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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)

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Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Introduction

Activities to promote the availability of veterinary medicines have been, and continue to be, given a high priority by the European Regulatory Network[1],[2]. One such activity is the minor use, minor species (MUMS)/limited market initiative aiming to facilitate the access to the market of products indicated for MUMS/limited market as part of measures to promote the availability of veterinary medicinal products.

The Agency first implemented its MUMS/limited market policy on 1 September 2009, which was updated in July 2013 and again in December 2018. The policy provides two types of incentives to stimulate the development of new veterinary medicines for minor species and for rare diseases in major species that would otherwise not be developed in the current market conditions: reduced data requirements and financial incentives by means of fee exemptions or fee reductions. In the first ten years of application of this scheme, the Committee for Medicinal Products for Veterinary Use (CVMP) successfully reviewed 272 requests for classification as MUMS/limited market and recommended the granting of a marketing authorisation for 22 applications for new products intended for a limited market[3].

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products (repealing Directive 2001/82/EC) introduces for the first time the legal basis for granting marketing authorisations for limited market products and defines conditions and requirements consistent with the aim of EMA policy of promoting availability of veterinary medicinal products for limited markets. In the preamble to the Regulation (Recital 30), it is stated that *"companies have less interest in developing veterinary medicinal products for markets of a limited size. In order to promote the availability of veterinary medicinal products within the Union for those markets, in some cases it should be possible to grant marketing authorisations without a complete application dossier having been submitted, on the basis of a benefit-risk assessment of the situation and, where necessary, subject to specific obligations. In particular, the grant of such marketing authorisations should be possible in the case of veterinary medicinal products for use in minor species or for the treatment or prevention of diseases that occur infrequently or in limited geographical areas."*

Based on Recital 30, it is understood that the objective of the Article 23 (Applications for limited markets) provision is to promote availability[4] where products may not be brought to the market because of small market size, by making it possible to grant marketing authorisations without a complete application dossier.

In preparing this reflection paper on the approach to implementing the Article 23 provision, it was considered that the primary objectives were to elaborate an approach that will:

- Ensure that the regulatory system can continue to issue marketing authorisations for the type of product that is being authorised currently as a MUMS/limited markets product; and, building on that,
- Allow for the authorisation of products classified as a limited market that are intended to treat a serious or life-threatening disease/condition or are considered to fulfil an unmet medical need (see definitions, section 4.5), in the absence of some (confirmatory) data required by Annex II for adequate characterisation of safety and/or proof of efficacy.

[1] EU Medicines Agencies Network Strategy to 2020 | European Medicines Agency (Theme 2; Objective 1)
[2] European medicines agencies network strategy to 2025
[3] https://www.ema.europa.eu/en/documents/report/10-year-annual-report-mums/limited-market-scheme-veterinary-medicines_en.pdf
[4] In this context, the focus is on facilitating access to (authorisation of) new products, as distinct from availability on the market which may be influenced by a range of other factors.

2. Terminology

'Limited market' - according to Article 4(29) of Regulation (EU) 2019/6, 'limited market' "*means a market for one of the following medicinal product types:*

(a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas;

(b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats."

'Limited market product eligible for Article 23' – a product that meets the definition of limited market and, in addition, it is accepted 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* (satisfies Article 23(1)(a) of Regulation (EU) 2019/6).

'Limited market product not eligible for Article 23' – a product that meets the definition of limited market, but it is not accepted 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* (does not satisfy Article 23(1)(a) of Regulation (EU) 2019/6).

'Limited market product authorised in accordance with Article 23' (LM-Art.23) – a product intended for a limited market that is authorised in the absence of certain/some technical documentation necessary for demonstrating safety and efficacy in accordance with the requirements set out in Annex II. This 'data gap' is to be interpreted as the absence of (confirmatory) data required by Annex II, going beyond the flexibility already provided for in Annex II.

'Limited market product authorised in accordance with Article 8' (LM-Art.8) - a product intended for a limited market that is authorised in accordance with the requirements set out in Annex II. For such products, there is an obligation that the dossier complies with the requirements of Annex II; however, the applicant may benefit from the flexibility provided in Annex II, where certain studies can be omitted if justified.

3. Scope

This reflection paper relates to requests from applicants seeking either confirmation on classification of a product as intended for a limited market (as defined in Article 4(29) of Regulation 2019/6) and/or confirmation on eligibility for consideration in accordance with Article 23, where such requests are made to the CVMP.

