9 September 2021
EMA/CVMP/148001/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on '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)

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

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

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Cruelty Free International welcomes the publication of new guidance on the data requirements for veterinary products intended for the limited market, which has been updated to reflect the new legal provisions set out in Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products (specifically Article 23) and introduces clearer guidance on the circumstances under which the data requirements for limited market veterinary products can be reduced. While we appreciate that efforts have been made to include reference to the EU Directive 2010/63/ (on the protection of animals for scientific purposes) and consideration of the 3R principles (of replacement, reduction and refinement) in the introduction to the guideline, we feel that some minor improvements could be made to the language to further encourage and prioritise the use of non-animal methods with a view to avoiding unnecessary animal testing. This is in line with the goals set out in the EMA's recently published strategic reflection (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf). We make some minor suggestions to the text to help improve the tone with this important regard.	Please find responses to the specific comments in the section below.

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2	EGGVP welcomes this guideline and the opportunity to comment. Efforts to increase availability for MUMS and limited markets is clearly set and acknowledged. The new provisions are seen as great opportunity for smaller companies in particular those more flexible to cope with specific needs of customers regarding species, or fill smaller geographical areas.	Just to mention for clarification, the terminology has changed with the new Regulation (EU) 2019/6: MUMS is a term not in use any more for marketing authorisations, guidelines and Regulation are dealing with limited markets only.
	With regards to the level of requirements: not much of objective data reductions, exemptions or omission of specific documentation - in comparison with current guidelines - are identified. A tabulated overview of differences would be highly appreciated.	Changes in the level of requirements were not within the scope of this update. The aim was to adapt the GL to the current legal basis. A tabulated overview was not considered useful, as requirements depend on the particular case and cannot be generalized. Instructions could better be given in text form.
	EGGVP notes that applications for Art. 23 limited market status will undergo a scientific advice, with subsequent increased resource efforts for applicants (which may be a limiting factor for some MAHs, SMEs in particular, which have proved to be great contributors to availability for limited markets in the past). EGGVP suggests the inclusion of possible reduction for scientific advice fees for limited market products to be applied.	It is mentioned in the guideline that scientific advice is available upon request if an applicant wishes to have clarity on precise data requirements. Scientific advice results in good planning and conducting of studies, which at large leads to reduction in costs. Fees for limited markets are outside the consideration of this guideline. Please also refer to the document *Overview of comments received on 'Reflection paper on classification of a product as intended for a limited market according to Article 4(29) and/or eligibility for authorisation according to Article 23 (Applications for limited markets)' (EMA/CVMP/235292/2020).*
	It is also noted that decisions will be taken on a case-by-case basis. This on the one had offers flexibility which is welcome, but it also	Comment is acknowledged. However, this guideline offers opportunities for use of new testing approaches apart from

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	involves a higher degree of uncertainty and lower predictability to the applicant, which are critical aspects for R&D plans and decision making for MAHs.	those mentioned in Annex II. Decisions on appropriateness and acceptability can only be taken on a case by case basis.
	Question has been raised about VMPs that do not comply with the eligibility criteria for an Art.23 application (already authorized as MUMS/limited market status under current guidelines or VMPs which shall fall under Art. 4(29) limited market status but not complying with eligibility criteria). It is not clear if the contents of the existing technical guidances on reduced data requirements (including those on quality data requirements) will still apply to these; or if a review and update of these existing guidances is to be expected. EGGVP suggests that options for these VMPs not fitting all criteria in Art 23 are clearly stated. For these, it may be critical to elaborate process allowing deviations from full annex II dossier (complementary guideline for VMPs for limited markets not falling under Art 23) as an incentive for MAHs towards minor use/species/limited markets development. In order help readers with scope and terminology, EGGVP suggests that the guideline is revised so as to provide the necessary clarity on that.	Please note that the current *Guideline on safety and residues data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market* (EMA/CVMP/SWP/66781/2005-Rev.1) will cease to apply as of 28 January 2022 and will be replaced by the present guideline (EMA/CVMP/345237/2020). As mentioned in the title, the scope of this guideline is restricted to VMPs for limited markets submitted under article 23 of Regulation (EU) 2019/6. Further discussion is on-going about VMPs that are classified as 'limited market' but not eligible for consideration under Article 23. Please be referred to another document, where these aspects are covered: *Reflection paper on classification of a product as intended for a limited market and eligibility for authorisation according to Article 23 (Applications for limited markets)* (EMA/CVMP/235292/2020) and *Overview of comments received* on this Reflection paper.
	Overall, EGGVP is in the opinion that withdrawing the existing guideline on quality requirements is not in line with the objective of Regulation (2019/6) to improve the availability of safe and effective	Quality guidelines are not within the scope of this guideline. Please also refer to the document *Overview of comments received on 'Reflection paper on classification of a product as intended for a limited market according to Article 4(29)*

