatly increase the amount of dossier content without providing information valuable to the assessment. We would propose to add only the pivotal data and critical development data which lead to the major conclusions to avoid unnecessary administrative burden.
12	*For veterinary medicinal products, all relevant monographs of the European Pharmacopoeia, including general monographs and the general chapters, are applicable for the appropriate part(s) of the dossier* **Proposed change:** For veterinary medicinal products, **with respect to the Quality part of the Dossier**, all relevant monographs of the European Pharmacopoeia, including general monographs and the general chapters, are applicable for the appropriate part(s) of the dossier **Rationale:** The addition of text to clarify for pharmaceutical products.
12	*Pharmacological, toxicological, residue and pre-clinical safety tests as well as laboratory studies for biological and or immunological veterinary medicinal products shall be carried out in conformity with the provisions related to Good Laboratory Practice (GLP) laid down in Directive 2004/10/EC of the European Parliament and of the Council and Directive 2004/9/EC of the European Parliament and of the Council.* **Proposed Change:** Pharmacological, toxicological, residue and preclinical safety tests as well as laboratory **safety** studies on target animals for biological or immunological veterinary medicinal products shall be carried out in conformity with …. **Rationale:** Laboratory studies for biological and immunological veterinary medicinal products can be for efficacy, and for these a mandatory GLP standard is not appropriate. Other more appropriate quality systems should be used. For laboratory target animal safety studies, reference to GLP is in line with current legislation and is appropriate.
12	*All experiments on animals shall be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the experiments.* **Proposed Change:** All ~~experiments~~ **new pre-clinical studies** on animals ~~shall~~ should be conducted taking into account the principles laid down in Directive 2010/63/EU, notwithstanding the place of conduct of the ~~experiments~~ **studies**. **Rationale:** The term “experiments” is not clearly defined in the regulation or annex and should therefore be avoided. It should be noted that “clinical studies” are exempt from Directive 2010/63/EU and this should not be changed. Excluding any studies, even bibliographic studies, conducted outside the EU or having been conducted prior to the implementation of Directive 2010/63, appears overdone, as this leads to further

	unnecessary studies to be conducted, which in itself is against the spirit of Directive 2010/63. We would therefore propose to rephrase to "all new pre-clinical studies" to be conducted by the applicant.
13	The DACS are generally considered to be less critical. When CTD is applied already the critical expert report is replaced by a Quality overall summary (which is something different). Suggest replacing DACS by summaries and remove the need for expert signatures.
13	Please insert: **10. In cases of applications for marketing authorisations for veterinary medicinal products where Scientific Advice has been obtained from the Agency, the relevant data requirements set out in the following titles can be replaced by the specific data requirements agreed by the Agency as part of the Scientific Advice.**
13	Please insert: **11. All studies intended to support the marketing authorisation are conducted taking into account existing guidelines such as VICH or others, as appropriate.**
13	*The critical expert reports shall be **signed** and dated, and …* This should cover both 'wet' signatures and e-signatures as document management systems are often used for the preparation of such reports and for the compilation of e-submissions.
13	*For Parts 3 and 4 the critical expert report should also include a tabulated summary of all technical documentation and relevant data submitted* In contrast to Dir 2009/9 ("… **whenever possible** in tabular or graphic form") more emphasis is placed on providing tabulated summaries of all technical documentation and relevant data. It is proposed to keep the previous (current) wording to prevent redundancies and allow flexibility. We should also underline that the usefulness of such a document (redundant with the summaries already prepared by the applicant for an easy understand of development data) is disputable and the additional administrative burden adds to the cost and delay in the already long development timeline. **Proposed change: Whenever possible f**For Parts 3 and 4 the critical expert report should also include a tabulated summary of all technical documentation and relevant data submitted
14	As the format presented in the Notice to Applicants is currently used to define the VNEES electronic format of dossiers, it is strongly suggested to leave the format and headings unchanged in order to avoid unnecessary administrative burden.
16	Please see comment to pages 38 and 60 regarding interactions with primary packaging**.**
17	*Where a certificate of suitability is referred to, the manufacturer shall give an assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability by the European Directorate for the Quality of Medicines and HealthCare.* Please delete this requirement as the assurance required is included in the certificate. By signing the 'box of access' of the certificate, the CEP holder also certifies that no changes to the operations as described in the CEP dossier have been made since the granting of the latest version of the CEP. This is additional administrative burden that serves no purpose.
20	Please insert in "2. Excipients" (before paragraph on novel excipients) the following (extracted from the AnimalhealthEurope position paper on Annex II) **Excipients used in oral dosage forms may alternatively comply with the appropriate food or feed legislation.**

20	*For novel excipients, that is to say excipient(s) used for the first time in the European Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to support both clinical and non-clinical safety data, shall be provided. For colouring matters the declarations of compliance above shall be considered sufficient.* **Proposed modification** 'An excipient used for the first time in a ~~veterinary~~ medicinal product ~~or by a new route of administration~~ shall be treated like an active substance **unless justified**. **When used by a new route of administration, the excipient shall be treated like a new active substance unless otherwise justified**. **Rationale**: The previous use in human medicine can, in most cases, provide sufficient assurance of the safety of the concerned excipient. Depending on the route of administration sufficient assurance of the safety of the excipient may be provided by the existing route.
20	*3.2 Finished product* The plastic packaging material guideline also gives the option (for solid oral and topical dosage forms) to use material that is just compliant to the food regulation. That possibility is missing here. Please add the following (extracted from the AnimalhealthEurope position paper on Annex II): **For oral and topical dosage forms packaging materials may comply with the relevant food regulation.** Additionally, it would be appropriate to include a definition of "novel packaging materials".
22	Part 2 E2: In the current Notice to Applicants a paragraph for shelf life was included, please reinstate this paragraph. "Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ±5% at the time of manufacture. **On the basis of the stability tests, the manufacturer shall propose and justify maximum acceptable deviation limits in the active substance content of the finished product up to the end of the proposed shelf-life."**
23	*Part 2.E.6* *In order to ensure the quality of the product is consistent from batch to batch and to demonstrate conformity with the specification, batch data shall be provided giving the results for all tests performed on 3 batches manufactured at the proposed manufacturing site(s).* **Comment:** This introduces a new requirement to provide in the dossier batch data on batches manufactured at the proposed manufacturing site, independent from formulation and manufacturing procedure. This will as a result significantly extend the time to market for new veterinary medicinal products. The wording should be revised. **Proposed change: "**In order to ensure the quality of the product is consistent from batch to batch and to demonstrate conformity with the specification, batch data shall be provided giving the results for all tests performed on 3 batches manufactured ~~at the proposed manufacturing site(s)~~ **according to the described production process and on products packed in the final container(s)."**
24	*Additionally, for veterinary medicinal products intended for incorporation into feed, information shall be provided on the stability and the proposed shelf life of the medicated feed. A specification for the medicated feed, manufactured using these veterinary medicinal products in accordance with the recommended instructions for use shall also be provided.* **Proposed modification:** 'Additionally, for veterinary medicinal products intended for incorporation into feed, information shall be provided on the stability and the proposed shelf life **after incorporation into feed** ~~of the medicated feed~~. ~~A specification for the~~

