EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2021
EMA/CVMP/147858/2021
Committee for Medicinal Products for Veterinary Use (CVMP)

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)

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	Triviumvet DAC
3	Association of Veterinary Consultants (AVC)
4	Animal Health Europe
5	European Group for Generic Veterinary Products (EGGVP)

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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.	Noted.
2	Additional reflection papers would be appreciated as soon as possible to clarify the submission process and review periods for requests for classification as limited market and eligibility for Article 23.	The procedures for classifying an indication/product as a limited market and/or for determining eligibility for Article 23 are detailed in section 5 of the final reflection paper. The procedures will be subject to review and will be revised, as appropriate, based on experience.
3	The Association of Veterinary Consultants (AVC) appreciates that there is a legal basis for products with a Limited Market – previously MUMS – in the new veterinary regulation 2019/6. We wish to express recognition for the large effort put into this important field over the last decades by the CVMP and all associated persons and institutions. We highly welcome that the CVMP has expressed the intention to maintain the same level of assistance and flexibility for LM-products in the future as what the current policy has allowed. The MUMS-policy and its flexibility in interpretation of the legal requirement for submission of studies and data for such products has allowed the development of many useful and important veterinary medicines and vaccines that would otherwise not have been introduced on the EU market, for the benefit of the animals, the farmers and pet-owners, and the veterinarians. It is of utmost importance that this	Noted. It is agreed that the MUMS/limited market policy has allowed for the authorisation of useful products that may not have otherwise been developed in the absence of the incentives offered under the policy. The intention of this piece of work is to implement Regulation 2019/6 in such a way that it builds on what is currently possible under the MUMS/limited market policy.

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	initiative maintains its momentum, so the many smaller sectors, diseases, and veterinary problems also will get medical weapons to fight for a better animal health. Based on the wording of the regulation, allowing the regulators to grant marketing authorisations on pure benefit: risk, we consider that, depending on the benefit, more risks than currently proposed, maybe possible to take. In our perspective, the current proposal is only a very limited reduction of data requirements, considering the limitation of the marketing authorisation defined in Art. 23 for limited markets. It is also not clear which reduction in data requirements would be available for product for limited market products applied for under Art. 8. We therefore consider that a lot more detailed discussion is required on the potential data requirements in order to promote the availability of registered products for limited markets.	Regarding the reduction in data requirements (relative to Annex II) foreseen for products eligible for Article 23, see the data requirements guidelines. Noted. Further clarity on this specific point is included in the revised reflection paper. Specifically, the following text is included in section 4.1 of the final reflection paper: "Detailed guidance on the flexibility already provided for in Annex II to meet data requirements for an application dossier under 'limited market' conditions, but not being eligible under Art 23, will be developed"
4	AnimalhealthEurope thanks the CVMP for this important reflection paper and is grateful for the opportunity to comment. Articles 23 and 24 are part of the tools within Regulation 2019/6 aimed at improving the availability of medicinal products in the veterinary, which is often characterised by small markets. The reflection paper is useful, bringing clarification to a number of questions concerning the application of the limited market provisions (see slides 3 and 4 of the industry presentation to the focus group meeting). In our comments we will endeavour to highlight and explain where we believe further clarification is needed. The clarification on p. 3 that one of the primary objectives was to elaborate an approach that will ensure that the regulatory system can continue to issue marketing authorisations for the type of	Noted.

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	products that are being authorised currently as a MUMS/limited markets product is welcome. AnimalhealthEurope understands this would apply to: - products currently not registered but having been granted as MUMS/limited markets status under the current CVMP policy and - products that will be granted a limited markets status in line with Art. 4(29) but will not be eligible under Art.23. It is indeed critical to ensure those products can continue to be authorized. The current MUMS policy The MUMS concept was welcome at the time it was developed (15 years ago), but in reality, at least from an IVMP standpoint, the implementation was ultimately not very successful. More than 270 MUMS classifications were assigned, but this led to the development and approval of only a few products. The cost of the data requirements in compliance with the Annex remained a significant barrier, even with the MUMS guidelines. However, for reasons explained below, industry fully supports the CVMP's intention, as described in lines 71 and 72, to continue the current MUMS policy in conjunction with a new limited markets policy. (a) The need for its own section The clarification in the footnote at the end of p. 3, that products classified as MUMS and which are already authorised are considered "standard" authorisations and Regulation 2019/6 will not affect their authorisation status, is very much welcome. The information is very important and would merit being placed in a more prominent position than a footnote. The fate of the current CVMP policy on MUMS classification warrants its own section, so that it can be fully elaborated in what ways it will cease to be applicable from 28 January 2022, and in what ways it can continue to cater for products classified as MUMS under the current policy, but which fail to qualify as limited markets under article 23. For example, the	Regarding the first bullet, products/indications classified as MUMS under the current policy but for which no application has been validated by 28 January 2022 will have to be re-considered in light of the provisions of Regulation 2019/6. A new request for classification as limited market will have to be submitted to the Agency. See procedural aspects as detailed in section 5 of the final reflection paper. Regarding the second bullet, the AhE understanding is correct. Contrary to the AhE view, the CVMP would view the MUMS/limited market policy as a success. See 'MUMS/limited market scheme for veterinary medicines: 1st decade Report' (https://www.ema.europa.eu/en/documents/report/10-year-annual-report-mums/limited-market-scheme-veterinary-medicines_en.pdf) Noted. Comment accepted. Information included in section 4.2 of the final reflection paper.

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	statement in the footnote that "From 28 January 2022, the EMA policy on MUMS classification will cease to apply" appears to directly contradict the intention stated in lines 71 and 72. For more clarity and to avoid confusion with the terminology used, it is suggested to distinguish more clearly between MUMS/Limited markets status under the current policy (and relation to article 4(29) and limited markets status in line with Art 23.	Comment accepted. Terminology relating to Article 23 is clarified in section 2 of the final reflection paper.
	(b) Future application of the current MUMS policy The feedback of the CVMP on the currently authorized products with MUMS status, explains that most of these products may not be candidates for article 23 submission, but the objective is to ensure they can continue to be authorised. This is important, including for those products that contain in their marketing authorization both minor and major claims and/or species. It is also stated that submissions according to article 23 will lead to a stand-alone application and marketing authorization. This leads to the need, as stated in the reflection paper, for some continued "flexibility" regarding annex II requirements, for products already authorized for major claims/species and willing to add minor claims and/or species. It is clear that the current MUMS guidelines must remain to cater for the products classified as "non-art23 but still MUMS". Furthermore, it should be clarified that the current MUMS guideline on quality data requirements will also continue to be applied to products that are classified as Art23 products (this is important because there can be no data gaps for the Part II (quality), therefore the continued application of the MUMS Quality GL becomes paramount). The reflection paper mentions that specific data requirements guidance should be elaborated (line 229). While this statement is very welcome, as further guidance in this area could be hugely beneficial, it is also confusing, because this guidance already exists (i.e., the current MUMS guidelines). Either way, we would support	Noted. As acknowledged in the draft reflection paper (lines 228-230), CVMP is of the view that specific data requirements guidance should be elaborated for indications/products that are classified as a 'limited market' but are not eligible for consideration under Article 23. While there is an obligation that the dossier complies with the requirements of Annex II, it is recognised that there is a need for some flexibility vis-à-vis data requirements expected for a standard dossier. While the existing 'MUMS guidance' can be taken as the starting point for these future guidelines, they need to be reviewed and revised to ensure that they are aligned with the revised Annex II. Comment on the quality guideline is noted. The intention is to elaborate guidance for quality requirements for limited market products that are Annex II compliant (noting that this is a requirement of the legislation), but highlighting the flexibility provided for in Annex II vis-à-vis data requirements expected for a standard dossier. Such