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

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	Otherwise the requirements will aggravate development of new products with limited market value because of the low or late return on investment	
3	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. Overall, it is expected that the GL will provide more clarity on the data requirements, although no general recommendation for omission of specific documentation or data reduction can be given and decisions on case-by-case basis are crucial for data reduction options. However, such decisions are associated with a high level of uncertainty for the applicant regarding acceptance by CVMP. Is a more intense scientific exchange between applicant and CVMP than the current standard "scientific advice" process intended to overcome this limitation? This Draft Guideline addresses VMPs /MAAs for limited markets submitted under Article 23. It replaces the Guideline for Safety and residue data requirements for MUMS/limited markets (EMA/CVMP/SWP/66781/2005 Rev.2). This leaves a gap for VMPs/MAAs for limited markets of Regulation 2019/6 that fall not under Article 23. Therefore, further (draft) Guidance is sought for VMPs/MAAs for limited markets of Regulation 2019/6 that fall not under Article 23 to complement this Guideline. In addition, it seems that this guideline still addresses in some sections VMPs /MAAs for limited markets, irrespective whether submitted under Art 23 or not (*e.g* section 5.2.2. on withdrawal periods).	Please find responses to the specific comments in the section below. The current standard "scientific advice" process is considered adequate. It is mentioned in the guideline that scientific advice is available upon request if an applicant wishes to have clarity on precise data requirements. Scientific advice results in good planning and conducting of studies. Please note that the current *Guideline on safety and residues data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market* (EMA/CVMP/SWP/66781/2005-Rev.1) will cease to apply as of 28 January 2022 and will be replaced by the present guideline (EMA/CVMP/345237/2020).

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	As it is not always obvious whether the GL (as the title suggests) addresses ONLY Art 23 submissions or whether partially 'limited market submissions' are addressed as well, it is suggested to consider a better differentiation within the GL and/or change the title of the GL.	As mentioned in the title, the scope of this guideline is restricted to VMPs for limited markets submitted under article 23 of Regulation (EU) 2019/6. Further discussion is on-going about VMPs that are classified as 'limited market' but not eligible for consideration under Article 23. Please be referred to another document, where these aspects are covered: *Reflection paper on classification of a product as intended for a limited market and eligibility for authorisation according to Article 23 (Applications for limited markets)* (EMA/CVMP/235292/2020) and *Overview of comments received* on this Reflection paper.
	It is not clear what the options for 'identifiable data gaps' (see reflection paper) would be for Safety data requirements (User safety, Environmental safety, Residue data and WPs) in dossier submitted that are eligible for Art 23. In general a tabulated overview on differences (Full Annex II versus gaps from Annex II) would be highly appreciated. A similar approach as provided in the reflection paper - Annex 2 – Understanding the limited market provision compared to current application of 464 MUMS policy/guidance.	If no pivotal data are available and the applicant also does not use a worst case assumption, bridging data like read across might allow for an assessment. However, this is a case by case decision, depending on the available data. A tabulated overview was not considered useful, as requirements depend on the particular case and cannot be generalized. Instructions could better be given in text form.
	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:	As this guideline is dealing with authorisation procedure and not with MRL procedures, Commission Regulation (EU) 2017/880 is not applicable here. Legal basis for this guideline is Regulation (EU) 2019/6.

