9 September 2021
EMA/CVMP/147926/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6' (EMA/CVMP/52665/2020)

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

Stakeholder no.	Name of organisation or individual
1	Syndicat de L'industrie du Medicament et Diagnostic Veterinaires (SIMV)
2	Cruelty Free International (CFI)
3	European Group for Generic Veterinary Products (EGGVP)
4	AnimalhealthEurope

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	SIMV thanks the CVMP for this important reflection paper and for the opportunity to comment. All the comments provided below are made with the view of Novel Therapies and especially Stem Cell Novel Therapies.	Thank you for the comment. Please find responses to the specific comments in the section below.
2	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. However, the guideline does not explicitly state that reduced data requirements also come with the added benefit of reducing animal testing. In Europe there is a legal obligation to use alternatives to animal tests if available (i.e. Directive 2010/63) and to take the principles of the 3Rs into consideration – both of which should be clearly mentioned in the guideline (as they are in a similar separate draft guideline on 'safety and residue requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/16'). We urge the CVMP to reference legislation relating to the protection of animals used for scientific purposes, and to incorporate the principles of the 3Rs into the revised guideline where appropriate in the interests of animal welfare. 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).	Thank you for the comments. Please find responses to the specific comments in the section below.

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	Also, while we realise that the Target Animal Safety (TAS) test is not the focus of this update, we do feel that the opportunity could be taken to strengthen the language on the circumstances under which this test could be avoided for limited market veterinary products.	
3	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.	Thank you for the comments. Please find responses to the specific comments in the section below.
	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.	The CVMP is of the opinion that objective data reductions, exemptions or omission of specific documentation can be easily identified in comparison with the *Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market* (EMA/CVMP/EWP/117899/2004–Rev.1). Please note that a tabulated overview was not considered feasible, as data requirements depend on the particular case and can be presented in a better manner in text format.
	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.	Please note that fees are outside 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) and/or eligibility for authorisation according to Article 23 (Applications for limited markets)' (EMA/CVMP/235292/2020)".

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	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 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.	As indicated in the guideline, not all scenarios can be foreseen and addressed in a general guidance document. The requirements and data reductions will depend on the type of the product (active substance, mode of action) and the availability of information (published literature, data in other species, other indications). Therefore, Scientific Advice procedure is available to applicants to confirm the precise requirements for a specific application and ensure that the data package is appropriate.
	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.	Please note that the current *Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market* (EMA/CVMP/EWP/117899/2004–Rev.1) will cease to apply as of 28 January 2022 and will be replaced by the present guideline (EMA/CVMP/52665/2020).
	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.	Please 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)".
	In order help readers with scope and terminology, EGGVP suggests that the guideline is revised so as to provide the necessary clarity on that.	The scope of the present guideline is clearly stated (applications for VMPs intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6). No further amendments are considered necessary.

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	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 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. 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. 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 Otherwise the requirements will aggravate development of new products with limited market value because of the low or late return on investment	Please note that quality data requirements 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) and/or eligibility for authorisation according to Article 23 (Applications for limited markets)' (EMA/CVMP/235292/2020)".

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	According to current guidelines, studies should be conducted according to GxP. In the new draft guidelines studies may not be GLP/GCPv-compliant, but these practices should be encouraged and proper justification may be provided in their absence. Proposal for a mention "in accordance with the GxP principles, unless properly justified", would be welcome by industry for the sake of predictability.	Please find responses to the specific comments in the section below.
4	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. This Draft Guideline addresses VMPs /MAAs for limited markets submitted under Article 23. It replaces the Guideline for Efficacy and TAS data requirements for MUMS. 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. This Draft Guideline on efficacy and TAS under Art 23 is seen complementary to the draft guideline on safety and residues under Art 23 (EMA/CVMP/345237/2020). Therefore, the same principle for data gaps to Annex II should apply, in particular with regards to surrogate methods and endpoint specific surrogate (non-Annex II/non-guideline) approaches. These options should be added to this Draft Guideline to the section 5 (Preclinical requirements) and 6 (clinical trials).	Thank you for the comments. Please find responses to the specific comments in the section below. 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)".