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	this being given priority as it is an important element in meeting the objectives of the limited market and unmet need approaches. (c) The example of parasiticides In recent years, CVMP has approved 'rare' antiparasitic indications that were not supported by a complete efficacy dataset (most commonly the lack of a second dose confirmation study or lack of field efficacy data). Even for those products without an official 'minor use' classification, the MUMS criteria are often cited in the respective EPAR to justify CVMP decisions since the MUMS guideline allows the waiver of dose confirmation or field data. In those applications, clinical data were not completely absent but were less than what is prescribed in relevant CVMP/VICH guidelines: it is assumed that if the same applications are submitted as from 2022, they would still be considered 'Annex II compliant', within the limits of permitted flexibility, while never-the-less allowing a conclusion on a benefit-risk assessment. It is also understood that the new legislative framework should not be an obstacle to CVMP to adopt similar opinions e.g., approval of antiparasitic indications not supported by the full efficacy dataset, in the future, even if such applications are not eligible for consideration under Article 23. Flexibility, as per the current MUMS GLs on Quality, has a major impact on development of these products. In addition to the examples and considerations provided in the "Specific comments" section below, AnimalhealthEurope is happy to provide some specific comments/suggestions on that separately as a follow up from the limited market focus group meeting held on 30th March 2021.	guidance could be applied regardless of the underlying legal basis (that is, Article 8 or Article 23). Noted. Noted. Agree with understanding. Regarding the MUMS quality guideline, see previous comments.
	Limited markets - a proposed approach for immunologicals For IVMPs, MUMS MA dossiers were very close to full MA dossiers (as reflected in the reflection paper). The "Limited Market" is an opportunity for a "real change", and Industry is hoping that its implementation will increase the availability of IVMPs. At this point,	Noted. It is accepted that the Article 23 provision allows for the opportunity to improve availability.

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	however, it seems that the big challenge will be the uncertainty and unpredictability of the complex process, which will be a disincentive to risk investment in an area that is already, by definition, an insubstantial business case. To overcome this problem, at least for one group of products, we propose that for every IVMP that meets the limited market classification (i.e., art 23b), it would *de facto* be accepted that the benefit of the availability of the IVMP to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided. In other terms, for "limited market IVMPs", application of the IVMP guideline would be accepted "by-default". Predictability could be further enhanced by producing lists of diseases for which vaccines would automatically qualify. Industry considers this is a reasonable approach for IVMPs, and especially vaccines, as this is a well-known category of VMPs (risks are understood early in development) and the draft Guideline on IVMPs for limited markets adequately reflects upon which data can be omitted for the different categories of vaccines (live versus inactivated). Applying the IVMP guideline as intended (with data reductions) would still allow proper assessment (including benefit-risk assessment) by the Authorities (and the SPC will clearly state the "limited market" nature of the product) and potentially allow to contribute reaching a key objective of Regulation 2019/6 (increase availability of VMPs while guaranteeing public, animal health and environment protection), and fit the scope of the European Veterinary Vaccine's availability initiative.	The legislation requires that in order for a product to be considered for authorisation in accordance with Article 23 the applicant is required to show that the benefit of availability outweighs the risk of certain documentation not being provided. This is a condition that has to be satisfied and should not be assumed. CVMP is of the view that all product types should follow the same two-step procedure for determining eligibility for Article 23. See section 4.3 of the final reflection paper.
5	EGGVP welcomes this reflection paper. 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.	Noted.

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	The paper is well written and structured and explains how the process has been set-up. It is seen as a clear step forward from the current guideline. The following aspects are particularly welcome: - Definitions and scope, decision tree demonstrating the two-step approach showing that not all products that can be classified for use in limited markets are eligible for authorization under article 23. - Annex II is very helpful as it clearly compares the changes between article 23 limited market provisions versus current MUMS policy - Clarification that products classified as MUMS and which are already authorised are considered "standard" authorisations and Regulation 2019/6 will not affect the authorisation status. - Clarification to ensure that the regulatory system can continue to issue marketing authorisations for the type of products that is being authorised currently as a MUMS/limited markets product.	
	However, there are some aspects that present uncertainty and so – in EGGVP's view – should be rewritten to provide the necessary clarity. Some of these are formulated under the detailed comments section. Most prominent question is 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	As acknowledged in the draft reflection paper (lines 228-230), CVMP is of the view that specific data requirements guidance should be elaborated for indications/products that are classified as a 'limited market' but are not eligible for consideration under Article 23. While there is an obligation that the dossier complies with the requirements of Annex II, it is recognised that there is a need for some flexibility

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	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 in the concept paper. 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 concept paper is revised so as to provide the necessary clarity on that.	vis-à-vis data requirements expected for a standard dossier. Relevant working parties have been mandated to develop these guidance documents. While the existing 'MUMS guidance' may be taken as the starting point for these future guidelines, they need to be reviewed and revised to ensure that they are aligned with the revised Annex II. Comment accepted. Terminology relating to Article 23 is clarified in section 2 of the final reflection paper.
	EGGVP notes that applications for Art. 23 limited market status will undergo a scientific advice, with subsequent increased resource efforts for applicants (and this 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 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.	There is no reference to scientific advice in the eligibility reflection paper. That said, it is noted that recommendations to seek scientific advice are included in each of the draft data requirement guidelines. This is not to be interpreted as a requirement, but rather as a means for the applicant to get further clarity/predictability around data requirements. It should be noted that SMEs benefit from fee reductions by virtue of their SME status.

2. Specific comments on text

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352-354	1	Comment: The clarification in the footnote at the end of p. 3, that products classified as MUMS and which are already authorised are considered "standard" authorisations and Regulation 2019/6 will not affect their authorisation status, is welcome. The information is very important and would be more readable if placed in a more prominent position than a footnote. Footnote in page 3 is explaining how the CVMP intends to manage the transition of legislation with regard to the status of the products classified as MUMS, depending on whether they were already approved before Jan 28th 2022, or whether their application was only deposited or validated before this date. Our understanding is that products classified as MUMS and authorised before Reg. 2019/6 comes into action, will be considered as answering to all requirements of a 'standard MA' with Art.8, and not Art.23. This position from the CVMP may be justified by the statement made by the CVMP in section 4.2 that a majority of the dossiers of products classified as MUMS and authorised before Jan 28th 2022 were considered as answering the requirements of Annex II. However, it is important that the CVMP takes notice that for some products classified as MUMS and authorised before Jan 28th 2022, and especially for those that would be classified as Novel Therapies considering the New Regulation, they will be considered as having a 'Standard' MA Art. 28 despite that their EPAR show a gap with Annex II. The consequence of this would be that for the same species	Comment accepted. The understanding is correct. Again, all products classified as MUMS and authorised before Jan 28th 2022, including those that would be classified as Novel Therapies, will be considered as having a 'Standard' MA. Therefore, as suggested, the availability of those products in the market place may have implications for future decisions on eligibility. However, as noted in section

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		and the same indication (Limited Market for equine species and probably eligible to Art.23), a new product classified as Novel Therapies would probably be not eligible to Art. 23 considering the provisions for "unmet medical need" and those for "available therapies", and therefore would need to apply with a dossier in agreement with Art 8. This would prevent innovation and would introduce a distortion in competition. To avoid such a situation, we suggest the following adjustments to adapt the wording of the lines 352-354: Proposed change (if any): In addition, products authorised in accordance with Article 23 of Regulation 2019/6, or those classified as MUMS under Article 79 of Regulation 726/2004 and for which current EPAR display an identifiable gap with Annex II requirements, are excluded from the definition of "available therapy" because they are/were granted an authorisation in the absence of comprehensive data relating to either the safety or efficacy.	4.2 of the draft reflection paper, most products classified as MUMS/limited markets, and for which a positive opinion was issued by the CVMP, were authorised based on adequate characterisation of safety and proof of efficacy. Therefore, the proposed change is not accepted.
Lines 82-83 266-267	1	Comment: According to Article 4(29) of Regulation (EU) 2019/6 'limited market' means a market fort one of the following medicinal product types: - *veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas.* *An indication for classification is when the potential market is estimated to be less than 0.5%:* It could be noted that this percentage seems particularly low.	As is clear from the draft reflection paper, the threshold of 0.5% for classification as a limited market relates to % of the EU target species population. In particular, see lines 285 – 291 of the draft reflection paper ("…..if an indication/product application is made to an individual MS for a disease that occurs frequently in that MS, but would be considered to occur infrequently when viewed in the context of the EU as a whole, that indication/product should be classified as a limited market."). The threshold was selected