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	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.*	There is a difference in definition of minor/limited market species between both regulations. However, the correct definition is included in the respective guidelines. In terms of MRL assessment *Salmonidae* is a major 'species', whereas for marketing authorisation procedures provisions concerning limited markets are applicable for *Salmonidae*.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
94-97	1	"In accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes and Directive 2010/63/EU on protection of animals used for scientific purposes, the 3R principles (replacement, reduction and refinement) should be applied to all testing involving animals". Comment: In this Scope section it would be beneficial to note that the guideline also has a 3Rs benefit in offering reduced data requirements for limited market veterinary products. Proposed change: **This guideline also presents several opportunities to waive animal testing requirements for veterinary products intended for limited markets, which is** in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes**,** ~~and~~ Directive 2010/63/EU on protection of animals used for scientific purposes~~,~~ **and** the 3R principles (replacement, reduction and refinement), and **which** should be applied to all testing involving animals".	Not accepted. The primary purpose of the Article 23 provision is to improve availability, not to address 3Rs. However, the guideline mentions the need to comply with Directive 2010/63/EC and with 3Rs principles: "All pre-clinical *in vivo* studies conducted by an applicant to support an application for marketing authorisation should be in accordance with the requirements of Directive 2010/63/EU on the protection of animals used for scientific purposes and the 3Rs principles of replacement, reduction and refinement (EMA/CHMP/CVMP/JEG-3Rs/450091/2012; EMA/CHMP/CVMP/3Rs/164002/2016)."

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Legal Basis section	1	Comment: Reference to Directive 2010/63/EC should be included in the Legal basis section. Proposed change: Add the following to the end of the Legal basis section (this is similar to the language that was accepted in the previously adopted MUMS/limited market guidelines): **"Directive 2010/63/EU on the protection of animals used for scientific purposes should also be considered in relation to the conduct of all testing involving animals. This Directive outlines the 3R principles of replacement, reduction and refinement, which should be taken into account whether the study is a pre-clinical study within the scope of Directive 2010/63/EU or a clinical field trial that is outside the scope".**	Not accepted. While Directive 2010/63/EC is applicable this directive is not the legal basis for the guideline on limited market.
211-221	1	"*Complementarily or alternatively to standard requirements and data reduction options above, for the purpose of supporting 'limited markets', it is possible to use endpoint specific surrogate (non-Annex II/non-guideline) approaches, if adequately justified. While most surrogate methods may have limitations, especially as to their use as standalone methods for quantitative (endpoint-related) hazard assessments, they may nevertheless prove*	Accepted. Text modified accordingly with minor amendments: "Complementarily to the possible data reductions mentioned above and/or as an alternative to standard requirements, for the purpose of supporting "limited markets", it is possible to use New Approach Methodologies (NAMs) that have not yet been included in Annex II or other guidelines, if adequately justified. While some NAMs are still in the early stages of development and may have limitations, especially as to their

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		appropriate and useful to screen and identify particular hazards, to inform the hazard assessment and to determine if specific mitigation measures are warranted. Examples of these surrogate approaches include ex-vivo/in-vitro approaches or in-silico tools including (quantitative) structure-activity relationships ((Q)SAR), extrapolation of existing data (e.g. short term to long term toxicity), prediction of endpoint information for one substance by using data for the same endpoint from (an)other substance(s) ("read-across" techniques), thresholds of toxicological concern (TTC) or Cramer Class scheme in conjunction with the associated TTC values". Comment: We are concerned with the use of the term "surrogate methods" to describe non-animal approaches throughout the draft guideline. This term is not a commonly used one and does not appear to have been used in any previous guidelines published by the EMA or other regulatory agencies. This term could imply that non-animal testing approaches are an inferior choice to standard animal tests, which is not the case. The term New Approach Methodologies (NAMs) is used in the EMA's regulatory strategy and has become a preferred term around the world.	use as standalone methods for quantitative (endpoint-related) hazard assessments, they may nevertheless prove appropriate and useful to screen and identify particular hazards, to inform the hazard assessment and to determine if specific mitigation measures are warranted. It is also possible that a combination of NAMs could be used to fulfil data requirements in lieu of standard testing approaches. Examples of NAMs include ex-vivo/in-vitro approaches or in-silico tools including (quantitative) structure-activity relationships ((Q)SAR), extrapolation of existing data (e.g. short term to long term toxicity), prediction of endpoint information for one substance by using data for the same endpoint from (an)other substance(s) ("read-across" techniques), thresholds of toxicological concern (TTC) or Cramer Class scheme in conjunction with the associated TTC values."