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 74-76	1	*Comments*: It is understood from the guideline that, as stated lines 74-76, a novel therapy VMP could also fall into the category of VMP other than biological VMPs or in the category of biological VMPs other than immunological VMPs. Then the Novel Therapies are included in the guideline EMA/CVMP/52665/2020. In Annex II, Novel Therapies were addressed in a specifically dedicated section, section V, and in this section V, it is indicated that a novel therapy could also fall under a third product categorie (c), immunological veterinary medicinal products (section V.1.1.1. page 75 of Annex II). As a result, Novel Therapies are also addressed in Guideline EMA/CVMP/59531/2020. It is stated in Annex II (section V.1.1.3.) that the manufacturing processes for novel therapy veterinary medicinal product shall comply with the principles of Good Manufacturing Practice adapted where necessary to reflect the specific nature of those products. This is again a special consideration for novel therapy that is different from the general rule stated in Art 23, in which reduction for data requirements are only consider for safety and efficacy documentation. Therefore, it would be worthwhile to consider the need for developing a specific guideline dedicated to	Not accepted. Novel therapy VMPs referred to in guideline EMA/CVMP/52665/2020 will be addressed on a case-by-case basis. The guideline will only apply to products that are eligible under Article 23 of Regulation (EU) 2019/6. In Annex II to Regulation (EU) 2019/6, novel therapies are addressed in a section specifically dedicated to products which are annex II-compliant, and the need for developing specific guidance on quality, safety and efficacy data requirements will be considered by the specific working party.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		requirements for applications for Novel Therapies intended for limited markets, considering quality, safety and efficacy, to be in accordance with the requirements of Regulation 2019/6.	
Lines 176-179	1	*Comments*: Section 5.2. Development of resistance or tolerance to the active substance This sentence, applied to the development of stem cells or monoclonal antibodies, can lead to significant uncertainties in the development: indeed, a possible decrease in efficacy after 5-6 administrations is described, caused by the development of antibodies directed against stem cells or monoclonal antibodies. Demonstrate that this is not the case would require specially designed field clinical trials, with a very long study timeline. Moreover, this contradicts point 6, which states that clinical documentation is not required if there is reasonable expectation of effectiveness, which is the case for the first administrations. Therefore, it proposed that novel therapies are excluded from the scope of this section.	Not accepted. See answer above. Applications for novel therapy VMPs submitted under Article 23 of Regulation (EU) 2019/6 will be addressed on a case-by-case basis.
Line 194	1	*Comments*: Section 5.4. Target Animal Safety The meaning of the following sentence "the absence of a VICH compliant TAS study may be accepted" should be clarified. Does that mean that no study is expected when enough data are available from other study (clinical study)?	Correct. Article 23 of Regulation (EU) 2019/6 foresees the possibility for certain safety data not to be required. The absence of a VICH GL43-compliant TAS study may be accepted if adequate data is otherwise available to permit a comprehensive evaluation of target animal tolerance.

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Introduction (60-64)	2	"*It is the intention of the guideline to indicate which data requirements can be reduced for applications submitted in accordance with Article 23 of Regulation (EU) 2019/6, to facilitate the applicant's work for estimating the required resources needed for a limited market application and preparing the application dossier, and provide for predictability*." *Comment*: In the Introduction to the guideline there should also be mention of the positive impact of reduced data requirements for limited market veterinary products on the reduction of animal testing. This would also be an appropriate place to reference the 3Rs principles and highlight the legal obligation to conduct animal tests only as a last resort. *Proposed change*: Add the following text to the end of this sentence (this is similar to the language that was accepted in the previously adopted MUMS/limited market guidelines): "It is the intention of the guideline to indicate which data requirements can be reduced for applications submitted in accordance with Article 23 of Regulation (EU) 2019/6, to facilitate the applicant's work for estimating the required resources needed for a limited market application and preparing the application dossier, and provide for predictability. 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	Partly accepted. Relevant wording added to the Introduction.

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		the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes, Directive 2010/63/EU on protection of animals used for scientific purposes and the 3R principles (replacement, reduction and refinement), which should be applied to all testing involving animals".	
Legal basis (115-154)	2	*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 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. Directive 2010/63/EU is not the legal basis for applications for VMPs intended for limited markets submitted under Article 23 of Regulation (EU) 2019/6.
188-201	2	"*Appropriate data to characterise the tolerance of the target species to the test product following administration by the proposed route(s) should be provided. Typically, target animal tolerance (local and systemic) should be confirmed in healthy animals of the target species in a negative-controlled target animal safety (TAS) study implemented under well-controlled laboratory conditions in line with the principles of VICH*	Not accepted. A VICH-compliant TAS study conducted in healthy animals is a standard requirement for applications for veterinary medicinal products. With reference to the concern expressed about target animal species being 'destroyed', as indicated in VICH GL43, post-mortem examination may not be necessary in the absence of