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249- 251-252		Moreover, when an applicant applies to Limited Market with or without eligibility to Art. 23, with a scope of disease/condition that is targeted and with a subpopulation defined by the extent of severity of the disease/condition, and which will be stated in the SmPC, CVMP should not invoke the potential use by the practitioner of the product in other conditions than the one mentioned by the applicant, to consider that the population targeted is greater than the one defined by the applicant provided it is based on reliable data. Particularly, the prevalence of a condition/medical or surgical procedure observed in one country can be higher than the prevalence globally observed in Europe, notably when in this country the level of medicalisation is high and the health insurance coverage is high Therefore prevalence observed in such country should not be transposed to whole Europe. This is of utmost importance when considering Novel Therapies. In fact, although it is not a general statement, some novel therapies have an important cost of manufacturing as the CVMP recognizes in lines 281-284. This is an important consideration in animal health, at the contrary to human context, since this may dramatically restrict the use of the product as a last line of treatment, after other treatments less costly would have been considered as unsatisfactory. Therefore, we propose the following adjustments to take into account this parameter which applies often to Novel Therapies: Proposed change (if any): 249- The intended target population (sub-category of target species, *e.g*. type of production, age, disease stratification depending on severity assessed by a well-recognized scoring system)	based on EMA experience with classification as MUMS/limited market under the EMA MUMS/LM policy: for the majority of indications/products (non-immunological VMPs) classified by the CVMP as MUMS/LM, the estimated potential size of the market was less than 0.5% of the EU target species population, whereas, for the majority of indications/products (non-immunological VMPs) classified by the CVMP as not MUMS/LM, the estimated potential size of the market was greater than 0.5% of the EU target species population. Any consideration of limited market status for products intended for use in major species will be based on the proposed indication. However, the CVMP reserves the right to take account of other potential uses, in particular, when it is clear that a product is likely to be used in the field more frequently for an indication other than that proposed (that is, off-label). It is agreed that cost of manufacture is a factor that will influence the extent to which a product is used. As recognised, this point is addressed in the draft reflection paper. However, the specific point relating to refinement of the target population depending on disease severity has not been captured. Rather than accepting the amendment as proposed, an additional bullet advising that the estimate of potential market size may be influenced by the precise wording of the indication has been included (See section 4.4 of the final reflection paper). Accept.

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253 206-261		251-252- "The frequency of the disease/condition in the EU relevant to the indication sought. Diseases/Conditions with low prevalence…" 253- Estimates of disease/condition prevalence should be supported by up-to-date data, as much as possible according to their public availability. 206-261- This annual estimate may be refined if the treatment is only medically justified or economically acceptable for a subset of animals at the geographical scale of the Union. Data from a specific MS should not be extrapolated to entire Union, unless soundly explained.	Accept with modification. The text has been amended to read: "Estimates of disease/condition prevalence should be supported by up-to-date data in the published literature, where available, and/or….." Change not acceptable. The issue of refining the estimate of potential market size based on the precise wording of the indication has been included (see section 4.4 of the final reflection paper). The issue of considering extent of use of a product in the EU context is adequately addressed in the final reflection paper.
340-346 and footnote 11	1	Comment: Lines 340-346 and footnote 11 CVMP proposes a scope for defining "unmet medical need". In the situation where there is a satisfactory method of diagnostic, prevention or treatment in the Union", CVMP creates an opportunity for new product to be eligible to Art 23. if it is "reasonably expected to provide a meaningful advantage over available therapy: that is, is safer, more effective or otherwise clinically superior". The words "clinically superior" are referred to the definition existing in regulation for human medicines. However, there are several issues arising from this provision. This definition of "clinically superior" triggers that the product shall first demonstrate either that it is safer or that it is more effective, two notions which are already in the sentence, but more importantly which requires that the applicant provides a pool of clinical data comparing the existing product with the new one, data which, in most of the case are not expected to	Accepted.

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340-346		exist, at the time an applicant apply for a LM classification and Art 23. eligibility. Furthermore, this definition implies that only if superiority in efficacy and safety cannot be demonstrated, then the potential for the product to bring major contribution to patient care is examined. For the Animal Health, this last consideration is known to be of utmost importance to ensure treatment compliance. It is also of utmost importance in the context of Novel Therapies which are expected to bring significant contribution to patient care. Therefore, to provide a nurturing environment for innovation rather that limiting it, we propose the CVMP to reconsider the wording of this paragraph as follow: Proposed change (if any): "A condition for which there exists no satisfactory method of diagnosis, prevention or treatment in the Union or, even if such a method exists, in relation to which the medicinal products concerned will be of ~~major~~ reasonable therapeutic advantage to those affected - available therapy does not exist for the same intended use proposed for the new product, or - available therapy does exist for the same intended use but the new product is reasonably expected to provide a meaningful advantage over available therapy: that is, is either safer or more effective or which is expected to bring a ~~major~~ significant contribution to patient care (*i.e* this could be exemplified by a lighter treatment regimen…)	Proposed change in text accepted with minor modification. See lines 371 - 373.
128-130 + 171-173 + 221-224	3	Comments: Unpredictability for LM-products that may not be accepted as art. 23 LM-products: The legal	The comment is noted; however, the principle concern expressed (LM *[products]* not eligible for art. 23 ....are left

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		base for art. 23 acceptance refers to a product intended for a minor species or a minor use in a major species, together with a clear benefit of availability and an identifiable data gap. The eligibility procedure is not developed or described, but the Reflection Paper seems to indicate that there will be many products similar to currently authorised MUMS-products that will not be eligible under art. 23, and hence must submit a full data package. This unpredictability for the developers is discouraging because it leads to difficulties with creating a development plan, including cost estimates, for a product. Companies cannot deduct which studies must be made prior to submission if they don't know whether a full data package or a reduced data package will be accepted. This means that the company must either seek eligibility at an exceedingly early stage where information is scarce or seek scientific advice for the development plan – with the delay of many months due to the time and money spent on planning, drafting, submission, and CVMP assessment – because of the uncertainty. Moreover, products similar to many currently authorised MUMS-products may now face the continuous hurdle that there is no firm legal basis for the reductions in data requirements, which are needed for their business plan to be possible, i.e., a continuation of the situation where the outcome is depending on the	without a legal base for such flexibility *[in data requirements]* and hence risk to be refused or abandoned) is not shared by the CVMP. Noting the legal framework provided in Article 23, it is clear that not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23. Additionally, the applicant will be required to show that *the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided* (Article 23(1)(a)). If a product satisfies the criteria to be classified as a limited market (according to Article 4(29)), but is not considered eligible for consideration under Article 23 then, by default, an Annex II compliant dossier in accordance with Article 8(1) will be required. Noting that one of the objectives of this current review (defining an approach to the implementation of Article 23) is to allow for a situation where the regulatory system can continue to issue MAs for the type of product that is being authorised currently as a MUMS/limited market product (that is, indications/products intended for limited markets should benefit from this classification even if not considered eligible for Article 23), CVMP is of the view that specific data requirements guidance should be elaborated for indications/products that are classified as a 'limited market' but are not eligible for consideration under Article 23. The purpose of this guidance would be to highlight how the flexibility provided in Annex II,

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		assessors' flexibility and case-by-case decisions on whether the Annex II is adequately fulfilled or not. This seems to be the case, e.g., for LM-products for which another (MUMS) product with the same indication is available, i.e., there is no unmet medical need because the already authorised MUMS-product "by definition" is a full dossier product. Proposed change (if any): We encourage the CVMP to further reflect if the proposed division is the correct one; particularly for those products that are LM but not eligible for art. 23, albeit still expected to need flexibility in relation to the full Annex II requirements. These products are left without a legal base for such flexibility and hence risk to be refused or abandoned. Experience shows that when there are no written guidelines for such intended flexibility, the stricter views will prevail over time, maybe because the unwritten intentions are forgotten, and this leads to fewer opportunities for authorisation of products falling just outside the margins of the written policy.	where certain studies can be omitted if justified, can be applied to such products. That is, while there is an obligation that the dossier complies with the requirements of Annex II, it is recognised that there may be a need for some flexibility vis-à-vis data requirements expected for a standard dossier. In conclusion, there is a clear legal basis for these products (Article 8, Annex II compliant) and the CVMP has provided a clear commitment to elaborate specific guidance to highlight how the flexibility provided in Annex II, where certain studies can be omitted if justified, can be applied to this category of product.
177-184	3	Comments: Antimicrobials + antiparasitics seems not accepted as eligible for art. 23: The AVC cannot read from the legal text that there is a legal basis to exclude certain groups of active substances prior to an evaluation. While it is understandable to be	Comment noted. It is agreed that there is no legal basis to exclude certain groups of active substances prior to an evaluation. However, the reflection paper is not absolute on this point ("……*those*

