25 March 2022
EMA/CVMP/148042/2021
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on 'Guideline on safety and residue data requirements for the establishment of Maximum Residue Limits in minor species' (EMA/CVMP/345236/2020)

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

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

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. In general, the context with NVR 2019/6 should be made transparent, if deemed helpful to differentiate requirements for some legal scenarios. In particular, the 'limited market species' should be mentioned (NVR 2019/6 Art 4 (29 (b)) and its options under Art 23 and the particular situation for animals of the equine species not intended for human consumption (NVR 2019/6 Art 8 (4)). Reduction of requirements seems not to be intended for minor species where no MRL was set before in other species. It seems that alternatives, read-across etc... are not proposed in this case for the safety requirements (Line 149-150). Otherwise, the GL stays very vague, *i.e*. biologics (not much experience) and guides very quickly to scientific advice. In principle, scientific exchange with CVMP is highly appreciated but current process is very formal and time intensive.	Proposal partially agreed. Both GLs have different legal basis. A footnote to explain this was added to the introductions of both GLs, but no further cross reference should be made. This guideline is applicable for MRL applications for minor species, falling under Commission Regulation (EU) 2018/782 (methodological principles for the risk assessment) and under Regulation (EC) 470/2009 (requirements for MRL applications for a substance for use in minor species). The content of the MRL GL was not significantly changed since Regulation (EU) 2019/6 is not applicable here but for marketing authorisation applications. As the HBGV resulting from the safety assessment is applicable in general (i.e. for all species) and would be used in further MRL procedures for other (major) species, a reduction in data requirements is not possible. The scientific advice is the adequate procedure to check that the scientific approach considered is adequate, especially for non-standard approach. The scientific advice is available upon request but not compulsory.
2	It is not clear what the differences would be for safety and residue data requirements with this draft guidance in comparison to the GL to be replaced (CVMP Guideline on safety and residue data	Splitting of the former CVMP Guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species/limited

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	requirements for veterinary medicinal products intended for minor uses or minor species/ limited market (EMEA/CVMP/SWP/66781/2005-Rev.2)). In general a tabulated overview on differences would be highly appreciated.	market (EMEA/CVMP/SWP/66781/2005-Rev.2) became necessary due to the differences in the legal basis for MRL applications versus marketing authorisation applications. Therefore, the updated LM GL (EMA/CVMP/345237/2020) intends to reflect the actual legal basis, i.e. the new Regulation (EU) 2019/6, specifying conditions for marketing authorisation procedures. Whereas the legal basis for MRL procedures remains and therefore, no major revision was foreseen in this GL (EMA/345236/2020) A tabulated overview was not considered useful, as requirements depend on the particular case and instructions could better be given in text form.
2	*According to Article 2 of Commission Regulation (EU) 2017/880 'major species' are defined as cattle, sheep for meat, pigs, chicken including eggs, and Salmonidae, whereas 'minor species' means any species other than major species* This is correct, but in our new EU regulation (Regulation 2019/6) Salmonidae are minor species: Article 4 (29) Limited market' means a market for one of the following medicinal product types: (a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas; (b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats; It should be made clearer how to deal with *Salmonidae.*	Regulation (EU) 2019/6 is applicable for marketing authorisations of VMPs, whereas for MRL procedures Regulation (EC) No 470/2009, specified by other regulations as Commission Regulation (EU) 2017/880, are applicable. In terms of MRL applications *Salmonidae* are a major species according to Regulation (EU) 2017/880.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
85	1	Comment: Salmonidae is still included as major species in this GL, but a different definition is used in the other draft guidelines for limited markets. Clarification / alignment would be welcome	Not accepted. Legal basis for this GL is Regulation (EC) No. 470/2009 whereas the GL LM Safety is based on Regulation (EU) 2019/6. While *Salmonidae* are a major species concerning MRL procedures according to Regulation (EC) No. 470/2009 as indicated in Regulation (EU) No. 2017/880, they belong to LM concerning authorisation of VMPs according to Regulation (EU) 2019/6. Hence, no alignment would be possible. No further clarification is needed as major/minor species are defined in section 3 of the GL.
149-150	1	Comment: Reduction of requirements seems not to be intended for minor species where no MRL was set before in other species. It seems that alternatives, read-across etc... are not proposed.	As the HBGV resulting from safety assessment is applicable in general (i.e. for all species) and would be used in further MRL procedures for other (major) species, a reduction in data requirements is not possible.
188	1	Comment: Analytical Methods – the guideline should note that, if no marker residues are remaining following metabolism, then no analytical method is required.	Difficult to understand what is meant here. If a residue depletion study is conducted, a sufficiently validated analytical method is required. An analytical method is still needed to see if marker residues are present or not. In case of 'no MRL required' status, a marker residue does not need to be defined, however an analytical method may be needed to prove that the consumer exposure to residue always remain at safe level.
16-17	2	Comment: Please re-consider the use of the term 'minor species' if not used in any current/future Legislation. Proposal Change: Please consider 'non-major' or 'limited market-species' to improve clarity.	Not accepted. As mentioned above, Regulation (EU) 2019/6 does not apply to MRL procedures. We need to stick to the wording of the currently applicable regulation. The wording in this GL may only be adapted after