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		GL43 in order to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. However, the absence of a VICH complaint TAS study may be accepted, if justified, where a comprehensive evaluation of target animal safety is possible by other means, foremostly based on data provided from exploratory and/or clinical studies following administration of the product at the recommended treatment dose and duration of therapy to an adequate number of animals representing the target (sub)species. Tolerance may also be supplemented with reference to use in another relevant species in which tolerance is expected to be similar, data from toxicity studies in laboratory animals, literature reports and pharmacovigilance data." *Comment*: We appreciate the minor changes that have been made to further clarify the conditions under which a TAS might not be required for limited market veterinary products. However, we would like to suggest some further strengthening of the language. The TAS has been criticised for being inhumane, wasteful and of limited scientific validity. For example, a 1996 review article highlighted that "there may be a significant number of drugs in which more target species animals may be destroyed during testing than would ever die from toxicity in clinical use" (A proposed design for conducting target animal safety studies for developing new veterinary pharmaceuticals. (1996).	systemic clinical signs or abnormal findings in clinical pathology. Section 5.4 of the present guideline already foresees the possibility to utilise tolerance data from clinical trials as an alternative to a specific TAS study, provided the tolerance data generated from clinical trials is sufficiently comprehensive. Although toxicity data from laboratory animals in which tolerance is expected to be similar may be used to supplement tolerance data, it is not considered appropriate to restrict such data to only that which is existing, i.e. prevent applicants from generating their own laboratory animal toxicity data if warranted.

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		Regulatory Toxicology and Pharmacology, 23: 49-54). It also concluded that "the upper limit of safety is not a single-point dose for the entire population of target species, and so any attempt to indicate an absolute upper limit creates a false sense of security". Furthermore, since single dose toxicity studies in two species are already requested as a standard requirement for the safety testing of new veterinary medicines, it is not clear what added value the TAST could have to the overall safety assessment. We request that stronger recommendation to avoid this superfluous test be included in this section of the guideline. For example, by the insertion of text that was in the CVMP's draft version of the 'Guideline on efficacy and target animal safety data requirements for veterinary products intended for MUMS/limited market', 21 January 2016. *Proposed change*: Appropriate data to characterise the tolerance of the target species to the test product following administration by the proposed route(s) should be provided. Typically, target animal tolerance (local and systemic) ~~should be~~ **is** confirmed in healthy animals of the target species in a negative-controlled target animal safety (TAS) study implemented under well-controlled laboratory conditions in line with the principles of VICH GL43 in order to characterise signs of intolerance and to establish an adequate margin of safety using the recommended route(s) of administration. However, the benefit of conducting standard target animal safety	

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		studies in healthy animals is questionable because use of the product in healthy animals may not provide a reliable indication of the expected tolerance in the target population associated with normal field use of the product. A more suitable approach may be to investigate tolerance within the scope of field studies on efficacy. Therefore, the absence of a VICH complaint TAS study may be accepted, if justified, where a comprehensive evaluation of target animal safety is possible by other means, foremostly based on data provided from exploratory and/or clinical studies following administration of the product at the recommended treatment dose and duration of therapy to an adequate number of animals representing the target (sub)species. Tolerance may also be supplemented with reference to use in another relevant species in which tolerance is expected to be similar, existing data from toxicity studies in laboratory animals, literature reports and pharmacovigilance data."	
155(full section 5) 202 (full section 6)	3	*Comment*: This Draft Guideline is seen complementary to the draft guideline on safety and residues under Art 23 (EMA/CVMP/345237/2020). Therefore, the same principle for data gaps to Annex II should apply, in particular with regards to surrogate methods and endpoint specific surrogate (non-Annex II/non-guideline) approaches. *Proposed change*: data gaps principle to be stated to the section 5 (Preclinical requirements) and 6 (clinical trials).	Not accepted. Section 4 (Legal basis) already clarifies that an applicant shall not be required to provide the comprehensive safety or efficacy documentation subject to certain conditions. Concerning pre-clinical and clinical data, it is not considered possible to specify what endpoints and/or surrogate markers might be acceptable as this would need to be determined on a case-by-case basis.