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		restrictive for widely used antimicrobial or antiparasitic products, e.g., for horses, there are uses and situations where eligibility would be justifiable, e.g., ophthalmological AM products, or emerging exotic parasites. Moreover, for extension of MAs to sub-groups, for which the authorised medicine is already used off-label, there should be a clear and obvious benefit in changing this to a labelled use, i.e. authorisation. For example, antimicrobials authorised for chicken which is currently used off-label for infectious diseases in ducks or pheasants would be better used on-label if authorisation was based on a small dose-effect study in the target species, than continuously used off-label at a dose judged by every vet individually. Also for addition of extra parasitic species to an existing product label, small effect studies should suffice. The vision to keep in mind, must be that it is better to have on-label use even if based on a small data set, than to maintain off-label use. The need for medicinal treatment of the diseased animals does not change, regardless of registration status of the medicine, but the usefulness of the treatment may improve. Proposed change (if any): We suggest that AMs and APs are also given the possibility of an eligibility assessment, however, with the guidance reflecting that the specific benefit of availability must be clearly	*products may not be candidates for authorisation in accordance with Article 23*"). As previously stated, it is clear that not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23. Additionally, the applicant will be required to show that *the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided* (Article 23(1)(a)). The intention of the CVMP was to highlight categories of product for which the absence of critical documentation (that would preclude an informed benefit/risk assessment) may not be accepted. In the example provided (extension of an AM used in chickens to duck/pheasants), the basic expectation would be adequate characterisation of safety (most of the safety data can be extrapolated from the major use, chickens) and confirmation of efficacy. Where such dossiers have been processed under the existing MUMS policy by the CVMP, they have been, invariably, Annex II compliant (albeit with a substantially reduced data package relative to the standard dossier) and it was possible to take a decision based on an informed benefit risk assessment. The CVMP absolutely agrees that it is better to authorised (on-label) use rather than off-label use; however, for antimicrobials and antiparasitics, in particular due to the potential for resistance emergence, there needs to be a

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		established for these types of products. Especially the extension of existing product label to include as many minor species and indications as possible, would be welcomed.	sound basis for the recommended treatment dose and efficacy at this dose needs to be confirmed in the target population. Again, the CVMP has provided a clear commitment to elaborate specific guidance to highlight how the flexibility provided in Annex II, where certain studies can be omitted if justified, can be applied to limited market products deemed not eligible for Article 23.
395-399	3	Comments: Renewal of art. 23 eligibility will not be possible if a full-dossier product has been authorised in the meantime with the same species and indications. However, for broadly worded indications, this may result in the loss of a useful product with another mechanism of action or a better safety or efficacy profile. The veterinarian needs a broad armamentarium of medicines preferably with diverging mechanisms of action for many minor diseases, e.g., epilepsy, cancer, some inflammatory diseases, or airway obstructions. Proposed change (if any): It is proposed to allow an individual re-evaluation of the continuous eligibility based on mechanism of action and patient considerations and not rely only on "same species and same indication". In addition, the LM-MAH should be given time to provide studies covering the original data gaps so the LM-product can change into an art. 8 legal basis in these cases and prevent an immediate	Accepted. This point has been addressed under the definition of 'Unmet medical need'. Point noted. However, at the 5 year time point, a decision has to be taken on the continued authorisation of a LM product and there is no provision in the legislation to grant

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		loss of an established and presumably useful LM-product.	an extension to allow generation of data. No change in text proposed.
5	4	Comment: The title of the reflection paper could be more aligned to the scope of the document and clarify limited markets classification and eligibility under Art 23 are separate procedures (see lines 88/90 where the scope refers to either limited markets classification and/or eligibility under Art 23, see also comment to line 194). As this is a major change compared to the current MUMS/limited market policy, it may be worth putting more emphasis on this. Proposed change: perhaps the title should be modified to read: *Reflection paper on classification of a product as intended for either a limited market and/or eligibility for authorisation according to Article 23 (Applications for limited markets)*	Accepted with modification. Procedure(s) to be further defined in section 5 of the final reflection paper. Title has been amended to read: "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)"
48	4	Comment: The second of the two incentive types of the current MUMS/limited market policy i.e., *financial incentives by means of fee exemptions or fee reductions,* is not specified anywhere in the reflection paper. As there is no obvious reason why that would not help stimulating innovation for limited markets, it should be re-introduced and applied for any type of limited market products, independent from species (food-producing / non-food-producing) or eligibility/non-eligibility under Art 23. Proposed change: Please add financial incentives for limited market products.	To be addressed separately by EMA.
71-77	4	Comment: We recognise the aim as stated and fully support this, however the way in which this will be applied, and the predictability of the accepted data	Noted.

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		reductions will be key to realise these aims. The way the concept of adequate characterisation of safety and proof of efficacy will be defined in the new guidelines, and how a benefit risk balance will be applied, will be critical. It may help to link this to the revision of the B/R GL.	
88-89	4	Comment: Section 3 scope: It is AnimalhealthEurope's understanding that products classified as MUMS under the current policy, but for which there is no intention to apply for a Limited markets status in line with Art 4(29), are also in the scope of the reflection paper. If so, this should be clarified in this section or in a new section.	Products/indications classified as MUMS under the current policy but for which no application has been validated by 28 January 2022 will have to be re-considered in light of the provisions of Regulation 2019/6. A new request for classification as limited market will have to be submitted to the Agency. See procedure as detailed in section 5 of the final reflection paper.
129-130	4	Comment: Clarification would be needed to reflect that 'limited markets' classification and 'Art 23' eligibility might be separate applications, and therefore separate procedures, i.e., more than one procedure. Proposed change: perhaps the sentence should be modified to read: ~~A procedure~~ *Procedures* to consider requests for classification as limited market and*/or* requests for eligibility for Article 23 will be established by the Agency.	See section 5 of the final reflection paper.
145-147	4	Comment: That MUMS products were Annex II compliant in the past and will have to be in the future is understood, but there is a risk this will lead to loss of flexibility and hamper innovation unless the current MUMs guidelines are retained. The differentiation of data requirements between VMPs classified as MUMS/ limited market (but not eligible under Art 23) and	The CVMP has provided a clear commitment to elaborate specific guidance to highlight how the flexibility provided in Annex II, where certain studies can be omitted if justified, can be applied to limited market products deemed not eligible for Article 23.

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		VMPs not classified as 'limited market' needs to be retained. Although the reflection paper states, in lines 71 and 72, that the aim is to continue to facilitate access to the market for MUMS products, this should be further elaborated to make the future policy completely clear (reference to the need for a separate section on this). A link to the guidance (to be developed or existing MUMS guidelines to be revised?) for limited market products not eligible under Art 23 (on the flexibility already provided for in Annex II) should be mentioned at the end of line 147. Proposed change: Please add the following sentence: "*… compliant dossier in accordance with Article 8(1) will be required." Detailed guidance on the flexibility already provided for in Annex II to meet data requirements for VMP application dossier under 'limited market' conditions, but not being eligible under Art 23, will [continue to] be provided.*	Accepted.
148-159	4	Comment: The situation that the limited market indication, for a product that carries other non-limited market indications, must be a separate product (i.e. dedicated presentation / product name / packaging) even if the pharmaceutical form, strength and presentation would be identical to the product(s) carrying the other non-limited market indications, would generate additional administrative burden and costs, potentially putting the launch of the limited market product at risk, which would counter to the intention of Regulation 2019/6.	Comment noted. No change in text proposed. However, further reflection is required in terms of what is needed to address this point from a regulatory perspective. This point will be addressed separately. Fees to be addressed separately by EMA.