The approach to classification by the CVMP and eligibility detailed in this document also apply to relevant products considered for authorisation under decentralised or mutual recognition procedures.

It is expected that this procedure and the other related documents will assist authorities in terms of classifying indications/products at a national level as limited market and eligible for consideration under Article 23. However, consideration by CVMP can be requested in the case of products intended for submission to national competent authorities, especially when mutual recognition is foreseen.

This document has been prepared for guidance only and applicants must comply with Union legislative provisions, currently in force and relating to veterinary medicinal products.

4. Discussion

4.1. Understanding the Article 23 provision (applications for limited markets)

Article 8(1) states: "*An application for a marketing authorisation shall contain the following:*

(*a) ….*

(b) technical documentation necessary for demonstrating the quality, safety and efficacy of the veterinary medicinal product in accordance with the requirements set out in Annex II; …"

Article 23(1) states: "*By way of derogation from point (b) of Article 8(1), the applicant shall not be required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II, if all of the following conditions are met:*

(a) 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;

(b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market."

Article 24(1) states: "*By way of derogation from Article 5(2), a marketing authorisation for a limited market shall be valid for a period of five years.*"

Article 24(6) states: "*The competent authority or the Commission, as applicable, may at any time grant a marketing authorisation valid for an unlimited period of time in respect of a veterinary medicinal product authorised for a limited market, provided that the holder of the marketing authorisation for a limited market submits the missing data on safety or efficacy referred to in Article 23(1).*"

Noting the requirements of the legislation, specifically the articles detailed above, the following basic principles will define the approach to application of the limited markets provision:

- 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)).
- Eligibility for consideration under Article 23 must be determined and agreed in advance of dossier submission. A procedure to consider requests for classification as limited market and requests for eligibility for Article 23 will be established by the Agency.
- Where eligibility for consideration in accordance with Article 23 is accepted, it follows that the absence of some (confirmatory) data required by Annex II for adequate characterisation of safety and/or proof of efficacy is acceptable.
  - If an application is considered eligible for Article 23 it would not be appropriate for the authorities to oblige the applicant to submit an Annex II compliant data package. That means, the dossier will have certain data gaps with the result that it does not comply with the requirements of Annex II. Post-marketing authorisation conditions in relation to the data gaps are not foreseen in the legislation.

  - A clear data gap should be identifiable. Guidance has been developed indicating what gaps in critical/pivotal data can be accepted for products deemed eligible to be considered for authorisation in accordance with Article 23.
  - At a subsequent time point, post-authorisation, the applicant may choose to address any data gaps to complete the 'standard' dossier and allow the granting of a marketing authorisation valid for an unlimited period.
- 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. 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.

Classification as a limited market may apply to a veterinary medicinal product or to a specific indication for a product that carries other non-limited market indications. 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. In this scenario, it should be noted that the Article 23 application would not come within the scope of global marketing authorisation for the related Article 8 product. 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.

Given that, Article 18 of Regulation 2019/6 (Generic veterinary medicinal products) does not make reference to Article 23 and that Article 23 is, itself, a derogation from point (b) of Article 8(1), it follows that it is not possible to apply for a generic of a product authorised in accordance with Article 23. 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.

4.2. Experience to date applying the MUMS guidance developed in accordance with Article 79 of Regulation 726/2004 to MUMS classified products/indications:

A list of centrally authorised products that have benefited from the MUMS/limited market initiative is provided as Annex 1.