	~~medicated feed, manufactured using these veterinary medicinal products in accordance with the recommended instructions for use shall also be provided'.~~ **Rationale:** The proposed inclusion of a specification for medicated feed into the dossier does not seem to be a realistic expectation. Medicated feed is defined as a feed, ready to be directly fed to animals, consisting of a homogeneous mixture of one or more veterinary medicinal products with feed material or compound feed. The MA-holder is responsible for the quality of the veterinary medicinal products (ex. Premix for medicated feed) but has no oversight on the manufacture of medicated feed which will usually be done at a feedmill or other feed business operators. The manufacture of medicated feed is performed by feed business operators and quality will be controlled in accordance with Regulation 2019/4 and specific national regulations from the member states.
25	*...the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects **in target species** which may occur under the proposed conditions of use*; **Comment:** It is not the aim of Part 3A to assess in detail undesirable effects in **target species**. Only a summary of TAS data is provided in order to assess whether additional toxicological endpoint may need to be considered for human safety. The text of the former annex better reflects this: "…the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in **animals**; these should be …" Comment that the potential toxicity of the veterinary medicinal product and any dangerous or undesirable effects which may occur under the proposed conditions of use in animals should be evaluated in relation to the severity of the pathological condition concerned through the benefit risk assessment, benefit risk assessment not mentioned in the recommendation.
25	*For novel excipients, that is to say excipient(s) used for the first time in the European Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to support both clinical and non-clinical safety data, shall be provided. For colouring matters the declarations of compliance above shall be considered sufficient.* **Proposed modification** 'An excipient used for the first time in a ~~veterinary~~ medicinal product ~~or by a new route of administration~~ shall be treated like an active substance **unless justified**. **When used by a new route of administration, the excipient shall be treated like a new active substance unless otherwise justified**. **Rationale**: The previous use in human medicine can, in most cases, provide sufficient assurance of the safety of the concerned excipient. Depending on the route of administration sufficient assurance of the safety of the excipient may be provided by the existing route.
27	*Repeated-dose toxicity tests are intended to reveal (...) induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to the dosage* **Proposed change:** "Repeated-dose toxicity tests are intended to reveal (...) induced by repeated administration of the ~~active~~ substance ~~or combination of active substances~~ under examination, and to determine how these changes are related to the dosage" **Rationale:** harmonisation with "3.1. Single-dose toxicity" and use of the general term "substance(s)" as the notion of "combination of substances" is indicated in the introduction 3. Toxicology. "(...) Generally, toxicology studies shall be conducted with the active substance(s) (...) ."

27	The notion of reproductive safety studies in case of use in breeding animals (VICH GL43) should be mentioned in the section 3.3. Tolerance in the Target Species.
27	*For the evaluation of user safety, standard developmental toxicity testing in accordance with VICH GL32 shall be performed (...).* **Proposed change:** "For the evaluation of user safety, standard developmental toxicity testing in accordance with standard tests based on established guidances (e.g. VICH GL32, OECD tests etc) shall be performed (...)." **Rationale:** The VICH GL32 concerns studies to evaluate the safety of residues of veterinary drugs in human food. More generalist standards should be proposed to select the most appropriate on case-by-case for drugs intended to be used in non- or food producing species.
28	*A standard battery of genotoxicity tests in accordance with VICH GL 23 shall usually be carried out on the active substance(s)* **Proposed change:** "A standard battery of genotoxicity tests in accordance **with standard tests based on established guidances (e.g. VICH GL23, OECD tests etc)** shall usually be carried out on the ~~active~~ substance(s)" **Comment:** Withdraw the notion of "active" substance as in the introduction it is indicated that the active substance, metabolites or a new excipient could be considered. The VICH GL 23 concerns studies to evaluate the safety of residues of veterinary drugs in human food. More generalist standards should be proposed to select the most appropriate on case-by-case for drugs intended to be used in non- or food producing species.
28	*Carcinogenicity testing should be conducted according to VICH GL28* **Proposed change:** "Carcinogenicity testing should be conducted according to **standard tests based on established guidances (e.g. VICH GL28, OECD tests etc.)**" **Comments:** The VICH GL 28 concerns studies to evaluate the safety of residues of veterinary drugs in human food. More generalist standards should be proposed to select the most appropriate on case-by-case for drugs intended to be used in non- or food producing species.
28	3.7 Exceptions **Rationale:** AnimalhealthEurope firmly believes that in line with the 3Rs principles scope should be made for othr exceptions when justified. **Proposed Change:** Please add the following sentence **In order to prevent the unnecessary use of animals other exceptions may be made on a case by case basis, for example basic toxicology data may be omitted for active substances widely used in human medicines in the Union.**
29	**4.2 Observations in humans** This should be limited to published data. As the applicant may not have access to all the respective data on products approved for human use or in clinical testing.
29	*Resistance in the environment shall be addressed.* **Rationale:** The CVMP 'draft Reflection paper on antimicrobial resistance in the environment' came to the clear conclusion that data on AMR in the environment cannot be requested from applicants at the moment because no assessment guidance can be given. **Proposed Change**: Please delete this sentence.
30	*For products intended for food producing species persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances should be*

