

EMA/CVMP proposals for the requirements for limited markets and minor species: an update in 2021

In less than a year, on January 28, 2022, Regulation (EU) 2019/6 will become applicable. The CVMP has now issued different guidance documents how the new Regulation impacts the registration for limited markets including minor species. While article 23 provides an abbreviated pathway for such products to obtain a marketing authorisation with a reduced dataset on safety and efficacy, resulting in a 5 years period for marketing authorisation, an unlimited authorisation is achieved with an adapted amount of data for such limited market products according to Article 8. CVMP reflects on the approach for classification of such products, and provides guidance for efficacy and safety data requirements in the target species for both, biological and non-biological products. Further guidance is given for safety and residue data requirements to establish an MRL.

The reflection paper on classification of a product as intended for limited market and eligibility for authorisation according to Article 23 published by EMA for consultation, first time outlines the understanding of CVMP of Article 23, here to obtain marketing authorisations for products defined as 'limited market products'.

To evaluate the eligibility for such an application, applicants need to address two questions as outlined in Article 23.

1. Is the product intended for a limited market as defined in Article 4 (29) and Art. 23 (1) b of the Regulation ()?

As compared to the current definition of Directive 2004/28/EC for MUMS, regulation 2019/6 defines 'limited markets' slightly different, being either intended for use in a non-major species (major species are cattle, non-lactating sheep, pigs, chicken, dogs and cats) or for the treatment of diseases that occur infrequently or in limited geographical areas.

While the categorisation by species is straight forward, a limited market in a major species targets 'diseases that occur infrequently' or in limited geographical areas. In the future, the decision is based primarily on the estimated potential size of the market applying the following formula:

$$\text{Estimated potential size of the market \%} = \frac{\text{total annual number of animals potentially treated}}{\text{EU (EEA) target species population}} \times 100$$

The calculated potential market size can be influenced by various factors.

- Whether the product is intended for prevention or treatment.
- The frequency of the disease/condition in the EU relevant to the indication sought. Diseases with low prevalence, occurring infrequently or sporadically and in only a small number of animals will be considered for classification as a limited market. Estimates of disease prevalence should be supported by up-to-date data in the published

literature and/or from appropriate and reliable sources.

- The geographical area in which the disease/condition is present. Diseases that occur in limited geographical areas or regions that are distinguished by physical, chemical, or biological factors that limit the distribution of a disease or condition will be considered for classification as limited market.

Although for guidance only, the following thresholds for potential market size are proposed:

- less than 0.5% of the EU target species population for veterinary medicinal products or
- less than 5.0% of the EU target species population for vaccines.

On top, other factors may be taken into account:

- The potential number of animal treatments in a standard treatment course (ranging from one-off, single administration to daily administration over the remaining life of the animal) or the need for repeated treatments during the course of one year.
- Time to return on investment. This parameter will be influenced by multiple factors including the nature of the product and associated development costs, cost of manufacture, potential market size, unit price, etc. The approach to estimating the time to return on investment should be clearly outlined in the request for classification and justified based on reference to appropriate data.

All these criteria meant to address the first question, are mentioned to be taken into account, which indicates that any such classification as a limited market in a major species will be a case-by-case decision and difficult to predict by an applicant when considering developing such product.

2. Does the benefit of the availability on the market outweigh the risk that certain documentation has not been provided in a dossier (Art. 23 (1) a)?

The said benefit in this case is proposed to be accepted if the medicinal product (intended for the treatment or prevention of disease) is intended to treat a serious or life-

threatening disease/condition or addresses an 'unmet medical need'. For the definition of these terms, guidance from human medicine as well as from US FDA served as a basis. 'Serious or life-threatening disease or condition' is defined to be associated with morbidity that has substantial impact or is associated with mortality, is zoonotic or has the potential to cause significant economic impact for individual producers. However, the proposal is made that products intended to treat diseases that have zoonotic potential including antimicrobials and parasiticides are not deemed to be eligible for authorisation under Article 23; they typically

require adequate characterisation of safety as well as proof of efficacy.

These proposals limit the political objective to improve the availability of veterinary medicinal products for limited markets. In the context of promoting the availability of veterinary medicinal products for limited markets including minor species, it is surprising to see antiparasitics and antibiotics excluded right away. Any products “preventing such diseases” should be included here.