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		Also, we do not think it is appropriate to state that "most" non-animal methods have "limitations" when the limitations of laboratory animal studies are not also considered (e.g. species differences, extrapolation from laboratory to target animals, high cost, duration, ethical issues etc.). Statements like this do not help establish confidence in the use of NAMs and may hinder progress. Because testing guidelines are not updated very frequently, it is important to future-proof all new and revised guidelines to allow for flexibility as the science evolves. Proposed change (if any): Complementarily **to data reductions above and/**or alternatively to standard requirements ~~and data reduction options above~~, for the purpose of supporting 'limited markets', it is possible to **use New Approach Methodologies (NAMs) that have not yet been included in Annex II or other guidelines** ~~endpoint specific surrogate (non-Annex II/non-guideline) approaches~~, if adequately justified. While ~~most~~ some **NAMs are still in the early stages of development and** ~~surrogate methods~~ may have limitations, especially as to their use as standalone methods for quantitative (endpoint-related) hazard assessments, they may nevertheless prove appropriate and useful to screen and identify	

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		particular hazards, to inform the hazard assessment and to determine if specific mitigation measures are warranted. **It is also possible that a combination of NAMs could be used to fulfil data requirements in lieu of standard testing approaches**. Examples of **NAMs** ~~these surrogate approaches~~ include ex-vivo/in-vitro approaches or in-silico tools including (quantitative) structure-activity relationships ((Q)SAR), extrapolation of existing data (e.g. short term to long term toxicity), prediction of endpoint information for one substance by using data for the same endpoint from (an)other substance(s) ("read-across" techniques), thresholds of toxicological concern (TTC) or Cramer Class scheme in conjunction with the associated TTC values.	
222-226	1	*"Any of the surrogate approaches or combination of approaches should be scientifically justified and valid, and adequately reported. Adequacy, reliability and limitations as well as the experimental/methodological conditions used should be thoroughly discussed and assessed. Care should be taken to identify limitations and uncertainties and to assess their impact on the estimate of the respective hazard/risk and the benefit-risk balance".* Comment: Replace the term 'surrogate approaches' with NAMs as above.	Accepted. Text was modified accordingly.

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		Proposed change (if any): Any of the **NAMs** ~~surrogate approaches~~ or combination of approaches should be scientifically justified and valid, and adequately reported. Adequacy, reliability and limitations as well as the experimental/methodological conditions used should be thoroughly discussed and assessed. Care should be taken to identify limitations and uncertainties and to assess their impact on the estimate of the respective hazard/risk and the benefit-risk balance.	
227-229	1	"*Where studies are considered necessary, applicants are encouraged to use, wherever possible, validated in vitro protocols (i.e. VICH, OECD) to replace laboratory animal studies. However, should standard animal studies be necessary, they should follow relevant scientific protocols (VICH, OECD)".* Comment: Whilst current replacement methods in OECD and VICH guidelines are most commonly in vitro methods, this is not always the case and is changing. Other valid non-animal approaches including ex vivo and in silico approaches also feature in these guidelines and will do so increasingly.	Partly accepted. The proposed change "should animal studies **still** be **required after appropriate scientific justification**" is not accepted. For a VMP application, specific data requirements, which currently still include animal studies, are commonly required by law. Therefore, the conduct of these required studies does not need to be scientifically justified.

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		Proposed change (if any): Where studies are considered necessary, applicants are encouraged to use, wherever possible, validated **non-animal** ~~in vitro~~ protocols (i.e. VICH, OECD) to replace laboratory animal studies. However, should ~~standard~~ animal studies **still** be **required after appropriate scientific justification** ~~necessary~~, they should follow relevant scientific protocols (VICH, OECD).	
239-243	1	*"Should the conducted studies and the submitted data not be sufficient and in the absence of appropriate scientific justification, standard toxicity studies might be necessary. Therefore, it is strongly recommended to seek scientific advice before submission of the application. This applies particularly to the use of surrogate approaches, as this an area where methodologies and knowledge are evolving fast, but still limited experience and guidance exists regarding their regulatory use."* Comment: Replace the term 'surrogate approaches' with NAMs as above. We prefer the term 'required' rather than necessary and 'last resort'. These terms are used in other sectors such as chemicals.	Partly accepted. The proposed change "standard toxicity studies might be **required as a last resort**" is not accepted. For an VMP application, specific data requirements, which currently still include animal studies, are commonly required by law. Therefore, if an applicant wishes to conduct such an animal study, it is covered by the regulation.