	classified according to the criteria in Annex XIII of the REACH regulation (Regulation (EC) No 1907/2006) and assessed according to the guidance for PBT assessment of veterinary medicines published by the Agency **Proposed changes: "**For products intended for food producing species persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances should be classified ~~according to the criteria in Annex XIII of the REACH regulation (Regulation (EC) No 1907/2006)~~ and assessed according to the Agency guidance for PBT and vPvB assessment of **active substance(s) in** veterinary medicines ~~published by the Agency~~ **Comments:** The EMA guideline on PBT and vPvB assessment of active substances in veterinary medicinal products defines the criteria to identify such substances and how to perform their assessment using the REACH regulation. Therefore, referring to only one guidance is sufficient and easier to understand.
32	*… of the veterinary medicinal product in the target species, particular if this concerns a new substance or formulation.* **Rationale:** Typographical error. **Proposed Change:** …, **in** particular if …
32	*Where a higher activity is being claimed for an active substance, the difference shall be demonstrated and shown to be statistically significant.* **Comment**: a similar sentence was already included in the Directive 2001/82/EC. The exact meaning is however unclear: 'higher' in comparison to what?
32	*– to compare bioavailability to support bridging of safety and efficacy information between different products, pharmaceutical forms, strengths or routes of administration, or to compare the impact of changes in manufacturing or composition.* **Proposed changes: "**– **where appropriate**, to compare bioavailability to support bridging of safety and efficacy information between different products, pharmaceutical forms, strengths or routes of administration, or to compare the impact of changes in manufacturing or composition." **Comment:** addition of text for clarifications.
33	*For formulations intended for use in veterinary clinical trials, the words "for veterinary clinical trial use only" shall appear prominently and indelibly on the labelling* **Proposed change:** "For formulations intended for use in veterinary clinical trials **in the European Union**, the words "for veterinary clinical trial use only" shall appear prominently and indelibly on the labelling" **Comment:** The labelling should comply with local requirements where the study is conducted. As an example, in the US, the wording should state: 'contains a new animal drug for use only in investigational animals in clinical trials.'
34	*Experimental data shall be confirmed by clinical trials, unless otherwise justified.* **Comment**: a similar sentence was already included in the Directive 2001/82/EC. No definition of 'experimental data' is provided. If 'experimental data' has the same meaning of 'exploratory/pilot trial' as per EMA/CVMP/EWP/81976/2010 (studies that indeed are followed by 'confirmatory/pivotal trials') then it would be helpful to amend as proposed below. Additionally as new tools such as computer modelling, for instance, PK/PD modelling become more widely accepted scope should be provided for their use when followed by confirmatory/pivotal studies. **Proposed Change:** 'experimental data, **such as 'exploratory/pilot trials**, **or results from non-experimental approaches** shall
34	*The purpose of clinical trials is to examine under field conditions the target animal safety*

	and efficacy of a veterinary medicinal product under normal conditions of animal husbandry and/or as part of good veterinary practice... **Comment**: The above is the purpose of field clinical trials. Dose confirmation studies (which are defined in various context as 'clinical' studies) can be also conducted under laboratory conditions and do not represent the 'normal conditions of animal husbandry'.
34	**Entire section 2.1 'results of pre-clinical studies'** This is a subsection of the 4B 'Clinical Trials'. **Proposed Change:** It is proposed to move this section under 4A 'Pre-clinical requirements' in order to have all the requirements for pre-clinical data under the same section.
35	*Finally, the investigator shall draw general conclusions on the efficacy and target animal safety of the veterinary medicinal product under the proposed conditions of use,* **Proposed Change:** Finally, the **author of the report** ~~investigator~~ shall draw general **Rationale:** For multicentric studies there are multiple investigators**.**
37	*Any special apparatus and equipment, which may be used, shall be described in adequate detail, possibly accompanied by a diagram.* **Proposed Change**: please delete this sentence. **Rationale:** Any specific descriptions of apparatus should not be included in detail in the dossier. Any slight change would require then a variation of the dossier. Appropriate validation of equipment is a GMP requirement and should be covered there.
37 (IIa) **39 (IIa)** **59 (IIb)**	*The list of organisms handled at the production site shall be given.* **Proposed Change**: please delete this sentence. **Rationale:** There is a mix here between data on the product to get the MA and on the conditions at site level qualified by the GMP accreditation/regular inspection. This request is linked with the site GMP compliance and not with the quality, safety or efficacy of the product. This would mean that both production sites as well as the organisms handled at the proposed production sites would be included in Part 2 of the dossier. Consequently, any change in relation to these aspects (for instance introduction of a new organism at production site A) would require a variation dossier. This doesn't appear to be in line with the aim of reducing the administrative burden.
38 (IIA) **60 (IIB)**	*a study of the interaction between finished product and the primary packaging shall be submitted wherever the risk of such interaction is regarded as possible, especially where injectable preparations are concerned*; **Rationale:** the requirement for an "interaction study" seems to be directly derived from "pharmaceuticals" (*id est*, non-biologicals), and (as suggested in the wording) may not be relevant for biological products. Such a study is not always technically feasible depending on the product. Certainly, it has not been a regulatory requirement for IVMPs for decades, and this has been accepted as such (without any issue, to AnimalhealthEurope's knowledge). **Proposed change:** please remove the proposed additional requirement as this will be considered for individual products when needed by nature of the concerned component/packing.
39	*Usually, the biological activity should be determined using an appropriate, reliable and qualified method..* **Proposed change:** "Usually, the biological activity should be determined **or evaluated** using appropriate, reliable and qualified method**s**." **Comment:** a combination of several methods can be used to evaluate the biological activity and in particular when in vitro testing are developed instead of an in vivo test

	(3R approach).
40 (IIa) **61 (IIb)**	*list of in-process controls including the stage of manufacture at which they are conducted and acceptance criteria;* Indicating the IPC's and the stages at which they are performed makes sense. This is less the case for the acceptance criteria, which are indicated in section 2.D. (unnecessary repetition of text and therefore additional administrative burden).
40 (IIa) **61 (IIb)**	*Antibiotics used during production and preservatives should be used in compliance with the European Pharmacopoeia.* **Comment**: Pharmacopoeial quality on antibiotics and preservatives used during production of starting materials for biological veterinary medicinal products (immunological and other than immunological) should refer to final culture for production of active ingredient. It should not apply to the single generation MCB/Master Seed, that are not considered as part of production, and which are largely diluted during all production steps. This level of detail is best placed in guidelines or monographs were the terms are well described. An annex to a regulation is a too strong regulatory text and, without proper definitions, it may create later misunderstanding and/or wrong expectations. The requirement (if not fine-tuned – see further explanation above) does not add to the quality of the final product.
40 (IIa) **62 (IIb)**	*For novel excipients, that is to say excipient(s) used for the first time in the European Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided. For colouring matters the declarations of compliance above shall be considered sufficient.* **Proposed Change:** "For novel excipients, that is to say excipient(s) used for the first time in the European Union in a veterinary medicinal product or by a new route of administration, details of manufacture, characterisation, and controls, with cross references to supporting safety data, both clinical and non-clinical, shall be provided. **For complex or novel excipients and adjuvants, data may be submitted by the excipient or adjuvant manufacturer using a master file concept similar to the provisions laid down for active substances in 4.A.1, Vaccine Antigen Master File.** For colouring matters the declarations of compliance above shall be considered sufficient." **Rationale:** The inclusion of a possibility to submit commercially sensitive data for complex or novel excipients and adjuvants via a direct route to Authorities could be made in a robust way by allowing these substances to use a master file system similar to the provisions laid down for active substances in 4.A.1, the Vaccine Antigen Master File system. This would provide a framework where complex or novel excipients and adjuvants could be assessed by the competent authority without the manufacturer of the adjuvant having to reveal manufacturing details, including proprietary ingredients, to the vaccine producer. European authorities have so far tried to handle the delicate situation of proprietary information in the manufacture and quality control of a proprietary adjuvant by accepting the use of trade names in the dossier and the separate submission of confidential data directly to the Regulatory Authorities on request, but this is increasingly difficult. This should be accompanied by adaptation of the SPC requirements of the EMA templates (where all excipients should be named and obviously cannot in case of proprietary commercially sensitive information.
42	*any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.* **Proposed change:** please delete **Rationale:** This requirement is not needed for starting materials of biological origin not listed in Eur. Ph.
43	*1. Active substance specification*