The term of an ‘unmet medical need’ is taken from human medicine and means a condition for which no satisfactory method of diagnosis, prevention or treatment in the Union exists or if such methods exist, they will be of major therapeutic advantage. This means that either no available therapy exists for the same intended use (if such therapy exists at all); the new product is reasonably expected to be safer, more effective, or clinically superior. In this context, it is noted that ‘available therapy’ means an authorised veterinary medicinal product, independent of the authorisation procedure but not including off-label use of an approved veterinary or human medicinal product.

The authors consider that the definition of “unmet medical need” should be broader in animal health as compared to human health: due to the variety of animal species and diseases, different mode of actions, technologies, route of administrations, safety profile, and assurance of availability should be considered as unmet medical need depending on the animal species and number of products available.

To apply for a marketing authorisation according to Article 23, the applicant has to provide evidence that the product falls under the definition of ‘limited markets’ to benefit from reduced data requirements for safety and efficacy. A complete quality part must be provided in any case.

EMA/CVMP request that there must be a ‘real’ consideration of the ‘benefit of availability’ versus the risk of absence of data on safety and/or efficacy. However, an application for

a product for a limited market can also be done according to Art. 8.

The marketing authorisation (MA) for a limited market under Article 23 will be valid for five years and either, based on a re-examination, be prolonged for further periods of five years, or can be upgraded to an unlimited full MA under Article 8 when providing the missing information on safety and efficacy. However, it is unclear for the moment, to which degree further data must be provided.

Furthermore, it remains unclear now, which are the specific data requirements for a limited market product authorised under Article 8, either being eligible or not for an authorisation under Article 23. This guidance will be much appreciated to be issued by EMA/CVMP; it is expected that such recommendations will be taken on a case-by-case basis, in many cases making consultation with the competent authorities highly recommendable. Certainly, any further guidance will be welcome.

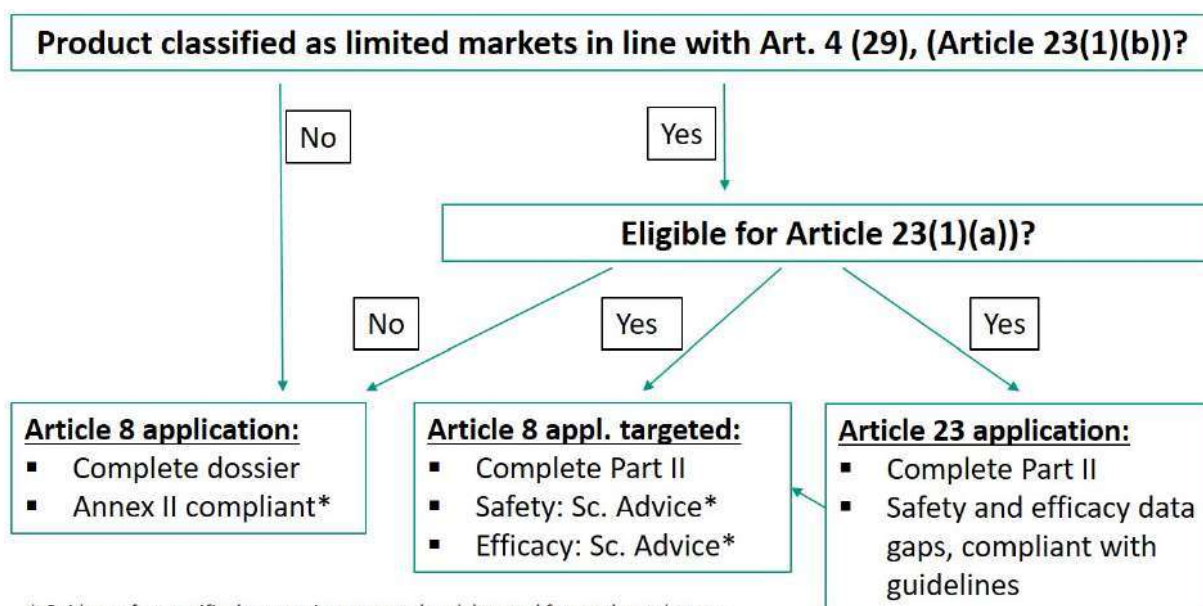
As EMA/CVMP proposes that all currently authorised MUMS products are considered Annex II compliant, these will get a full marketing authorisation according to Article 8, without re-evaluation.

Considering this, it will be interesting to see if products for limited markets to be registered according to Article 8 still need the same data requirements for safety and efficacy as required for a major species. The authors consider that there will also be room for negotiation that reduced data requirements may also be possible for limited market products authorised under Article 8.