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155 (full section 5) 202 (full section 6)	3	*Comment*: Overall, the content of sections 5 and 6 of this draft guideline is gives too few indications. I.e. - Exploratory studies not defined/precised - Vague terminology of requirements "expected efficacy", "adequacy of data"… Does it mean that previous recommendations (in current guideline) will apply implicitly regarding these points?	Not accepted. As indicated in the guideline, not all scenarios can be foreseen and addressed in a general guidance document. The requirements and data reductions will depend on the type of the product (active substance, mode of action) and the availability of information (published literature, data in other species, other indications). The Scientific Advice procedure is available to applicants to confirm the precise requirements for a specific application and ensure that the data package is appropriate.
158-160	3	*Comment*: The guideline mentions the possibility for extrapolation of preclinical data between species, but clear examples of such extrapolation would be welcome. *Proposed change*: To precise species that are known to be comparable as regards of the metabolism	Not accepted. As indicated in the guideline, not all scenarios can be foreseen and addressed in a general guidance document. The possibility to extrapolate pre-clinical data from one species to another will depend on the type of the product (active substance, mode of action) and the comparability of the pharmacology of the product between the species. However, data on metabolism might be one aspect used by an applicant in support of such extrapolation. The Scientific Advice procedure is available to applicants to confirm the precise requirements for a specific application and ensure that the data package is appropriate.
173	3	*Comment*: Alignment terminology with definitions in section 3 is recommended. *Proposed change*: Dose confirmation / clinical trial	Accepted. Text amended as suggested.
170-175	3	*Comment*: Alignment or clarification of terminology 'Basic pharmacokinetic data' and 'specific pharmacokinetic would be welcome	Partly accepted. It is intended to clarify that comprehensive pharmacokinetic data is not required (given the nature of the application). A definition of 'basic pharmacokinetics' is provided in the CVMP Guidelines for the conduct of

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			pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL) and has been introduced as further clarification. The last sentence in this section has also been amended to clarify that product-specific PK data can be omitted. See proposed text.
202 (section 6)	3	*Comment*: GCPv is not mentioned. It can be appreciated that all studies as mentioned (»Exploratory/pilot studies, pre-clinical studies (e.g. dose determination or dose confirmation studies), data stemming from clinical trials conducted outside the Union«) may not be GLP/GCPv-compliant *Proposed change*: These practices should be encouraged and proper justification may be provided in their absence.	Accepted. Wording indicating that confirmatory clinical trials (where provided) shall be conducted in compliance with established principles of good clinical practice (GCP), unless otherwise justified, has been added at the end of section 6 'Clinical trials'.
211-212	3	*Comment*: EGGVP suggests more openness regarding the geographical origin of data from clinical trials (within or outside the European (?) Union), which is considered to be of little relevance if requirements for clinical trials are fulfilled. *Proposed changes*: *"…data stemming from clinical trials ~~conducted outside the Union~~ along with relevant information…"*	Not accepted. Principally, clinical trials should be performed in the European Union. The guideline opens up for alternatives to comprehensive clinical documentation, including clinical trials conducted outside the EU.
10	4	*Comment*: Clarify that this GL will replace a previous GL. • Same approach as for 'Safety and residue data requirements for the establishment of maximum	Accepted. Clarification added on the 1st page of the guideline.

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		residue limits in minor species Draft guideline' in lines 9-11. • In line with statement on EMA homepage (Efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 | European Medicines Agency (europa.eu)) *Proposed changes*: Please add the following: 'This guideline will replace the Guideline on efficacy and target animal safety data requirements for veterinary medicinal products intended for minor uses or minor species (EMA/CVMP/EWP/117899/2004 Rev.1).'	
70	4	*Comment*: In addition to the reference to the EMA reflection paper also reference to further guidance on VMPs for 'limited markets' should be made. (i.e. 'limited markets' not falling under Article 23). *Proposed change*: Please add the following: Specific data requirements guidance to be elaborated for products that are classified as a 'limited market' but are not eligible for consideration under Article 23.	Not accepted. Please 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)".
82	4	*Comment/rationale*: Differentiate between VMPs for limited markets under Art 23 and VMPs for limited markets (not under Art 23). *Proposed change*: Please add the following:	Not accepted. Please note that the text in brackets referred to is in line with the title of Article 23 of Regulation (EU) 2019/6.