	Specifications for active substances are asked for. Whereas currently specifications of the active substances are considered to be part of in-process control testing / specifications. This demonstrates that having different dossier structure for Biologicals and IVMP, even if similar in nature, may create confusion.
44	*Appropriate tests to demonstrate the absence of contamination by extraneous agents or other substances, including bacterial endotoxins, shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture.* **Rationale:** According to ongoing Ph. Eur. 5.2.5 revision, for viral vaccines, the EA testing may be omitted (if several conditions are met) bacterial endotoxins testing is not required for all types of vaccine (bacterial inactivated and product issued from DNA recombinant technology for example) **Proposed change:** Please replace the text with the following paragraph: **Risk Assessment should be conducted in order to ensure absence of contamination by extraneous agents. Depending upon the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture, the Risk Assessment may be supplemented when justified by tests to demonstrate the absence of contamination by extraneous agents or other substances, including bacterial endotoxins.**
44, 65	*Insofar as is necessary, the excipient(s) shall be subject at least to identification tests. An upper and lower limit test shall be obligatory in respect of preserving agents. An upper limit test for any other excipient components liable to give rise to an adverse reaction shall be obligatory.* **Rationale:** A "blanket" identity requirement for all excipients was not deemed necessary so far, and the need for such requirement is debatable, except for preservatives and antioxidants. This requirement (actually, the need to set-up an upper specification) should be limited to those types of components, and any other excipient likely to give rise to adverse reactions. This would appear to stem from the belief that all biologicals will be of high purity from a highly defined environment, but in an innovative area that may not always be the case. **Proposed change:** ~~Insofar as is necessary, the excipient(s) shall be subject at least to identification tests.~~ An upper and lower limit test shall be obligatory in respect of preserving agents. An upper limit test and any other excipient ~~components~~ liable to give rise to an adverse reaction shall be obligatory.
45 (IIa) and 65 (IIb)	*Stability tests for the finished product shall be carried out on not fewer than 3 representative consecutive batches produced according to the described production process and on products stored in the final container(s)*; **Rationale:** the requirement for consecutive batches is new. While this is an obvious requirement for assessing the consistency of manufacturing, this is much less so for stability. For example, companies sometimes decide to assess stability early on during their development programs, using (clinical) batches of product manufactured according to the part II of the MA dossier, and filled in final containers as for commercial product. This typically allows to generate relevant stability data for MA submission purposes, and document an appropriate shelf-life (as opposed to rely on the consistency batches to assess stability produced sometime very late during development reducing the shelf life at approval time). This has been accepted till now, and allows to accelerate MA submissions (and products approvals). The explicit requirement for 3 batches is also new, and does not apply to MUMS/Limited markets-products. Overall, the previous wording of the annex appeared more relevant, and is proposed to be re-instated. **Proposed change:** '*Stability tests for the finished product shall be carried out on* ~~*not fewer than 3 representative consecutive*~~ ***a sufficient number of*** *batches produced according to the described production process and on products stored in the final container(s)*;'

49	**Safety for biological products – General comments:** There are increased expectations compared to traditional immunologicals in terms of reproductive and developmental toxicity as well as genotoxicity and carcinogenicity. It is critical that the requirements are adapted to the nature of the product. It is especially relevant to note that standard batteries have not been considered appropriate for most biologicals assessed and approved for human health.
50	*4.2 Observations in humans* *Information should be provided showing whether the pharmacologically active substances of the veterinary medicinal product are used as medicinal products in human therapy; if this is so, a compilation shall be made of all the effects observed (including adverse reactions) in humans and of their cause, to the extent that they may be important for the assessment of the safety of the veterinary medicinal product, where appropriate including results from published studies; where constituents of the veterinary medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated.* **Proposed change: <u>If relevant</u>,** information should be provided ~~showing~~ **<u>on</u>** whether the pharmacologically active substances ^…] ~~where constituents of the veterinary medicinal products are themselves not used or are no longer used as medicinal products in human therapy, the reasons shall be stated~~. **Rationale:** Considering that (most) biologicals may be species-specific, adding the requirement to compile the above information on humans would not add to the assessment and would be an additional administrative burden except "if relevant".. Also, it is not realistic/fair to ask veterinary medicines-companies to justify why an active substance (or any "constituent of the VMP", like any excipient) is not used or no longer used in human medicines. Sometimes, this information may just not be publicly available, and the Applicant would be unable to provide the reason(s) why the corresponding constituent(s) is (are) not used in humans. Overall, this section should not be mandatory. The Applicants would use human observations to address user safety (the user safety section may better reflect this) and other aspects <u>if relevant</u> due to the nature of the active biological substance, mechanism of action and intended therapeutic indication. It seems as for some other paragraphs that existing 'specific' products already developed for use in Humans were in the mind of experts drafting this advice. This, as emphasised earlier, may create issues for all types of therapies as yet unknown.
50, 55	*The data requirements mentioned hereafter are related to antibacterial substances and may not be fully applicable to other types of antimicrobial (i.e. antivirals, antifungals and antiprotozoals) although in principle the approach may be followed, where applicable.* *Data on the potential emergence of resistant bacteria or resistance determinants of relevance for human health and which are associated with the use of veterinary medicinal products are necessary.* **Rationale:** With the wording as it stands, it is clear that the expectations from the assessors will not only focus on antibacterials, but also on other types of antimicrobials. The wording should be adjusted according to what is a realistic concern, not on any <u>theoretical</u> <u>potential</u> concern. **Proposed change:** "The data requirements mentioned hereafter are related to antibacterial substances and may not be ~~fully~~ applicable to other types of antimicrobial (i.e. antivirals, antifungals and antiprotozoals) ~~although in principle the approach may be followed, where applicable~~. **<u>For antibacterial substances,</u>** data on the potential emergence of resistant bacteria or resistance determinants of relevance for human health and which are associated with the use of veterinary medicinal products are necessary."
53 and beyond	**Efficacy for biological products – general comments** Pharmacodynamics and pharmacokinetics should preferably be addressed only in the Efficacy section and not in Safety too. Relevant aspects can be discussed in other Safety