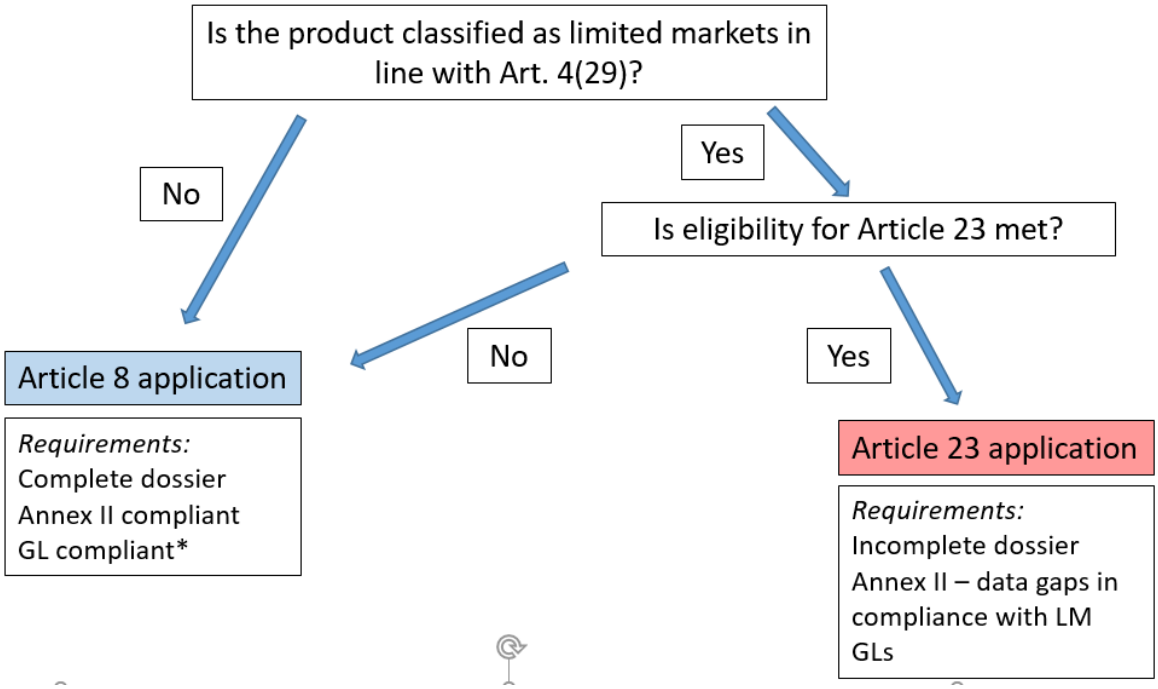
Experience to date with the application of MUMS guidance indicates that most products classified as MUMS/limited markets, and for which a positive opinion was issued by the CVMP, were authorised based on adequate characterisation of safety and proof of efficacy and the application dossiers can be considered 'Annex II-compliant'. The CVMP and CMDv (Coordination Group for Decentralised and Mutual Recognition) view, and the principle point to be made here, 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. It is something different. A comparison of

the limited market provision as provided for in Regulation 2019/6 and of the current application of MUMS policy/guidance is presented in tabular form in Annex 2 of this reflection paper.

Note: From 28 January 2022, the current EMA policy on MUMS/limited market classification will cease to apply. The products 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 (see section 5.1). Applications for MUMS products (classified under the current EMA policy) submitted and validated before 28 January 2022 will be processed under the current legislation. Products classified as MUMS and which are already authorised are considered 'standard' authorisations and Regulation 2019/6 will not affect the authorisation status.

4.3. Proposed approach for applying the Article 23 (limited market) provision:

It is proposed that the limited market provision will be applied as follows:



*Specific data requirements guidance to be elaborated for products that are classified as a 'limited market' but are not eligible for consideration under Article 23.

Eligibility for authorisation in accordance with Article 23 will be determined and agreed in advance of dossier submission. A procedure to consider requests for classification as limited market and eligibility for Article 23 will be established by the Agency (see section 5).

There are two questions that have to be addressed when considering eligibility for authorisation of products intended for a limited market. The first of these questions is "is the proposed indication/product for a limited market as defined in Article 4(29) of the Regulation?" (that is, has the applicant provided evidence that the veterinary medicinal product is intended for a limited market as required by Article 23(1)(b)?). See section 4.4.

Any product that is not classified as a limited market will automatically by default require a full application in accordance with Article 8(1) (Annex II compliant).

For those products that are classified as limited market, the second question to be addressed in order to be considered eligible for authorisation in accordance with Article 23 is "does the proposed product satisfy the condition detailed in Article 23(1)(a)?". An approach to determining if the "*benefit of 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*" is outlined in section 4.5 below.

Where eligibility for consideration in accordance with Article 23 is accepted, the absence of some pivotal data (critical for a definitive conclusion on safety or efficacy of the product) will be accepted. Guidelines detailing the gaps in pivotal data (relative to Annex II) that may be accepted for a product deemed eligible for consideration in accordance with Article 23 have been developed.

If a product that is classified as a 'limited market' is not eligible for consideration under Article 23 then, by default, an Annex II compliant dossier in accordance with Article 8(1) will be required. Based on experience to date, it is the case that products currently classified as MUMS and authorised based on data submitted according to existing MUMS guidance could under Regulation 2019/6 be accepted as satisfying the requirements of Article 8(1)(b) by complying with basic Annex II requirements.