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		The fees applicable to such limited market applications would also warrant clarification. Also, it is expected that a simple reference to the quality information (and possibly some toxicity information) of the already registered product (for the non-limited market indications) would be fully acceptable. Protection of technical documentation It is understood from Annex 2 (row at line 466 on protection of technical documentation), that protection would apply for the full time of validity of a limited market MA, as a generic is not possible. This is very much welcome. It should be clarified that after the missing data have been provided by the MA holder, and the MA is converted to a stand-alone product under article 8, the article 8 MA would then qualify for 10 years protection under article 39.	As a stand-alone application, a complete part 2 dossier (Annex II compliant) should be provided. Regarding the possibility to extrapolate safety data, see the relevant data requirements guideline. This understanding is correct. Comment accepted. Clarification provided in section 4.1 of the final reflection paper.
149-159	4	Comment: It is unclear what are the legal grounds to conclude that the Regulation does not allow authorisation in accordance with Article 23 in combination with other non-limited market indications (not benefitting from Article 23). There are no provisions in the Regulation that specifically exclude this type of combined indications. Moreover, excluding this type of indications from the scope of Article 23 would create an obstacle to limited market product development (see 156-159) in contrast with the intent of the legislator to promote availability of products for minor species or rare indications.	Not accepted. Having consulted with EMA Legal Services and the Commission, the CVMP has been advised that a marketing authorisation having two legal bases would not be possible.

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		Proposed change: Please delete following sentence (149-154): ~~"However, Regulation 2019/6 does not provide for a situation whereby a limited market indication for a product that carries other non-limited market indications could be considered eligible for authorisation in accordance with Article 23. That is, a marketing authorisation having two legal bases – Article 8 and Article 23 – would not be possible. In order to be considered for eligibility for authorisation in accordance with Article 23, the limited market indication would have to be considered in the context of a stand-alone application."~~	
156-159	4	Comment: As discussed above, if a VMP is already registered according to a standard application and according to an Annex II compliant dossier – why shouldn´t there be the option to apply for a certain additional indication under the eligibility of Art 23? If the current wording is kept and all applications would be required to follow the legal basis of the original application, nearly no application for new indications under the eligibility of Art 23 would be possible. Proposed change: Please amend the sentence to read: "For existing marketing authorisations, an application for authorisation of a new indication classified as a limited market could be submitted as a variation", ~~but, consequently, such applications would be required to follow the legal basis of the original application. In this scenario, the legislation requires that an Annex II compliant dossier is provided~~.	Not accepted. Having consulted with EMA Legal Services and the Commission, the CVMP has been advised that a marketing authorisation having two legal bases would not be possible. Therefore, from a regulatory perspective, an application for a limited market indication would have to follow the legal basis of the original application if submitted as a variation to that MA. Alternatively, to be submitted as under Article 23, it would need to be submitted as a stand-alone application. Commission to confirm.
162-182	4	Comment: section 4.2 should be re-written as it is based on a circular argument. This section concludes that "experience to date" shows that the application of MUMS guidance leads to MUMS products	Accepted. However, it should be noted that this section was included to address a perception/misconception that Article 23 simply

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		"authorised based on adequate characterisation of safety and proof of efficacy". But this is a self-fulfilling argument, because the MUMS guidance requires this (they cannot allow data gaps under the current legislation). This circular argument is repeated in the paragraph beginning at line 177, where "experience with application of the MUMS/limited market guidance" is used to conclude "an Annex II compliant dossier" should be a basic requirement for certain products. Instead, the reflection paper should recognise that the current MUMS products *are* Annex II compliant *because* the MUMS guidelines require them to be (and only a few MUMS products passed that hurdle).	gives legal effect to the current MUMS policy. That may indeed have been the original intention, but we have ended up with something different. The principle point to be made is that the Article 23 provision (which allows for deviation from Annex II requirements) should not be seen as giving legal basis to the current approach to handling MUMS/limited market products.
166	4	Comment: Please refer to the comment on lines 145-147: an adequate characterization of safety and efficacy might still include room for negotiation around data flexibility. It should be highlighted in the reflection paper that for MUMS applications there is still some flexibility in data submission, in line with the current MUMS guidelines, otherwise the aim of improving market accessibility is not met.	Accepted. Text amended to clarify that guidance on data requirements for limited market products not eligible for Article 23 will be developed. See section 4.1 of the final reflection paper.
167	4	Comment: Regarding the current "MUMS/limited market" status for centrally authorised products (Annex 1), would it be possible to also include the MUMS marketing authorisations through MRP/DCP/national procedures. As limited market classification can also be requested for such procedures, this might provide a more complete overview of Europe regarding currently authorized MUMS status products and if the same conclusion applies to the MRP/DCP/National procedures that	Not accepted. While it is agreed that a more complete overview of 'MUMS products' authorised in the Community would be desirable, CVMP does not have information on such products that are authorised at the level of the Member States.

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		some would also not qualify for article 23 limited market eligibility.	
171-174	4	Comment: It is well-understood from the reflection paper that the Article 23 provision should not be seen as giving a legal basis to the current approach to handling MUMS/limited markets. Industry was therefore surprised (and disappointed) to see a very similar level of data reductions in the new guideline, as currently applied for MUMS/limited market, for IVMPs eligible for Article 23 provision, despite the information provided in the reflection paper that, when applying the Article 23 provision, it is on the understanding that there will be an identifiable data gap at the end of the procedure (as reflected by a consequential SPC/PI wording). Similarly, lines 308-311 describe that when considering the absence of documentation in the context of the article 23 provision, the absence of critical data to evaluate safety or efficacy is meant (for example, authorising a product based on a 'reasonable expectation of effectiveness' being distinct from 'proof of efficacy'). Industry does not consider the current data reductions proposed for indications/IVMP products aligning to that scope.	Comment noted. It is the case that the level of data reduction accepted for vaccines deemed eligible for Article 23 may not differ substantially from data reductions currently applied under the EMAs MUMS policy. The reason for this is that where products are used to control disease in healthy animals, there needs to be basic assurances in terms of safety and there needs to be data to show that the immunological product is effective. 'Reasonable expectation of effectiveness' may be an appropriate threshold for vaccines in an emergency situation (use under exceptional circumstances), but may not be appropriate for a limited market vaccine. See the relevant data requirements guideline for more detail.
177-184	4	Comment: The reasoning why certain product types intended for limited markets (such as antimicrobials and anti-parasitics) and related indications should (continue to) be based on an Annex II compliant dossier, on the basis of experience to date with the application of MUMS guidance, is difficult to follow. It is AnimalhealthEurope's opinion that if those product types and related indications meet the criteria	Accepted. It is agreed that there is no legal basis to exclude certain groups of active substances prior to an evaluation. The paragraph in question has been deleted from the reflection paper; however, as previously stated, it is clear that not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23. Additionally, the applicant will

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		for limited markets classification under Art 4(29) and for eligibility under Art. 23, they should not be excluded. Regulation 2019/6 does not foresee exclusions from eligibility under Art. 23 based on product types. Applications for these product categories should still be judged on a case-by-case benefit-risk assessment. AnimalhealthEurope takes the opportunity to ask the CVMP to reflect, whether excluding antimicrobials and anti-parasitic indications by default from the scope of Article 23 would not discourage research and development on novel molecules that could bring increased benefits to animal and public health for both categories of molecules.	be required to show that *the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided*. The intention of the CVMP was to highlight categories of product for which the absence of critical documentation (that would preclude an informed benefit/risk assessment) may not be accepted. For antimicrobials and antiparasitics, in particular due to the potential for resistance emergence, there needs to be a sound basis for the recommended treatment dose and efficacy at this dose needs to be confirmed in the target population.
193-194	4	Comment: It is well noted that eligibility for authorisation under Article 23 will be determined and agreed *in advance of dossier submission*. As it is the intention to indicate which critical data gaps can be accepted and therefore 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, the "in advance" should be compatible with a development plan for such a product that might foresee pilot/ exploratory/proof of effectiveness studies. I.e., several years could be needed. Proposed change: Please amend the sentence to read: "… authorisation in accordance with Article 23	Accepted. Based on information in section 5 of the final reflection paper, it should be noted that a CVMP confirmation on classification of a product as intended for a limited market and a confirmation on eligibility for consideration in accordance with Article 23 will be considered valid for a period of five years from the date of the decision.