	sections. It also should be considered that some novel therapies may not fit such requirements well (e.g. stem cells). Clear indication on how to ensure it will not be considered is needed as data is sometimes requested that is obviously not necessary for that type of product.
55	*Section 4. Tolerance in the target animal species* *The conduct of target animal safety studies should be in accordance with the relevant guidance published by the Agency.* **Proposed Change**: "The conduct of target animal safety studies should be in accordance with **the international guidelines on good clinical practice of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products ('VICH') and** the relevant guidance published by the Agency.
58	*All the test procedure(s) shall be described in sufficiently precise detail so as to be reproducible in control tests carried out at the request of the competent authority* It is acknowledged that documentation provided in the dossier should be sufficiently detailed to give confidence in the method but it is not a detailed procedure for laboratory purposes. Increasing the level of details may have a huge impact on product regulatory maintenance (i.e. number of variations) and associated need for more resources in both Agencies and Industry, contrary to the goal of new regulation to reduce administrative burden. Full SOPs are supplied to the OMCLs by the manufacturer upon request. **Proposed change:** All the test procedure(s) shall be described in sufficient~~ly precise~~ detail so as to be ~~reproducible in control tests carried out at~~ **properly assessed by the competent authority and** reproducible for the **finished product control** ~~in~~ tests possibly carried out at the request from the competent authority.
58	*All monographs, including specific monographs, general monographs and general chapters of the European Pharmacopoeia, or failing that, of a Member State are applicable. In the absence of a European Pharmacopoeia monograph, the monograph of a Member State pharmacopoeia may be applied.* **Proposed Change:** ~~All monographs, including specific monographs, general monographs and general chapters of the~~ European Pharmacopoeia, or failing that, of a Member State **should be** ~~are~~ applicable, **unless proper justification is provided.** In the absence of a European Pharmacopoeia monograph, the monograph of a Member State pharmacopoeia may be applied. **Rationale:** This change is to allow innovation where following the wording of the monograph may otherwise block the introduction of new techniques.
59	the constituent(s) of other excipients, whatever their nature or the quantity used, including preservatives, stabilisers, colouring matter, flavouring and aromatic substances, markers, solvents etc. Please insert the following text after the above sentence to better align: **with reference to one or more diluent master files, where applicable, or another marketing authorization in case of associated use with the vaccine. Different diluents may apply to a vaccine for administration by different routes or methods of administration. The reference to each diluent master file in the dossier shall include the qualitative and quantitative particulars of the diluent and the route and method of administration.**
60	*Solvents may be packed together with the vaccine vials or separately.* **Proposed Change: For s**~~S~~olvents **supplied with the vaccine, these** may be packed together with the vaccine vials or separately. **Rationale:** Some oral vaccines are reconstituted with drinking water.

60	*The validation of key stages in the production process shall be demonstrated and the validation of the production process as a whole shall be demonstrated with provision of results of three consecutive batches produced using the method described. Validation of critical assays used in the manufacturing process shall be described, documented and the results provided.* **Comment:** This paragraph is repeated on page 61 so it should be removed.
61	The details of the blending, with the quantitative particulars of all the substances used, including an example for a representative production batch; **Comment:** Representative batches are already described in part IID (In-process Controls) and IIF (Batch-to-batch consistency); the addition of this example in IIB is repetitive and serves no purpose.
62	*Vaccine production shall be based on a seed lot system and on established cell seeds* **Proposed Change: Whenever possible v~~V~~**accine production shall be based on a seed lot system and on established cell seeds **Rationale:** Not all vaccines can be produced using the seed lot system, inserting whenever possible means that the door is not closed to possible innovation.
62	*Seed materials, including cell seeds and raw serum for anti-serum production shall be tested for identity and demonstrated to be free from extraneous agents according to the Ph. Eur.* Please see the general comments section
63	*2D - Validation of the control tests for parameters considered critical to the manufacturing process should be provided* It should be noted that existing processes were assessed, approved and implemented with no issues. Applicants when dealing with new approaches or technology normally propose themselves specific tests for control. GMP inspections are regularly checking this, so the reason for adding to current requirements is unclear. For some tests, it is not feasible. For others, depending on the technique used, it may add some in-vivo tests, which is not in alignment with to the Directive 2010/63/EC. Thus, the following statement should be added: unless justified (or where possible). It should be noted that consistency of the production and controls as well as well-established processes should be an option to serve as indirect validation.
63	*any special precautions which may be necessary during storage of the starting material and, if necessary, its storage life shall be given.* **Comment:** This requirement is not mentioned for starting materials of biological origin not listed in Eur. Ph., therefore please delete.
63	**Proposed change:** "If the presence of extraneous agents is detected or suspected, the corresponding material shall be discarded or **processed to reduce the risk of presence with a validated treatment. If after treatment presence is detected or suspected, the corresponding material shall be** used in very exceptional circumstances only when further processing of the product ensures their elimination and/or inactivation; elimination and/or inactivation of such extraneous agents shall be demonstrated." **Rationale:** The inserted wording brings the paragraph into line with the EMA Reflection paper on the use of heat treatment to inactivate endogenous retroviruses in live immunological veterinary medicinal products
65	*Appropriate tests to demonstrate the absence of contamination by extraneous agents or other substances, including bacterial endotoxins, shall be carried out according to the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture.*