Noting the above and the fact that one of the objectives of this current review 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, 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.

4.4. Approach (criteria) for classifying an indication/product as a 'limited market' (Article 4(29))

Classification as a limited market based on species is straightforward in that veterinary medicinal products intended for any animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats qualify as a limited market.

When considering classification of an indication/product intended for cattle, sheep for meat production, pigs, chickens, dogs or cats as a limited market based on the claim that it is intended for "*diseases that occur infrequently or in limited geographical areas*", the decision will be based primarily on the estimated potential size of the market. That is the total number of animals that could potentially be administered the product annually. This value should be expressed as a percentage of the EU (EEA) target species population.

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

This value will be influenced by factors such as:

- The expected target population (sub-category of target species, e.g. type of production, age).
- Whether the product is for prevention or treatment.
- The frequency of the disease/condition in the EU relevant to the indication sought. Diseases/conditions with low prevalence[5], occurring infrequently or sporadically and in only a small number of animals will be considered for classification as a limited market. Estimates of disease/condition prevalence should be supported by up-to-date data in the published literature, where available, and/or from appropriate and reliable sources.
- The precise wording of the indication, for example, if the disease/condition to be treated is limited to a specific stage, severity or underlying pathophysiological mechanism. Nevertheless, when considering such 'restricted' indications, the likelihood that the product may, in practice, be used for a broader indication will be taken into account.
- The geographical area in which the disease/condition is present. Diseases/conditions 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.

The approach to estimating the potential market size should be clearly outlined in the request for classification and justified based on reference to appropriate data. This annual estimate may be refined if the treatment is only medically justified for a subset of animals. Any such refinement should be justified based on reference to appropriate data. Data provided should be the most recent set of data available at the time of submission of the request. Species population numbers used should be attributable to recognised and reputable/reliable sources at European level (for information on sources of EU population data, see Annex 3).

An indication/product will be considered for classification as limited market when the potential market size is estimated to be less than 0.5% of the EU target species population or, in the case of vaccines only, is estimated to be less than 5.0% of the EU target species population. It is proposed that the market size threshold for vaccines will be greater than that for other products recognising that: the intended target population for a vaccine is typically expected to be greater than that for a product intended to treat disease; vaccine development is to be incentivised; and, vaccines represent the majority of requests for classification as MUMS for products intended for food-animals processed by the EMA in recent years.

It must be emphasised that these threshold values will be used for guidance purposes only and that a final decision on limited market status will be taken case-by-case.

When considering classification as a limited market other factors that may be taken into account include:

- The potential number of animal treatments in a standard treatment course (ranging from once-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

[5] 'Prevalence' is defined as: the total number of animals in a given population affected by a disease or health condition at a specific period of time, usually expressed as a percentage of the population.

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.

When considering classification requests, the current EMA approach is to consider potential extent of use of a product in an EU context, rather than at the level of individual Member States. It is considered that this approach should continue to apply in any future system regardless of the proposed route of authorisation of the product in question (that is, centralised, decentralised or national). That is, 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.

This document describes the factors that will be taken into account for classification of products as limited market in the EU/EEA. Whilst the CVMP will take note that products have been designated as limited market in other regions outside EU/EEA, this will not affect directly classification by CVMP as the definition of limited market may not be the same and the prevalence and incidence of a disease may be different in different regions. However, limited market status in other regions can be provided for information to CVMP.

4.5. Approach (criteria) for accepting eligibility for Article 23(1)(a)

As noted above, all products that satisfy criteria to be classified as 'intended for a limited market' are not automatically eligible for consideration under Article 23.

A product classified as 'intended for a limited market' will be deemed eligible for Article 23 where:

- It is intended to treat a serious or life-threatening disease/condition or addresses an 'unmet medical need' (see definitions below); and
- The absence of certain documentation typically required for adequate characterisation of safety and demonstration of efficacy can be accepted.

These would be the subset of 'limited market' products for which there would be a 'real' consideration of the 'benefit of availability' versus the risk of absence of documentation. 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'). 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.

When considering requests for eligibility for Article 23, reference can be made to lists of essential substances that have been established by reputable sources in order to facilitating or promoting the availability of authorised veterinary medicinal products (e.g. the EU list of substances essential for the treatment of equidae[6] and the WSAVA list of essential medicines for cats and dogs[7]).