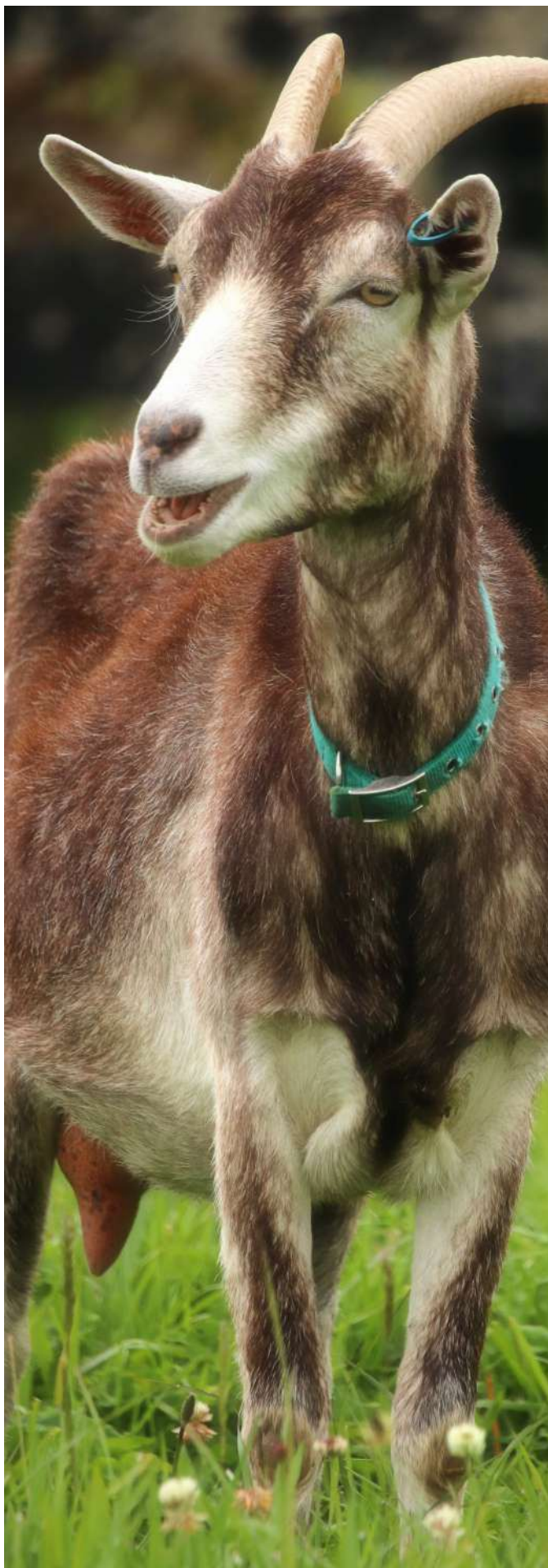
The guidelines on safety and residue data requirements and on efficacy and target animal safety data requirements for non-immunologicals continue to outline data gaps that may be accepted for applications under Article 23.

A more specific guidance is provided for immunologicals (guideline on data requirements for immunologicals). In

Thus, the following approach for limited market products can be taken:



* Guidance for specific data requirements to be elaborated for products that are classified as a ‘limited market’ but not eligible for consideration under Article 23. Same for moving an Art. 23 to an Art. 8 marketing authorization.



line with the current approach under Directive 2001/82/EC as amended, the draft guideline proposes that specific requirements, like GLP and GCP compliance, may be lifted, but also some safety and efficacy studies may be possible to omit (e.g. safety of first re-vaccination or field efficacy studies).

In summary, the guidance issued by EMA/CVMP give hope to a pragmatic approach for obtaining marketing authorisations for limited markets in the future under Regulation 2019/6. While the minor species are clearly defined in legislation, the guidance on the definition of limited markets in major species is welcome, although still quite vague. It will be interesting to see how this will be implemented in a case-by-case manner. The safety and residue guideline provides evidence that the safety for the consumer is paramount, even in the absence of products to treat diseases. The requirements for immunological VMPs appear to be reduced slightly more than those for non-immunological products; however, this will all depend on the final version of these guidance documents and its practical implementation. Meetings with the ITF and/or ADVENT group of CVMP and furthermore approaching CVMP for scientific advice in a well-organised manner will be even more important for any applicant for a successful registration of a VMP in the future.

REFERENCE

1. <https://www.ema.europa.eu/en/veterinary-regulatory/research-development/minor-use-minor-species-limited-markets>



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