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		Proposed change (if any): Should the conducted studies and the submitted data not be sufficient ~~and in the absence of appropriate scientific justification~~, standard toxicity studies might be **required as a last resort** ~~necessary~~. Therefore, it is strongly recommended to seek scientific advice before submission of the application. This applies particularly to the use of **NAMs** ~~surrogate approaches~~, as this an area where methodologies and knowledge are evolving fast, but still limited experience and guidance exists regarding their regulatory use.	
97	2	Comment: We suggest more alignment of this paragraph and the equivalent one in the draft Safety MRL guideline (EMA/CVMP/345236/2020). Wording is slightly different.	Accepted
128	2	Comment: it seems there is a typo, reference should be made to section 5.2.2. instead of 5.1.2.2.	Accepted.
200	2	Comment: it seems there is a typo, reference should be made to section 5.1.1. instead of 6.1.1.1.	Accepted.
201	2	Comment: In the current guideline the use of Summary report EMEA/CVMP MRL SR (not only EPMARs) was also accepted. Could this be included again?	Accepted. Text was amended.

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210, 241	2	Comment: Klimisch et al. (1997) reference is not included in the reference list at the end of the GL. Proposed change: include reference at the end of the GL	Accepted. Reference was added.
217-222	2	Comment: No defined quality standards exist for the described surrogate approaches, so it remains unclear how acceptability of such data can be ensured, i.e. - Acceptance for approaches using QSAR, TTC / Cramer Class concept, read-across techniques, or a combination of these to address genotoxicity endpoint? - Acceptance for ICH guidelines to be referenced since there is no VICH guideline for in silico testing?	So far there is no guidance and there are no established standards for those approaches. Also, not single endpoints, but the overall picture of available data, their plausibility and the entire evidence is assessed. It is recommended to request scientific advice in those cases. In principle ICH guidelines are accepted, provided they are adequate for the particular purpose.
235	2	Comment: further details and specification on the level of requirements needed for novel therapies. The terms "a more comprehensive safety data package may be required" appear to be too vague for applicants.	Partly agreed. The "more comprehensive safety data package" refers to substances novel in veterinary medicine and not to novel therapies (these are addressed three lines below the "comprehensive data package"). However, It is agreed that "comprehensive" could be misunderstood, therefore, propose to replace "more comprehensive" with "standard"
236	2	Comment: the text reads "In accordance with Annex II, Title III, 8, 'Annex II", but it is unclear which annex the text is referring to.	Accepted.

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		Proposed change: add complete annex reference	
306	2	Comment: May be useful to cross refer in this section to draft MRL guideline under development (EMA/CVMP/345236/2020)	Partly accepted. A footnote was added to the introduction of both guidelines for explanation.
9	3	**Comment:** Clarify that this GL will replace a previous GL. • Same approach as for '*Safety and residue data requirements for the establishment of maximum residue limits in minor species Draft guideline*' in lines 9-11. • In line with statement on EMA homepage Safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6 | European Medicines Agency (europa.eu) **Proposed change (if any):** Please add the following: **'This guideline will replace the Guideline on safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (EMA/CVMP/SWP/66781/2005 Rev.2).'**	Accepted with minor modification: "This guideline replaces the Guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor uses or minor species (MUMS)/ limited market (EMEA/CVMP/SWP/66781/2005-Rev.1)" The previous guideline was covering both marketing authorisations and MRLs. Since marketing authorisations for limited markets under article 23 and MRLs for minor species are based on different regulations, they are now addressed in two different guidelines, as mentioned in the footnote to the introduction.