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		will be determined and agreed *up to several years in advance of dossier submission."*	
194-195	4	Comment: Clarification is needed on whether 'limited markets' classification and 'Art 23' eligibility might be separate applications, and therefore separate procedures, i.e., more than one procedure. (see also comment to lines 129-130) Proposed change: perhaps it should read as follows: "~~A procedure~~ *Procedures* to consider requests for classification as limited market and*/or* requests for eligibility for Article 23 will be established by the Agency (as mentioned under 4.1)."	See section 5 (Procedures for marketing authorisations for limited markets) of the final reflection paper.
203-208 And 299-324	4	Comment: We view the application of Art 23(1)(a) as one of the biggest challenges. The CVMP should consider that there will be many products where it will be difficult to make the decision on Art 23(1)(a) at the point in development at which that decision is needed. Deciding if the benefit of the product outweighs the risk of any data gaps may require data for the CVMP to make an informed decision. However, in many cases the level of data may end up to such an extent that the benefits of a limited market classification and subsequent data reductions are no longer of any use, as data close to Annex II requirements would need to be generated. This provision will make this decision very difficult in many cases and application for limited market status not of any value.	The comment, and the challenges ahead, are noted. However, the legislation requires that Art 23(1)(a) is satisfied. The EMA will look to develop a procedure whereby the decision on eligibility will not require significant data generation, with a focus on publically available information highlighting likely benefits of 'availability on the market' of the substance/product concerned (for example, by reference to lists of essential substances as suggested in section 4.5 of the draft reflection paper).
225-234	4	Comment: These specific data requirements guidance elaborated for indications/products that are classified as a 'limited market' but are not eligible for	Not accepted. The comment is noted and understood. However, proposed change is not considered necessary because it is clear from

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		consideration under Article 23 should also be applicable for antimicrobials and parasiticides. Proposed change: Please modify this sentence in line 232 to read: "The purpose of this guidance… can be applied to such products (including for antimicrobials and parasiticides)."	the reflection paper that any guidance for products classified as limited market, but not eligible for Article 23, should apply to all such products.
267	4	Comment: The percentage of 0.5% of an EU target population seems particularly low and somehow unrealistic in relation to the animal population of pets and food producing animals. The calculation might also be biased by some geographical repartition of disease (e.g., vector borne diseases, climate related diseases) and some minor species distribution, which might not be homogeneous around Europe. Moreover, prevalence data, especially in limited market diseases can be scarce and not numerous enough to have a proper estimate. A higher threshold might help to take into account these uncertainties. It would be interesting to understand, from the 272 successfully reviewed requests for classification as MUMS/limited market, for those covering non-immunological products, how many would meet the 0.5% threshold. Proposed change: Even though this number is only here for guidance and that it will be defined on a case-by-case basis, to take into account all the variability around this estimate, it is proposed to raise the threshold to 5%, as for vaccine products.	Not accepted. The threshold was selected based on EMA experience with classification as MUMS/limited market under the EMA MUMS/LM policy: for the majority of indications/products (non-immunological VMPs) classified by the CVMP as MUMS/LM, the estimated potential size of the market was less than 0.5% of the EU target species population, whereas, for the majority of indications/products (non-immunological VMPs) classified by the CVMP as not MUMS/LM, the estimated potential size of the market was greater than 0.5% of the EU target species population. As is clear from the draft reflection paper, the threshold of 0.5% for classification as a limited market relates to % of the EU target species population ("…..if an indication/product application is made to an individual MS for a disease that occurs frequently in that MS, but would be considered to occur infrequently when viewed in the context of the EU as a whole, that indication/product should be classified as a limited market.").
311-315	4	Comment: The aim of the limited market approach should be to promote the availability of VMPs. As previously mentioned, the current wording of the reflection paper will prevent industry developing	Not accepted. It is clear that not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically

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		specific VMPs for antimicrobial and parasiticidal use in several species and/or for specific diseases that occur infrequently or in limited geographical areas, even though they would address an unmet medical need. It is proposed this text in the reflection paper should be deleted and to allow eligibility also for antimicrobials and parasiticides to be assessed on a case-by-case basis (based on the approach criteria set out in this reflection paper), bearing in mind also that the level of risk is diminished as by definition exposure is diminished by virtue of being a limited market. Proposed change: Please delete the sentence: "~~As already stated, for certain limited market products, including products that may be considered necessary to address an unmet medical need, adequate characterisation of safety and proof of efficacy is expected to be a basic requirement (for example, antimicrobials and parasiticides). Accordingly, such products may not be candidates for authorisation under Article 23.~~"	eligible for consideration under Article 23. Additionally, the applicant will be required to show that *the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided*. The intention of the CVMP was to highlight categories of product for which the absence of critical documentation (that would preclude an informed benefit/risk assessment) may not be accepted. For antimicrobials and antiparasitics, in particular due to the potential for resistance emergence, there needs to be a sound basis for the recommended treatment dose and efficacy at this dose needs to be confirmed in the target population.
322-324	4	"*when a product is considered eligible for authorisation under Article 23, similar products intended for the same indication in the same target species will also be deemed eligible for authorisation under Article 23*." Comment: The above statement is very much welcome. It could be clarified in addition if similar products intended for the same indication in the same target species based on a full application under Art. 8(1) would likewise not influence the decision on eligibility under Article 23.	As highlighted in section 4.6 of the final reflection paper, similar products for the same indication authorised in accordance with Article 8 may influence a decision on eligibility under Article 23: "*If, at the time of re-examination, a specific medical need is met by the availability of an alternative product(s) (same target species, same indication) authorised in accordance with Article 8 of the Regulation based on an Annex II compliant dossier, it may be concluded that the conditions referred to in Article 23(1) do not continue to be fulfilled. However, when considering this*

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			specific aspect, the EU market coverage of any authorised alternative product(s) should be taken into account to avoid, for example, a situation whereby an Article 8 product authorised under national/MR/DC procedures in a limited number of Member States would impact on the availability of an Article 23 product authorised either under national/MR/DC procedures in another MS(s) or via the centralised procedure."
334-336	4	Comment: It is unclear, why products to treat diseases that have zoonotic potential would typically require the full characterization of safety and efficacy according to an Annex II compliant dossier. In the past e.g., certain indications with zoonotic potential were classified by CVMP as being MUMS (e.g., *Dirofilaria repens* in dogs). Proposed change: Please delete this sentence: "~~Note that products intended to treat diseases that have zoonotic potential (for example, antimicrobials and parasiticides) will typically require adequate characterisation of safety and proof of efficacy as a basic requirement and may not be deemed eligible for authorisation in accordance with Article 23.~~"	Proposed amendment not accepted. The intention of the CVMP was to highlight categories of product for which the absence of critical documentation (that would preclude an informed benefit/risk assessment) may not be accepted. For products used to treat diseases that have zoonotic potential, there needs to be a sound basis for the recommended treatment dose and efficacy at this dose needs to be confirmed in the target population.
356 - 362	4	Comment: Clarification is needed to reflect that 'limited markets' classification and 'Art 23' eligibility might be separate applications, and therefore separate procedures, i.e., more than one procedure. (see also comment to lines 129-130 and 194) Proposed change: should the section heading read as follows: "4.6. Proposed procedures for classifying an	The procedure set up by the Agency will involve a two-step process which allows for a separate determination of the limited market status (Art.4(29)) and the confirmation of eligibility for an Article 23 marketing authorisation application (compliance with Art. 23(1)(a) and (b)). See section 5 (Procedures for marketing authorisations for limited markets) of the final reflection paper.