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		… according to Article 23 (Applications for limited markets under Art 23).	
83	4	*Comment/rationale:* The Concept paper EMA/CVMP/539861/2019 announced the introduction the revision of the guideline with the aim to establish the minimum data package required for assessing efficacy and in particular addressing the concepts of 'proof of efficacy' or 'proof of concept'. Therefore, respective definitions are deemed necessary. *Proposed changes:* Please add the following: Proof of Efficacy: Comprehensive, Annex II compliant, clinical documentation including confirmatory clinical trial data. Based on this data package efficacy can be proven for the VMP. This is in contrast to a reasonable expectation for effectiveness, which is based on a 'Concept for Efficacy/Effectiveness' (see below). Proof of Concept for Efficacy / Effectiveness: Collection of data/information (e.g. pre-clinical studies, non-pivotal data, exploratory studies, pilot studies, published literature, review articles, expert statements or justification) that allow to conclude on the efficacy under art 23 conditions, i.e. showing identifiable data gaps with regards to basic Annex II requirements, more specific, an absence of (confirmatory) data required by Annex II, going beyond the flexibility already provided for in Annex II. 'Proof of concept for efficacy' is the conclusion that there is reasonable expectation of effectiveness.	Not accepted. Please note that the terms 'proof of efficacy' and 'proof of concept' are not referred to in the guideline, therefore no definition for these terms is deemed necessary.

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97	4	*Comment/rationale:* Better explanation/differentiation/definition on terminology in context with studies and trials needed, beside the definitions of 'clinical trial' 'pre-clinical study'. E.g.in section 5.3. Dose justification / confirmation of this GL the terms 'exploratory or pilot studies in the target animals' are mentioned that warrant further attention. In section 5.4 'exploratory studies' are mentioned and in section 6 'Exploratory/pilot studies' are mentioned. *Proposed changes:* Please add the following definitions after the definition of 'pre-clinical study': • exploratory studies in the target animals: …… • pilot studies in the target animals: …….	Accepted. Definition for 'exploratory trials / pilot studies' has been included in Section 3 of the guideline.
156-157	4	*Comment/rationale:* Reference to Definition of 'Pre-clinical studies' needed within this GL to indicate that statements complement each other. Otherwise the statements seem to contradict each other. *Proposed changes:* Please add the following: Pre-clinical studies aim to investigate the pharmacological activity, pharmacokinetic properties, dose and dosing interval, resistance (if applicable) and the target animal tolerance of the product. (see also section '3. Definitions – Pre-clinical study' of this GL).	Accepted. Text included as suggested.
166	4	*Comment:* Alignment with draft guideline on safety and residues under Art 23 (EMA/CVMP/345237/2020).	Not accepted. Section 4 (Legal basis) already clarifies that an applicant shall not be required to provide the comprehensive safety or efficacy documentation subject to certain

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		Proposed changes: Please add the following: Complementarily or alternatively to standard requirements and data reduction options, for the purpose of supporting "limited markets under Art 23", it is possible to use surrogate methods, such as endpoint specific surrogate (non-Annex II/non-guideline) approaches, if adequately justified.	conditions. Concerning pre-clinical data, it is not considered possible to specify what endpoints and/or surrogate markers might be acceptable as this would need to be determined on a case-by-case basis.
170-175	4	*Comment:* The terms 'Basic pharmacokinetic data' (line 170) and 'specific pharmacokinetic … data' (line 175) need to be better differentiated/explained, or aligned, (using the same expression) in case the same type of data is meant.	Accepted. A definition of 'basic pharmacokinetics' is provided in the CVMP Guidelines for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-FINAL) and has been introduced as further clarification. The last sentence in this section has also been amended to clarify that product-specific PK data can be omitted. See proposed text.
182	4	*Comment:* Better explanation of 'In principle, specific…' warranted. In case 'In principle, …' is to be understood as 'In an Annex II compliant data package, specific …' it needs to be better defined where the identifiable data gap could be within this topic of 'Dose justification/confirmation'.	Not accepted. No data gap in terms of justifying the proposed dose, dosing interval, duration of treatment and any re-treatment interval is foreseen. The term 'In principle' is used on the grounds that proprietary dose justification and/or dose confirmation studies may not always be required if acceptable data is available from other sources, e.g. published literature.
184-185	4	*Comment:* According to the wording in this paragraph, the pre-requisite to waive certain dose justification or dose confirmation studies is the absence of a disease model. Which implies: if a disease model exists, then full dataset of dose justification/confirmation is mandatory.	Partly accepted. It is anticipated that it will be more likely that clinical trial data is omitted rather than dose justification/confirmation data. However, additional wording has been introduced to address the scenario whereby clinical trial data is provided.