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45	3	**Comment:** In this context the term "critical" should be explained, the provision of examples would be helpful.	Accepted. The term "critical" was replaced by "relevant".
83	3	**Comment:** Examples could support reader comprehension **Proposed change:** please add examples for the defined categories	Not accepted. Definitions are provided in Art 4(43) of Regulation (EU) 2019/6.
86	3	**Comment:** Please specify that consumer safety only applies for VMPs for food-producing animal, *e.g.* "...consumer safety (intended for food-producing animals) ..."	Not accepted. Consumer safety is a standard wording in the regulation. It does not need to be explained further here.
92-93	3	**Comment:** Clarify that the CVMP and VICH guidelines concerning safety and residues apply to 'limited market products not submitted under Art 23.' **Proposed change (if any):** Please add the following: … applicable to limited market products **not submitted under Art 23.**	Not accepted. This guideline is dealing with 'limited market products submitted under Art 23' only.
104	3	**Comment:** The listed animal species largely comply with "major species" as defined in other guideline but does not include salmon. This deviation might be emphasized to ensure proper understanding of the species that fall under the "limited market" definition.	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.

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			In terms of MRL applications *Salmonidae* are a major species according to Regulation (EU) 2017/880, in terms of marketing authorisations they belong to limited market.
201	3	**Comment:** EPMARs may be used if data is not subject to protection or access to data is granted by the data-owner. However, it is not clear if reference to respective EPMAR is sufficient or if the original data (*e.g*. reports) need to be submitted.	Accepted. Reference to EPMAR is sufficient if data is not subject to protection and it is not needed to submit the original data. This is not specific to limited market. Please refer to Annex II.
204	3	**Comment:** The option to use literature data appears unrealistic as it is most often difficult to evaluate the reliability and relevance of the published data. Moreover, it remains opens what quality level is expected by CVMP for acceptance of respective data. Which Klimisch score is considered sufficient (1 or 2)?	Klimisch scores are mentioned as an example for score, which might be useful for evaluation of literature data as supporting information. Concerning literature data please refer to the information given in Annex II.
210	3	**Comment:** Reference is made to Klimisch et al.,1997. Please add the full citation to the reference list, so it can be retrieved by the reader of this guidance. **Proposed change (if any):** To add in the list of references for the guideline the complete reference: **Klimisch H.J., Andreae M. Tillmann U.– A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data, Regulatory Toxicology and Pharmacology, 1997, 25(1), 1-5**	Accepted. Reference was added.

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217	3	**Comment:** Examples of surrogate approaches include different endpoints including genotoxicity as a very crucial endpoint. How high is the chance of acceptance for approaches using QSAR, TTC / Cramer Class concept, read-across techniques, or a combination of these to address this endpoint.	Some of these methods have already been accepted in case by case. The standard approach is recommended where there is a potential for genotoxicity.
222	3	**Comment:** There are no defined quality standards for the described surrogate approaches and hence it remains unclear how acceptability of such data can be ensured. Is there any idea for reliable guidance?	The surrogate approaches mentioned are only to be considered as examples. For the approaches with no guideline in practice yet, it is recommended to seek for scientific advice.
231	3	**Comment:** Typically, an applicant is not aware of other companies developing a product for a limited market in parallel. Even if a marketing authorisation holder is known it depends on the willingness of the marketing authorisation holder to share data and economic considerations may be deemed more important than 3R obligations.	Agreed that this depends on knowledge of product development and the willingness to share. However, the Directive 2010/63/EU clearly states that duplications of animal studies should be avoided and this regulation applies to toxicological testing of VMPs.
233	3	**Comment:** A substance novel to veterinary medicine might already have substantial data in human medicine, in addition it often drives innovation, therefore flexibility should be possible as well depending on the overall knowledge.	Agreed that "novel" in VMP does not necessarily mean "novel" in general. We consider that flexibility is still possible for these substances, as it is stated in the guideline that the scope for data reduction "may" be limited.
236	3	**Comment:** Reference is made to 'Annex II, Title III,8. …' As it is not clear to which document this	Accepted.