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		indication/product as a 'limited market' and/or for determining eligibility for Article 23." And should lines 358-362 read as follows: "*Both, a* ~~*A*~~ CVMP confirmation on classification of a product as intended for a limited market *as well as* ~~*and*~~ a confirmation on eligibility for consideration in accordance with Article 23…" ~~"*This*~~ *These respective* procedures will be clarified during the post-consultation phase."	
395-399	4	Comment: If, at the time of re-examination, a specific medical need is met by the availability of an alternative product(s) (same target species, same indication) authorised in accordance with Article 8 based on an Annex II compliant dossier, the MA for the Article 23 authorised product cannot simply not be renewed. Depending on the progress made by the MA holder of the Article 23 authorised product in generating data aiming at completing the data gaps from the initial Article 23 application, a plan for bringing the Article 23 authorised product in line with Article 8 should be agreeable with the EMA/relevant national agencies. In case a full application under Article 8 would be required, it should be agreeable that already authorised data (e.g., part II) would not need to be reassessed.	Point noted. However, at the 5-year time point, a decision has to be taken on the continued authorisation of a LM product and there is no provision in the legislation to grant an extension to allow generation of data. No change in text to address the first part of the comment is proposed. For upgrading to an Article 8 application, it is proposed that this would be achieved via a variation requiring assessment rather than submission of a new Article 8 application. See section 5 of the final reflection paper.
401-402	4	Comment: More clarity on this particular situation would be helpful. Proposed change: *Please provide more detailed guidance for this situation.*	The situation referred to in the comment is the following: To avoid a situation whereby an Article 8 product authorised under national/MR/DC procedures in a limited number of Member States would impact on the availability of an Article 23 product authorised via the centralised procedure,

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			consideration will be given to the EU market coverage of any authorised alternative product. The CVMP is not in a position to provide more guidance for this situation at this time other than to say that decisions taken will be case-by-case with a view to ensuring that any decision not to renew an Article 23 authorised product will not create a medical need in one or more MSs.
407	4	Comment: The conditions for renewal, in particular about 'unmet medical need' contradict the strategy outlined in lines 320-324. If (competitor) products under Art 23 should not prevent each other from gaining access to the market, then they should also not prevent each other from staying on the market. Proposed change: Please delete third bullet point: "~~*there is an unmet medical need,* ~~"	Not accepted. However, the relevant text has been reworded slightly to be less definitive. It now states: "If, at the time of re-examination, a specific medical need is met by the availability of an alternative product(s) (same target species, same indication) authorised in accordance with Article 8 of the Regulation based on an Annex II compliant dossier, it may be concluded that the conditions referred to in Article 23(1) do not continue to be fulfilled. However, when considering this specific aspect, the EU market coverage of any authorised alternative product(s) should be taken into account to avoid, for example, a situation whereby an Article 8 product authorised under national/MR/DC procedures in a limited number of Member States would impact on the availability of an Article 23 product authorised either under national/MR/DC procedures in another MS(s) or via the centralised procedure." Decisions taken will be case-by-case with a view to ensuring that any decision not to renew an Article 23 authorised product will not create a medical need in one or more MSs.

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			Note: as explained in section 4.5, products authorised in accordance with Article 23 of Regulation 2019/6 are excluded from the definition of "available therapy" because they are granted an authorisation in the absence of comprehensive data relating to either the safety or efficacy.
Annex 2, line 3 (eligibility)	4	Comment: In the comment section, it is described that an approach (criteria) has been developed for interpretation of "benefit of availability outweighs the risk inherent in the fact that certain documentation has not been provided". However, section 4.5 of the reflection paper describes the approach for accepting eligibility for Article 23(1) only partly as it provides definitions around "a serious or life-threatening disease" and "unmet need" but not about when the absence of certain documentation related to safety and efficacy can be accepted. Clarity in this regard would be appreciated by industry.	Comment noted. However, this point is addressed in lines 307 – 315 of the draft reflection paper: "*When considering the absence of documentation in this context, the absence of critical data to evaluate either safety or efficacy is meant (for example, authorising a product based on a 'reasonable expectation of effectiveness', as distinct from 'proof of efficacy'). As already stated, for certain limited market products, including products that may be considered necessary to address an unmet medical need, adequate characterisation of safety and proof of efficacy is expected to be a basic requirement (for example, antimicrobials and parasiticides). Accordingly, such products may not be candidates for authorisation under Article 23.*"
Annex 2, p.17	4	"*No reduction in quality requirements according to the limited markets provision*." Comment: The flexibility allowed under the current MUMS policy for the quality information must be retained for Art. 23(1) applications. AnimalhealthEurope would like to point out that the final version of Annex II requires information from the proposed commercial batch size(s) (section 2B) and test results performed on batches manufactured at the proposed manufacturing site(s) (II.2E5 batch-to-	Comment on the quality guideline is noted. The intention is to elaborate guidance for quality requirements for limited market products that are Annex II compliant (noting that this is a requirement of the legislation), but highlighting the flexibility provided for in Annex II vis-à-vis data requirements expected for a standard dossier. Such guidance could be applied regardless of the underlying legal basis (that is, Article 8 or Article 23).

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		batch consistency). It is unclear at this stage how an application under Art. 23 may contain full quality data in Part II while at the same time pivotal safety or efficacy data may be missing. Some degree of flexibility as to the contents of Part II may be required in practice, and the MUMS guideline on quality requirements should be revised to reflect the new Annex II.	
Annex 2, P.18	4	*"it is not possible to apply for a generic of a product authorised in accordance with Article 23."* Comment: this statement is very much welcome and should apply also after the missing data have been provided by the MA holder.	Not accepted. In the situation where an applicant, post-authorisation, chooses to address any data gaps to complete the 'standard' dossier and allow the granting of a marketing authorisation valid for an unlimited period, the product would benefit from protection of technical documentation for a period defined in Article 39 of Regulation 2019/6 starting on the date the MA of unlimited validity is granted.
48	5	Comment: When compared to the current version of the guideline, this draft concept paper does not specify financial incentives for limited market authorisations. EGGVP proposes these are kept in the text as an incentive for MAHs towards minor use/species/limited markets development. Proposed change: Add reference to financial incentives for applications under Art 23	Financial incentives to be addressed separately by EMA.
61	5	Comment: The format of a benefit-risk assessment is not entirely clear: - Is this a separate document submitted by the applicant	See section 5 (Procedures for marketing authorisations for limited markets) of the final reflection paper.

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		- Is it a document on 'justification' of the limited market product or a 'benefit-risk' document where all the scientific and literature data is assessed and prevalence of the benefit is explained - In which part of the application/dossier should this document located Proposed change: EGGVP would welcome clarification on these points	
145-147	5	Comment: A better differentiation for data requirements is needed between VMPs classified as limited market (but not eligible under Art 23) and VMPs not classified as 'limited market'. A default requirement for an Annex II compliant dossier in accordance with Article 8(1) for limited markets VMPs is not in line with the intention of NVR 2019/6. Proposed change: *If a product satisfies the criteria to be classified as a limited market (according to Article 4(29)), but is not considered eligible for consideration under Article 23 then, by default, an Annex II compliant dossier in accordance with Article 8(1) will be required. A process for these VMPs considering acceptable deviations from full annex II compliance (complementary guideline) will be developed.*	Proposed change in text accepted, with modification. Noting the legal framework provided in Article 23, it is clear that not all products that satisfy criteria to be classified as 'intended for a limited market' are automatically eligible for consideration under Article 23. If a product satisfies the criteria to be classified as a limited market (according to Article 4(29)), but is not considered eligible for consideration under Article 23 then, by default, an Annex II compliant dossier in accordance with Article 8(1) will be required. CVMP is of the view that specific data requirements guidance should be elaborated for indications/products that are classified as a 'limited market' but are not eligible for consideration under Article 23. The purpose of this guidance would be to highlight how the flexibility provided in Annex II, where certain studies can be omitted if justified, can be applied to such products. That is, while there is an obligation that the dossier complies with the requirements of Annex II,

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			it is recognised that there may be a need for some flexibility vis-à-vis data requirements expected for a standard dossier. In conclusion, there is a clear legal basis for these products (Article 8, Annex II compliant) and the CVMP has provided a clear commitment to elaborate specific guidance to highlight how the flexibility provided in Annex II, where certain studies can be omitted if justified, can be applied to this category of product.
157-159	5	Comment: It is understood that a variation of non-limited market indication for an existing marketing authorization should follow the legal basis of a MA according article 8 - full dossier. This would involve substantial administrative burden and costs and will not encourage applicants unless some flexibility and reduction of requirements are allowed. Proposed change: Flexibility should be considered in these cases	Not accepted. Having consulted with EMA Legal Services and the Commission, the CVMP has been advised that a marketing authorisation having two legal bases would not be possible. Therefore, from a regulatory perspective, an application for a limited market indication would have to follow the legal basis of the original application if submitted as a variation to that MA. Alternatively, to be submitted as under Article 23, it would need to be submitted as a stand-alone application.
177-184 314-315	5	Comment: Regulation 2019/6 does not detail exclusions of antimicrobials and antiparasitics from Art. 23 eligibility. EGGVP proposes that these are not excluded de facto, and that possibility for such applications is given if B/R assessment presents a clear positive output for animal and public health. Proposed change: remove these sections.	Comment noted. It is agreed that there is no legal basis to exclude certain groups of active substances prior to an evaluation. However, the reflection paper is not absolute on this point ("……*those products may not be candidates for authorisation in accordance with Article 23*"). As previously stated, it is clear that not all products that satisfy criteria to be classified as 'intended for a limited