	Rationale: According to ongoing Ph. Eur. 5.2.5 revision, for viral vaccines, the EA testing may be omitted (if several conditions are met) bacterial endotoxins testing is not required for all types of vaccine (bacterial inactivated and product issued from DNA recombinant technology for example) **Proposed change:** Please replace the text with the following paragraph: **Risk Assessment should be conducted in order to ensure absence of contamination by extraneous agents. Depending upon the nature of the immunological veterinary medicinal product, the method and the conditions of manufacture, the Risk Assessment may be supplemented when justified by tests to demonstrate the absence of contamination by extraneous agents or other substances, including bacterial endotoxins.**
65	**Rationale:** This is an unnecessary constraint and a barrier to innovation in the case of vaccines that are not intended for parenteral route administration. In line with ongoing discussions with EDQM/IWP, it is proposed to keep the flexibility in the Annex by adding the following sentences: "Sterility is a requirement for parenterally administered products. Compliance to a maximum bioburden limit is required for non-parenterally administered products, where appropriately justified in absence of sterility." **Proposed change:** Please add the following sentences under "6. Sterility and purity test": **Sterility is a requirement for parenterally administered products. For non-parenterally administered products, where appropriately justified compliance to a maximum bioburden limit instead of sterility test may be acceptable.**
65	Please insert the following text into section F to reduce cost of developing in EU only to satisfy requirements and increase availability of well-targeted medicines (smaller combinations are sometimes needed by the field). **Consistency data obtained from combined products may be used for derivative products containing one or more of the same components**
65	*A description shall be given of the tests undertaken to support the shelf life, the recommended storage conditions and the specifications at the end of the shelf life proposed for the active substance and the finished product. These tests shall always be real-time studies.* *Stability tests for the finished product shall be carried out on not fewer than 3 representative consecutive batches produced according to the described production process and on products stored in the final container(s); these tests include biological and physicochemical stability tests carried out at regular intervals, for the finished product until 3 months beyond the claimed end of the shelf life* **Rationale a:** We do not see a justification for the requirement of the representative batches to be consecutive. Actually, this would cause in many cases significant delays in development as to get appropriate shelf-life the stability studies are initiated as early as possible in development and therefore frequently include a mix of R&D, pilot and/or industrial batches. As the shelf life studies go on, the manufacturer produces the required representative **AND** consecutive batches for the purpose of demonstration of consistency in production. **Proposed Change a***:* Stability tests for the finished product shall be carried out on not fewer than 3 representative ~~consecutive~~ batches produced according… **Rationale b:** The traditional EU approach to test stability until "3 months beyond the claimed shelf" is no longer justified by the current technical tools and the quality standards of IVMP set now. It jeopardises the EU based companies competitiveness for export (following the approved SPC) when compared to other regulations that no longer maintain this additional safety span. **Proposed Change b:** **…** these tests include biological and physicochemical stability tests carried out at regular

	intervals, ~~for the finished product~~ until ~~3 months beyond~~ the claimed end of the shelf life.
66	*If intermediate products obtained at various stages of the manufacturing process are stored, the intended conditions and duration of storage shall be defined on the basis of stability data.* The terminology "Intermediate products" is not well defined for immunological products (i.e. all active ingredient production is in part IIB and not in IIC as for other products). Such a vague statement may lead to multiple interpretations. Moreover, stability testing of the intermediate may not always be feasible, thus use of indirect stability of the AI or FP should be sufficient to validate the process. If knowledge of such stages is important to assessors, it should have been added to part IIB/IIF (as part of the supporting data of the process) instead of in IIG (stability). This will add unnecessary work for stability demonstration instead of authorising the storage period applied to the batches presented in IIF (approaches already approved by assessors in various instances).
66	*the safety of the immunological veterinary medicinal product when administered to the target species and any undesirable effects which may occur under the proposed conditions of use; these should be evaluated in relation to the severity of the pathological condition concerned* The current version from the Directive reads "these shall be evaluated in relation to the potential benefits of the product" We propose to keep the current version as the benefit-risk ratio represents a commonly accepted principle with a broader view. This is especially important in animals that are kept in herds or flocks where herd immunity, epidemiological situation etc. are taken into consideration for the benefit of a vaccine.
66	*Laboratory safety studies (pre-clinical studies) should be carried out in compliance with good laboratory practice (GLP) requirements. Deviations should be justified.* **Proposed Change:** please add "… **Non-target studies as well as studies evaluating immunological, biological or genetic properties of the vaccine strains shall be performed under adequately controlled conditions fully considering 3R principles**" **Rationale:** Not all cases will allow for GLP conditions (e.g. spread to non-target, research type studies for biological properties especially when dealing with GMO at early stages). It becomes more and more difficult to convince assessors that deviations from this principle are fully acceptable and do not have an influence on the quality of the documentation as there is quality management system in place even if not formal GLP. This in addition asks for repeat of studies for a compliance to "standard" when research and early development took place outside of EU (where no formal "GLP" is required)
67	*The safety studies shall be in line with the relevant European Pharmacopeia requirements.* **Proposed Change:** please add **"Deviations should be justified."**
67	*This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2. have revealed no major signs of systemic or local reactions* **Proposed change:** This study may be part of the repeated dose study required under point 3 or omitted if the results of the overdose study required under point 2. have revealed no major signs of systemic or local reactions **or are taken as the basis for describing safety of the product in the Summary of Product Characteristics.**
68	*The number of administrations must not be less than the maximum number recommended; for vaccines, this shall take account of the number of administrations for primary vaccination and the first re-vaccination.*

	The interval between administrations should be justified with respect to the proposed conditions of use. **Proposed Change:** The number of administrations must not be less than the maximum number recommended **<u>in the basic administration scheme</u>**; **<u>in case of regular re-vaccination</u>** ~~for vaccines~~, this shall take account of the number of administrations for primary vaccination and the first re-vaccination. **<u>For practical considerations,</u>** ~~t~~he interval between administrations **may be shorter than the one claimed in the summary of product characteristics and** should be justified ~~with respect to the proposed conditions of use~~.
68	*4. Examination of reproductive performance* *For immunological veterinary medicinal products that are recommended for use in pregnant animals, examination of the reproductive performance must address safety of administration during the entire gestation period or during specific period of gestation reflecting the intended use of the product.* This chapter is not following risk evaluation as previously, but makes the testing of all vaccines recommended for use during pregnancy mandatory. The proposed text is not harmonised with Ph. Eur. (are tested in each of the specific periods of gestation recommended for use on the label). This study is especially long and difficult to carry out in laboratory conditions for majority of species.
69	*Spread of the vaccine strain from vaccinated to unvaccinated target animals shall be investigated, using the recommended route of administration most likely to result in the spread. Moreover, it may be necessary to investigate the spread to non-target animal species which could be highly susceptible to a live vaccine strain. An assessment of the number of animal-to-animal passages likely to occur under normal conditions of use and potential consequences must be provided.* **Proposed Change**: susceptible to a live vaccine strain. ~~An assessment of the number of animal-to-animal passages likely to occur under normal conditions of use and potential consequences must be provided.~~ **Rationale:** This requirement is very difficult to assess and testing to provide the information is almost impossible, only the reversion to virulence test is of help if the natural spreading route is used. It should be noted that the experimental conditions required to run such studies are far removed from field conditions and the relevance and value such studies is questioned. In addition this is contrary to VICH guideline 41, where such assessment is by exception and limited to certain cases (generally, serial passages should be made in target animals through five groups of animals, unless there is justification to make more passages).
69	*Increase in virulence* For international harmonisation and clarity, we suggest that the wording remains aligned with VICH “absence of reversion to virulence”
69	*For vector vaccines, an evaluation of the risk of changing the tropism or virulence of the strain shall be carried out and, where necessary, specific tests shall be conducted. Such tests are systematically carried out where the product of a foreign gene is incorporated into the strain as a structural protein.* **<u>Proposed Change:</u>** Please replace the paragraph above with the following text: **<u>For vaccines made from genetically modified organism(s), where the product of a foreign gene is incorporated into the strain as a structural protein, the risk of changing the tropism or virulence of the strain should be addressed when carrying out the tests for live vaccine listed here and the specific ones required for the assessment of vaccines made from genetically modified organism(s).</u>**
69	*6.5 Recombination or genomic re-assortment of strains* *The probability of recombination or genomic reassortment with field or other strains*