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			a future revision of Regulation (EC) No. 470/2009 and accompanied regulations.
51/52	2	Comment**:** *'When MRLs have already been established for one species, residue depletion studies may be waived for subsequent minor species (extension) applications under certain conditions'.* Please give more details about these conditions or refer to relevant sections.	Not accepted. This is only an executive summary, in which normally no cross reference to other parts of the document is made. Details about conditions are mentioned in the relevant sections.
74 and 75-78	2	Comment: The context with NVR 2019/6 and further guidance should be made transparent. In particular, the 'limited market species' should be mentioned (NVR 2019/6 Art 4 (29 (b)) and its options under Art 23 and the particular situation for animals of the equine species not intended for human consumption (NVR 2019/6 Art 8 (4)). Proposed change: Please add the following (after line 78): For safety and residue data requirements in 'limited market species' please refer to a separate *Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 (EMA/CVMP/345237/2020).* *For animals of the equine species not intended for human consumption please refer to guidance in context with NVR 2019/6 Art 8 (4).*	Not accepted. These are two different regulatory issues. Regulation (EU) 2019/6 is applicable for the authorisation of VMPs, whether this guideline is applicable for MRL-procedures, falling under Regulation (EC) No 470/2009. Therefore, the GL LM Safety (EMA/CVMP/148042/2021) is not applicable here.

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79	2	Comment: The definition of Minor/Major species should be made transparent in context with the 'limited market species' in NVR 20219/6. Proposed change (if any): Please add the following (after line 86): According to Article 4 (29)(b) of NVR 20219/6 'limited market' means a market for veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens including eggs, Salmonidae, dogs and cats. (Note: Cats and dogs have no relevance in context with MRL).	Not accepted. Definitions mentioned in Regulation (EU) 2019/6 are applicable for the authorisation of VMPs. This guideline is applicable for MRL procedures and therefore the definition in Commission Regulation (EU) 2017/880 is applicable here, which is already included.
142	2	Comment: The paragraph explains why consumer safety must not be compromised for minor species. A differentiation to "limited markets" might be helpful to understand these two different approaches.	The risk for the consumer cannot be weighed against a benefit the VMP would have for the target animal. For differentiation to LM, please see comments above.
155	2	Comment: It is not clear under which circumstances it can be demonstrated that all residues of concern are known and can be analysed by validated methods without the conduct of total residue studies. Can this option be more clearly elaborated?	Not accepted. It cannot be foreseen which data might be available for a particular substance. If an applicant takes the position, that this exemption might be applicable, a request for scientific advice is recommended.
163	2	Comment: It remains unclear in which cases ADME data from *e.g.* laboratory species can be extrapolated to minor species. How is this extrapolation expected to be done (allometric scaling, uncertainty factors)?	Partly accepted. It is up to the applicant to provide scientific justification in this case. This might be accompanied by sufficient in vitro data. An example was added to the text.
165	2	Comment: Similar to the comment above, it is unclear where the requested data can originate from if no MRL has been previously established	Partly accepted. An example was included in the text.

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189	2	Comment: For more clarity it might be appropriate to define the options to reduce the validation of analytical methods without endangering acceptance	Not accepted. The minimum criteria listed need to be fulfilled. It is in the interest of an applicant to apply a validated analytical method to allow for the results of a study to be accepted. Analytical standards are necessary only in case numerical MRLs are set.
202 and 221-225	2	Comment: *'However, the suitability of the safety data shall be assessed by comparing the metabolites produced in the laboratory animals to those seen in the target animals.'* and *'If the application for extension concerns the same food commodities and the residue depletion study was conducted according to current requirements, only data showing that metabolism in the new target species does not significantly differ from the previous species are necessary (thus indicating that residues produced in the new target species, like those produced in the original target species, reflect those produced in the laboratory animals). Also ratios of marker to total residues between the original target species and the new target species need to be similar.'* Please could you give more details/examples on how this could be performed other than a conducting a VICH 46 metabolism study? Under which circumstances in vitro data are acceptable or radiolabelled studies can be waived? Could details in line 156ff be used?	Partly accepted. Examples as well as reference to VICH GL 47 were added to the text.
212	2	Comment: For substances with an established ADI, no additional safety data are required – does this mean	It is clearly stated that "The ADI that has already been determined can be used to establish MRLs in the minor

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		that it is sufficient to only reference to the respective EPMAR? Please clarify.	species, provided that the data underlying the ADI are not subject to protection of technical documentation (especially according to Articles 38 to 40 of Regulation (EU) 2019/6) or that permission to access those data is granted by the data-owner, together with the relevant residue data."
214	2	Comment: Please add the reference for the appropriate "in vitro" study.	Accepted. Reference to VICH GL 47 was added to the text.
223	2	Comment: The term "does not significantly differ" is imprecise and may lead to discussion, please clarify.	Not accepted. An explanation is already given in the text: "thus indicating that residues produced in the new target species, like those produced in the original target species, reflect those produced in the laboratory animals". For more specific guidance for a particular substance a request for scientific advice is recommended.
226	2	Comment: The term "need to be similar" is imprecise and may lead to discussion, please clarify.	Not accepted. This is a case by case decision, depending on the substance and the metabolites of concern. For more definite guidance for a specific substance a request for scientific advice is recommended.