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		refers, it is proposed to better describe the reference. (Please note The Annex II of NVR2019/6 displays meanwhile (as of 8 March 2021) 'Sections' instead of 'Titles', though in the previous (Nov 2020) Annex II, Title III, there is no sub-section '8'; it stops at '7'. Same applies to current 'Section IV' within Annex II to NVR 2018/6, which is the successor of 'Tiitle III' of Annex II. In the Annex II proposed on 29 Aug 2019 there is a Title III with subsection 8 referring to novel therapies. Novel therapies are addressed in Annex II, section V in sub.section 1 **Proposed change:** amend reference to state the full document. E.g. 'Annex II **to NVR2019/6**, ~~Title III, 8.~~**SECTION V, 1** …'	
252-255	3	**Comment:** For calculation of human exposure, it is stated that study data can in most cases be substituted by theoretical models. One may substitute product-specific study data with conservative estimates in regulatory literature, using reasonable worst-case exposure scenarios. The meanings of the terms "study data" and "theoretical models" are unclear in the context of human exposure assessment, as human study data are not generated.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is assumed that by 'study data' animal (lab animals, target animal) data are meant. **Proposed change:** Please revise to state "For the calculation of human exposure~~, realistic theoretical considerations can be used, and study data 252 can in most cases be substituted by theoretical models.~~ **t**he principles of the…'	
258	3	**Comment:** For limited market product, a worst-case assumption can be made when toxicological studies are omitted. The User Safety Guidelines only reference "reasonable worst-case assumptions". The alternative to reasonable would be "unreasonable worst-case assumptions". Even in the context of missing toxicological studies, the exposure and risk should continue to be based on reasonable rather than unreasonable worst-case assumptions. The fact that they are worst case accounts for gaps in toxicology data. **Proposed change:** Please add the following: "For limited market products, **reasonable** worst-case assumptions can **continue to** be made when toxicological studies are omitted in some cases. In these instances, sufficiently protective and reasonable risk mitigating measures should be put in place."	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
263	3	**Comment:** With regard to "unknown" risk of genotoxicity, no differentiation of food-producing and non-food producing animal species is made. What is about the "unknown" risk of genotoxicity for evaluation of consumer safety?	The risk of genotoxicity for the consumer is part of the assessment within the MRL procedure. For the authorisation procedure only user safety and target animal safety need to be addressed.
306	3	**Comment:** There is also a CVMP GL "Safety and residue data requirements for the establishment of MRL in minor species" in preparation / in public consultation. Would it be reasonable to cross-reference to this guideline?	Agreed. A footnote was added to the introduction of both guidelines for explanation.
370/371	3	**Comment:** Additional information on when scientific advice would be considered necessary would be helpful.	This cannot be dealt with in general and needs to be decided on a case by case basis.
393	3	**Comment:** The sentence should be made clearer: For products having a potential to leave local residues, additional residue studies are needed; 'additional' here means no extrapolation of withdrawal periods via the "bioequivalence" approach is therefore possible. From the BE guideline EMA/CVMP/EWP/16/2000: 'It should be noted that bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues (for example intramuscular and subcutaneous injectables, dermal and transdermal applications). In this case, information on the	Accepted. Reference to the bioequivalence guideline was added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		behaviour of residues at the site of administration needs to be assessed before the withdrawal period is extrapolated.	
441	3	**Comment:** Reference is made to Klimisch et al.,1997. Please add the full citation to the reference list, so it can be retrieved by the reader of this guidance. Recommend deletion of "or equivalent". There is not a well recognized equivalent, although the ToxRTool using Klimisch reliability categories, may harmonize the approach (Schneider, 2009). *Schneider K, Schwarz M, Burkholder I, Kopp-Schneider A, Edler L, Kinsner-Ovaskainen A, Hartung T, Hoffmann S. "ToxRTool", a new tool to assess the reliability of toxicological data. Toxicol Lett. 2009 Sep 10;189(2):138-44.* **Proposed change (if any):** **Klimisch H.J., Andreae M. Tillmann U.– A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data, Regulatory Toxicology and Pharmacology, 1997, 25(1), 1-5**	Accepted.
471	3	**Comment:** For marketing authorisation in accordance with Article 23 of Regulation (EU) 2019/6 the GL requested the inclusion of a standard statement in the SPC without considering the areas for which only	Not accepted. This is out of scope of this guideline. More specific information on the areas with reduced data sets will be included in the EPAR, as mentioned now in the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		reduced data requirements are implemented or if the possibility of limited data requirements is used at all. Would it be reasonable to provide more specific information in the SPC and define the areas that make use of the option to use reduced data requirements more precisely?	