	shall be evaluated and the consequences of such events discussed **Proposed Change:** and the consequences of such events are discussed **under 9.C or D** **Rationale:** This evaluation is part of the environmental risk assessment and/ or GMO and should be discussed under 9.C or D.
72	*Part 4 – Intro : …The influence of passively acquired maternally derived antibodies on the onset of immunity of a vaccine shall be adequately evaluated, if appropriate. The influence of pre-existing actively acquired antibodies on the efficacy shall be investigated, if relevant* **Rationale**: The need to assess the influence of "pre-existing actively acquired antibodies" is new and is concerning. Addition of this requirement to the already existing requirement to assess (where needed) the potential influence of passively acquired antibodies (MDA) will most likely lead to the systematic requirement to perform a specific study to address this. In our opinion, this requirement is already covered by the MDA study (where carried out). Up to now, authorities have been satisfied with lab efficacy studies conducted using seronegative animals-only (and MDA-interference study, where MDA may be present at the time of vaccination). This proposed addition, in addition to the proposal to keep the field trials requirement "as is" (see comments elsewhere) will most likely not lead to increased availability of vaccines in the EU, which does not appear in line with Authorities' expectations. **Proposed Change:** please retain the wording from the current annex of the Directive. The influence of passively acquired maternally derived antibodies on the onset of immunity of a vaccine shall be adequately evaluated, if appropriate. ~~The influence of pre-existing actively acquired antibodies on the efficacy shall be investigated, if relevant~~
72	*Whenever a product forms part of a vaccination scheme recommended by the applicant, the priming or booster effect or the contribution of the veterinary immunological product to the efficacy of the scheme as a whole shall be demonstrated.* **Proposed change:** "Whenever a product forms part (…) shall be demonstrated. **In case of an application where two or more products are needed for providing claimed efficacy (e.g. prime-boost concept), the studies should assess the complete treatment as a whole (and not independently).** **Rationale:** The insertion is to provide clarity.
72	*The following general requirements should be complied with:* *– the efficacy studies shall be in line with the relevant European Pharmacopeia requirements;* **Proposed Change:** The following general requirements should be complied with: – the efficacy studies shall be in line with the ~~relevant~~ **general** European Pharmacopeia **efficacy** requirements **for immunological veterinary medicinal products;** **– when the vaccine falls into the scope of a specific vaccine Ph. Eur. monograph, the corresponding immunogenicity test should be conducted;** **Rationale:** The insertion is to provide clarity and avoid possible confusion between Immunogenicity tests which should be conducted as per specific Ph. Eur. monograph, when available and relevant; and all other efficacy tests should be conducted in line with general monograph 5.2.7.
72	*In general, these laboratory trials (pre-clinical studies) shall be supported by trials carried out in field conditions, including untreated control animals.* **Proposed Change:** ~~In general, these L~~laboratory **Clinical** trials ~~(pre-clinical studies) shall~~ may be supported by trials carried out in field conditions **and should include~~,~~** ~~including~~ **when possible** untreated control animals. **When laboratory trials fully**

	<u>support the claims made in the Summary of Product Characteristics, trials carried out in field conditions are not required.”</u> **Rationale:** In practice, maintaining untreated animals is generally impossible (public health, animal welfare, epidemiological risks, economical losses, etc.) particularly for companion animals. In addition, attention should be drawn to the EMA analysis of the contribution of field data to the overall conclusions on efficacy for veterinary vaccines authorised through the centralised procedure recognising the frequently poor value brought by such studies. We propose to reverse the current situation and state that efficacy field trials are not necessary if all claims are fully validated in laboratory studies.
73	*an introduction defining the subject and indicating the tests which have been carried out in compliance with Parts 3 and 4 as well as a summary,* This adds a summary in addition to the DAC summary, this is unnecessary repetition and administrative burden.
74	*The raw data shall be presented in tabular form. By way of explanation and illustration, the results may be accompanied by reproductions of recordings, photomicrographs, etc.;* **Proposed Change:** The ~~raw~~ **<u>individual</u>** data shall be presented in tabular form. **Rationale:** Depending on the interpretation, raw data could imply the provision of handwritten papers from the investigators or electronic files from a data capture system.
76	*- a review of the user safety risk assessment focusing on differences between the generic and reference veterinary medicinal products (e.g. composition in excipients)* **Proposed change:** “- a review of the user safety risk assessment focusing on differences between the generic and reference veterinary medicinal products (e.g. composition in excipients); **<u>where relevant</u>**”
76	*For generic medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided* **Comments:** In some cases, strictly identical formulations as an example, tolerance studies and residue depletion studies may be waived, if justified. **Proposed change:** “For generic medicinal products intended to be administered by intramuscular, subcutaneous or transdermal routes, the following additional data shall be provided **<u>or omission justified</u>**”
76	**Comments:** We propose adding the same sentence applicable to hybrid dossiers to generic dossiers as well. The scope here is limited to pre-clinical studies, such as bioequivalence studies. **Proposed change :** “**<u>In case of new studies performed with batches of a reference veterinary medicinal product authorised in a third country, the Applicant shall demonstrate that the reference veterinary medicinal product has been authorised in accordance with requirements equivalent to those established in the Union, and are so highly similar that they can substitute each other in pre-clinical studies.”</u>**
77	*If new studies are conducted with batches of a reference veterinary medicinal product authorised in a third country, the Applicant shall demonstrate that the reference veterinary medicinal product has been authorised in accordance with requirements equivalent to those established in the Union, and are so highly similar that they can substitute each other in the clinical trial.* **Comments:** Proposition for minor adjustment, adding the preclinical studies as well in the scope. **Proposed change:** “If new studies are conducted with batches of a reference veterinary medicinal product authorised in a third country, the Applicant shall