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		This criterion is against the spirit of the 2019/06 to offer an incentive to development 'on the basis of a benefit-risk assessment of the situation' (Recital 30). Even if disease models exist, it should still be possible, if adequate scientific justification is provided, to waive the generation of certain dose justification/confirmation data. One example could be the avoidance of dose justification/confirmation in an application supported by robust PK/PD data to justify the dose and field clinical efficacy data.	
187-201	4	*Comment:* Better differentiation to flexibility already provided for in Annex II is needed, as the absence of a VICH compliant TAS study may be accepted, if justified, already for VMPs with a dossier compliant with Annex II. The identifiable data gap interpreted as the absence of (confirmatory) data required by Annex II, going beyond the flexibility already provided for in Annex II, needs to be better specified for this section here (5.4 Target animal safety) in this GL.	Not accepted. It is considered that section 5.4 already provides sufficient clarifications in terms of the data requirements needed to support the absence of a VICH GL43 compliant TAS study.
210	4	*Comment:* Alignment with draft guideline on safety and residues under Art 23 (EMA/CVMP/345237/2020). *Proposed changes:* Please add the following: Complementarily or alternatively to standard requirements and data reduction options, for the purpose of supporting "limited markets under Art 23", it is possible to use surrogate methods, such as endpoint	Not accepted. Section 4 (Legal basis) already clarifies that an applicant shall not be required to provide the comprehensive safety or efficacy documentation subject to certain conditions. Concerning clinical data, it is not considered possible to specify what endpoints and/or surrogate markers might be acceptable as this would need to be determined on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		specific surrogate (non-Annex II/non-guideline) approaches, if adequately justified.	
211-212	4	*Comment:* In general, the geographical origin of data from clinical trials (within or outside the European (?) Union) seems to be of little relevance. Referring to 'data stemming from clinical trials conducted outside the Union' would rather distract and therefore it is proposed to keep the information independent from geographies. Exploratory/pilot studies, pre-clinical studies (e.g. dose determination or dose confirmation studies), data stemming from clinical trials conducted outside the Union along with relevant information from the published literature may be used to provide information to support the safety and expected efficacy of the product in the absence of comprehensive clinical documentation, if minimum requirements for clinical trials are fulfilled (e.g. provision of control (group) data, anecdotal data from single animals only are not acceptable). However, in the absence of confirmatory clinical trials, the data provided should be adequate to allow a reasonable conclusion to be made on target animal safety and expected efficacy of the VMP. Specific situations, *e.g*. for VMPs in the antiparasitics area, where geographies may play a more important role are addressed already in other concepts and guidelines. *Proposed changes:* Please delete the following:	Not accepted. Principally, clinical trials should be performed in the European Union. The guideline opens up for alternatives to comprehensive clinical documentation, including clinical trials conducted outside the EU.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		… data stemming from clinical trials ~~conducted outside the Union~~ along	
215-216	4	*Comment:* The exact meaning of '*confirmatory clinical trials*' in this context should be clarified or the wording revised. This definition can create confusion as earlier in the document, the 'confirmation' studies are included within the 'pre-clinical trials'. It is proposed that the term 'confirmatory' is deleted as this won't change the meaning the sentence.	Not accepted. It is considered that the risk of confusion between "dose confirmation studies" (i.e. pre-clinical studies) and "confirmatory clinical trials" (i.e. clinical trials) is low.
216	4	*Comment*: 'Target animal safety' terminology needs better alignment with section 5 and the 'Target animal tolerance' mentioned therein. Consider a better differentiation of terminology for efficacy (performance of an intervention under ideal and controlled circumstances) and effectiveness (performance under 'real-world' conditions). *Proposed changes:* Please add the following: … be made on target animal ~~safety~~ tolerance and expected ~~efficacy~~ effectiveness of the VMP.	Not accepted. Safety and efficacy are routinely used in CVMP GLs to equate to tolerance and effectiveness without misunderstanding. Section 5.4 is entitled 'Target animal safety'. For consistency purposes, it is proposed to retain the same terminology in this guideline.