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			market' are automatically eligible for consideration under Article 23. Additionally, the applicant will be required to show that *the benefit of the availability on the market of the veterinary medicinal product to the animal or public health outweighs the risk inherent in the fact that certain documentation has not been provided* (Article 23(1)(a)). The intention of the CVMP was to highlight categories of product for which the absence of critical documentation (that would preclude an informed benefit/risk assessment) may not be accepted. For antimicrobials and antiparasitics, in particular due to the potential for resistance emergence, there needs to be a sound basis for the recommended treatment dose and efficacy at this dose needs to be confirmed in the target population. This notion is retained in section 4.5 of the final reflection paper, but is deleted from other sections.
232-234	5	Comment: Fully supported. As pointed under general comments, it is essential to have guidelines to better understand the requirements for these submissions.	Noted.
242-247	5	Comment: It is not clear if the applicant can restrain the number of 'potentially treated animals' to 'medicalized animals showing the disease'. The prevalence on the population is not the same that the prevalence that can be studied on the field by vets (For instance: a disease was estimated to be 1% in a medicalized population, but actually only 50% of	The comment is noted, but the intention is to use whatever data are available to justify the limited market status. The threshold of 0.5% is based on experience with classification as MUMS/limited market under the current EMA policy. The threshold is only there for guidance and the final decision will be case-by-case, as explained in the reflection paper.

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		animals are likely to be seen by a vet and to be treated, thus resulting in a number of potentially animals treated of 1% * 0.5 = 0.5% , instead of the theoretical 1% ?). Furthermore, experience has shown that there is insufficient data in the veterinary domain with respect to the incidence and prevalence of diseases to enable objective cut off values to be established below which a disease is considered to present a minor market. For certain diseases, no further data are available in 2021. Actually, when data are available it does not deal with a single percentage but with a range (more and less broad) of percentages that can be below and above a threshold. Thus, it seems not realistic to require a cut-off for the prevalence.	
267	5	Comment: The 0.5% percentage is very low and will have a direct impact especially on clinical studies. If the prevalence is low and if no other model (in vitro) is available, the implementation of a field (pilot or pivotal) study is likely to take a very long time, maybe years for the inclusion of a sufficient number of animals. In addition, the text is not really clear because it says that a case-by-case decision will be taken and that the percentage of 0.5% is only indicative. Therefore, how to know if the dossier is likely to be classified	Comment noted. However, as advised in section 4.6 of the draft reflection paper, CVMP confirmation on classification of a product as intended for a limited market and a confirmation on eligibility for consideration in accordance with Article 23 will be considered valid for a period of five years from the date of the decision. That is, a request for classification can be submitted to the EMA at an early stage in product development. Proposed change in threshold not accepted. The threshold was selected based on EMA experience with classification as

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		MUMS before preparing it almost completely and submitting it in a scientific advice if the prevalence has been estimated slightly above 0.5 %? Furthermore, What happen if a product that has been classified as a limited market during development (as described in Article 23), but the conditions (geographical areas, ie expansion of transmitting vectors) change and the results of the formula of estimated market indicate that is not limited geographical area anymore when is being assessed? Proposed change: < 5% for VMPs (both pharmacologicals and immunologicals)	MUMS/limited market under the EMA MUMS/LM policy: for the majority of indications/products (non-immunological VMPs) classified by the CVMP as MUMS/LM, the estimated potential size of the market was less than 0.5% of the EU target species population, whereas, for the majority of indications/products (non-immunological VMPs) classified by the CVMP as not MUMS/LM, the estimated potential size of the market was greater than 0.5% of the EU target species population.
322-324	5	Comment: It is good news seeing that authorization of (competitor) products under article 23 intended for the same indication in the same target species will be possible. It should be clarified if previous authorisation of a similar - competitor product could influence decision, i.e VMP already authorised as MUMS under current guideline with almost no gaps - complete trials of duration of immunity, MDA test..(not required according EMA/CVMP/59531/2020); will the new product under development be required to present all these data?	Products classified as MUMS/limited market already authorised based on current MUMS guideline are recognised as 'standard' marketing authorisations. The availability of such products will be taken into account, as appropriate, when considering future eligibility requests. If, when considering a future eligibility request, it is considered that the product in question is deemed not eligible for consideration under Article 23 on the basis that there is no 'unmet medical need', then an application for authorisation would have to be submitted under Article 8. In that scenario, the applicant could prepare a dossier in accordance with guidance for products classified as limited market, but not eligible for Article 23 (to be developed).

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395-399	5	Comment: Substantial investments may have taken place, so not renewing does not seem appropriate. Better find solution for the pragmatic conversion of the Art 23 application into Art 8.	Comment noted. For upgrading to an Article 8 application, it is proposed that this would be achieved via a variation requiring assessment rather than submission of a new Article 8 application. See section 5 of the final reflection paper.
401-402	5	Comment: It is not clear what this provision mean (maintenance of the limited market MA in the countries in which the product article 8 has not been registered?)	The relevant text has been reworded slightly to be less definitive. It now states: "If, at the time of re-examination, a specific medical need is met by the availability of an alternative product(s) (same target species, same indication) authorised in accordance with Article 8 of the Regulation based on an Annex II compliant dossier, it may be concluded that the conditions referred to in Article 23(1) do not continue to be fulfilled. However, when considering this specific aspect, the EU market coverage of any authorised alternative product(s) should be taken into account to avoid, for example, a situation whereby an Article 8 product authorised under national/MR/DC procedures in a limited number of Member States would impact on the availability of an Article 23 product authorised either under national/MR/DC procedures in another MS(s) or via the centralised procedure." Decisions taken will be case-by-case with a view to ensuring that any decision not to renew an Article 23 authorised product will not create a medical need in one or more MSs.
Annex 2, under	5	Comment: Overall, EGGVP is in the opinion that withdrawing the existing guideline on quality	Comment on the quality guideline is noted. The intention is to elaborate guidance for quality requirements for limited market products that are Annex II compliant (noting that

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"standard applied"		requirements is not in line with with the objective of Regulation (2019/6) to improve the availability of safe and effective VMPs for MUMS/Limited market. Thus, 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 (only 'safety and efficacy'). Proposed change: EGGVP suggests that exceptions from Annex II for limited market products can be made also for parts 1 & 2.	this is a requirement of the legislation), but highlighting the flexibility provided for in Annex II vis-à-vis data requirements expected for a standard dossier. Such guidance could be applied regardless of the underlying legal basis (that is, Article 8 or Article 23). Proposed change not accepted. 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	
Annex 2, under "marketing authorisation status"	5	Comment: *"A mechanism should be found for ensuring that, in addition to the SPC, the package leaflet should also state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data."* It seems that this disposition goes further than what is stated in regulation (SPC only). We would like to suggest CVMP further reflection re. the interest to bring to the attention of unexperienced owners/people in the leaflet that a limited assessment was conducted. It may devaluate the product.	Not accepted on the basis that the point of including this statement in the SPC is to be transparent with the users of these products.
Annex 2, under "post authorisation requirements"	5	Comment: It is not clear which pharmacovigilance signals would lead to a situation for which, at the five-year time point, the conditions for 'eligibility' do not continue to be met. Example: if numerous but mild adverse reactions had been detected, but risk-benefit has been demonstrated and remains clearly a positive balance, will the product lose the "limited market" classification? It is understood the product could then apply for an Art 8.	For upgrading to an Article 8 application, it is proposed that this would be achieved via a variation requiring assessment rather than submission of a new Article 8 application. See section 5 of the final reflection paper.

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		Proposed change: Mechanisms, timeframes etc for the transfer of an Art 23 to an Art 8 would be welcome.	