	demonstrate that the reference veterinary medicinal product has been authorised in accordance with requirements equivalent to those established in the Union, and are so highly similar that they can substitute each other in the **pre-clinical** or clinical ~~trial~~ **studies** ".
77	*Unless the omission is justified, a target animal safety study with the final formulation should be provided.* **Comment**: The requirement for the use of final formulation is not included in the target animal safety section for a standard mono-substance product, but it is included in this section on combination medicinal products. VICH GL43 on TAS (section 2.3) states that non final formulation can be used as long as relevance between formulations is demonstrated by bioequivalence or other data. The current wording introduces the obligation to always use final formulation. **Proposed change**: Potential modifications of this sentence could be Unless the omission is justified, a target animal safety study with the ~~final~~ **combination** formulation should be provided. **OR** Unless ~~the omission is~~ **otherwise** justified, a target animal safety study with the final formulation should be provided.'
77	**Proposed change:** "For applications submitted under Article 20, a full dossier containing Parts 1, 2, 3 and 4 shall be provided for the combination veterinary medicinal product, in accordance with the relevant guidance published by the Agency **which will describe the needed information considering history and information from field use in case of pre-existing products with due consideration to 3Rs with a benefit/risk assessment.** "
79	*For such applications, the applicant shall submit Parts 1 and 2 as described in this annex. For Parts 3 and 4, some of the safety or efficacy data required by this annex may be omitted. As regards the extent of safety and efficacy data that may be omitted, the relevant guidance published by the Agency shall be taken into account.* **Comment:** For immunological products, some data required in Part 2 by this annex may also be omitted as listed in the relevant guidance. **Proposed change**: For such applications, the applicant shall submit all parts as described in this annex **except for the data that may be omitted. As regards the extent of these data that may be omitted, the relevant guidance published by the Agency shall be taken into account**"
80	*A full dossier containing Parts 1, 2, 3 and 4 shall normally be provided in accordance with the requirements described in Title I or II and to any relevant guidance published by the Agency. Deviations from the requirements of this annex may be possible when scientifically justified. Where appropriate and taking into account the specificities of novel therapy products, additional requirements may be relevant for particular types of products."* **Comment:** The principle should be introduced that the requirements set out in the annex can be adjusted to ensure that the data provided are wholly appropriate to that product whilst ensuring quality, safety and efficacy. This will enable appropriate adaptation needed for novel therapies, support 3Rs and provide the flexibility that is needed to manage innovation. **Proposed change:** "Deviations from the requirements of this annex may be possible ~~when scientifically justified~~ according to the specific nature of the novel therapy product."
80	*Depending on the active substance and the mode of action…could fall under any of the 3 product categories… and shall follow the format and data requirements…* This can be understood such that if one of the two conditions is fullfiled, requirements of

	one of the categories will fully apply. This appears to be in contradiction with paragraph "8.2 specific requirements" which resembles a GL and not legislation. Additionally, for example, monoclonal antibodies are immune-active substances, nevertheless the approach may not be accepted as being part of Immunologicals as they may be pharmaceutical by nature. This is one of the main reasons that AnimalhealthEurope strongly advises not to put this depth of detail on novel therapies in such a strong regulatory document (i.e. to leave more detail for guidelines). Inclusion of this level of the current level of detail will cause a need for systematic exchanges very early on with regulators to agree on one of the part of this annex, adding administrative burden to current system.
81	*To address data gaps or uncertainties at the time of product authorisation, implementation of post-authorisation measures or…* It is acknowledged that post-authorization measures can be considered in the event of gaps or uncertainties. However, any such measure should not be part of the initial dossier submission and therefore it would be appropriate to keep this consideration for the discussions during evaluation phase and not to include this in the annex II. If authorities wish to have reference to this possibility, it should clearly be highlighted that this is not a requirement for each submission.
82	*These specific requirements established for a particular type of novel therapy product represent a non-exhaustive list of requirements that may need to be adapted to the specific product concerned on a case-by-case basis and based on a risk analysis….* The wording used above clearly highlights the complexity of the topics and multiplicity of cases. Moreover, it is stated that novel therapies enter in one of the 3 categories for which details are provided in the 80 pages before. Therefore, adding another layer of complexity in this long technical annex and risking contradictory requirements, the need for § 8.2 is not obvious and may even trigger contradiction. It is therefore requested to delete it, recognising the technical difficulties and unknown.
84	With regard to safety, the kind of hazards that are introduced by using nanoparticles for drug delivery are beyond conventional hazards imposed by chemicals in classical delivery matrices. Therefore the following aspects should be considered with regard to safety: **General comment:** Detailed requirements should not be included to allow flexibility for innovation and to keep the annex future proof (particularly for novel therapies). **Proposed Change:** "With regard to safety, the kind of hazards that are introduced by using nanoparticles for drug delivery ~~are~~ **may be** beyond conventional hazards imposed by chemicals in classical delivery matrices. Therefore the following aspects ~~should~~ **could be** considered **when appropriate** with regard to safety:"
84	*The quality and quantity of the bacteriophages to be used in the finished product are normally variable. Therefore, a fixed qualitative and quantitative composition of bacteriophages will not be the usual situation as the phages need to be adapted on an ongoing basis.* The acknowledgement that a fixed composition is not the usual case for bacteriophage products in appreciated. However, further clarity is needed on how to "legally" authorise such products.
87 & 89	*The submission of a vaccine antigen master file shall comply with the relevant guidance published by the Agency* **Proposed Change:** Please amend as follows: "The submission **and approval** of a … master file shall comply with the relevant guidance published by the Agency" **Comment:** We note in this case that the text refers to guidelines, whereas this was not the case for other sections, which would also benefit from this approach for predictability and support of innovation. In the present situation, absence of such guidance today may

	explain absence of use of this new approach in the past.
88	**Comment:** The continued inclusion (and further expansion of guidance on requirements) of the VAMF is welcomed, and Industry is looking forward the "real implementation" of the concept in the veterinary field.
88	*For new vaccines containing new vaccine antigen(s) where no Vaccine Antigen Master File already exists, the applicant shall submit to the Agency a full marketing authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended*. **Rationale:** The certification should not be restricted to "new vaccine antigen(s)". "New vaccines" may (and actually, they frequently do) contain "existing antigens" (*id est*, antigens already approved for use in authorised vaccines). **Proposed modification:** For new vaccines containing ~~new~~ vaccine antigen(s) where no Vaccine Antigen Master File already exists, the applicant shall submit to the Agency a full marketing authorisation application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen for which the use of a Vaccine Antigen Master File is intended.
88	**Comment:** The expansion of the concept of "multi-strain" beyond AI, FMD and BTV is welcome, and Industry is looking forward to further guidance on the topic.
88	*Each multi-strain dossier is applicable only to one virus species; mixtures of various viruses belonging to different families, genera, species, etc. cannot…* **Proposed Change:** "Each multi-strain dossier is applicable only to one virus **induced disease** ~~species~~; mixtures of various viruses belonging to different families, genera, species, etc. cannot…" **Comment**: as the antigen may be vectored or of different nature than the virus of the disease.
89	**Comment:** The inclusion of the concept of "vaccine platform technology" is welcome, and Industry is looking forward to further guidance on the topic.