It is considered that accepting a product as eligible for authorisation in accordance with the limited market provision because it addresses an availability need should not prevent access of other (competitor) products to the market. Therefore, when a product is considered eligible for authorisation

[6] Commission Regulation (EU) No 122/2013 (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:042:0001:0017:EN:PDF)
[7] https://wsava.org/wp-content/uploads/2020/03/WSAVA_List_of_Essential_Medicines_for_Cats_and_Dogs_final.pdf

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.

Definitions:

Serious or life-threatening disease/condition[8]:

- a disease or condition that is associated with morbidity that has substantial impact on day-to-day functioning or is associated with mortality in the target animal; or
- a disease or condition in animals that is zoonotic and that presents a risk of a serious or life-threatening disease or condition to human beings, whether or not it also presents a risk of harm to the target animal receiving the product; or
- a disease or condition that has the potential to cause significant economic impact for individual producers, even if the effect of the disease or condition on an individual-animal basis is minor.

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. However, vaccines intended for the prevention of infectious disease with zoonotic potential may be considered for authorisation under Article 23.

Unmet medical need:

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 therapeutic advantage to those affected[9].

- 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 safer or more effective or otherwise makes a major contribution to diagnosis or to patient care.

When considering the availability of alternatives, it is recognised that there may be a need for a number of substances with different pharmacological properties (for example, the substance is acting at a different site of action and/or with a different mode or mechanism of action compared to authorised alternatives) to successfully treat the specific condition.

'Available therapy' means a veterinary medicinal product that is authorised under Directive 2001/82/EC (as amended) or in accordance with Article 8(1) of Regulation 2019/6, by any authorisation procedure (national, MRP, DCP or centralised). It should be noted that off-label use (use under the 'cascade') of an approved veterinary or human medicinal product does not qualify as an "available therapy" because safety and substantial evidence of effectiveness have not been established

[8] The terms 'life-threatening', 'seriously debilitating' and 'serious and chronic condition' are referred to in legislation relating to human medicines, in particular in relation to orphan medicines and conditional use authorisations. However, those terms relate to impact on the target population only. That is, possible impacts for non-target populations and/or commercial impacts of disease are not a primary concern. Therefore, when considering 'serious disease' in the context of veterinary medicines, there is a need for a veterinary specific definition which encompasses all relevant elements (impact on target population, possible impact on non-target populations (zoonosis) and economic impact). The definition of 'serious or life-threatening disease/condition' used here is a modification of definitions used in EMA/CHMP/509951/2006, Rev.1 and the working definition of "serious or life-threatening disease or condition" used by the FDA in draft guidance for industry on "Eligibility Criteria for Expanded Conditional Approval of New Animal Drugs" (https://www.fda.gov/media/130706/download).

[9] Based on the definition provided in Commission Regulation (EC) No. 507/2006 of 29 March 2006 on the conditional marketing authorisation for medicinal products for human use falling within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council.

for the off-label use. In addition, 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.

4.6. Approach to applying Article 24 – validity of a marketing authorisation for a limited market and procedure for its re-examination.

Article 24 states:

"1. By way of derogation from Article 5(2), a marketing authorisation for a limited market shall be valid for a period of five years.

2. Before the expiry of the five-year period of validity referred to in paragraph 1 of this Article, marketing authorisations for a limited market granted in accordance with Article 23 shall be re-examined on the basis of an application from the holder of that marketing authorisation. That application shall include an updated benefit-risk assessment.

3. A holder of a marketing authorisation for a limited market shall submit an application for a re-examination to the competent authority that granted the authorisation or to the Agency, as applicable, at least six months before the expiry of the five-year period of validity referred to in paragraph 1 of this Article. The application for re-examination shall be limited to demonstrating that the conditions referred to in Article 23(1) continue to be fulfilled.

4. When an application for re-examination has been submitted, the marketing authorisation for a limited market shall remain valid until a decision has been adopted by the competent authority or the Commission, as applicable.

5. The competent authority or the Agency, as applicable, shall assess applications for a re-examination and for an extension of the validity of the marketing authorisation. On the basis of that assessment, if the benefit-risk balance remains positive, the competent authority or the Commission, as applicable, shall extend the validity of the marketing authorisation by additional periods of five years."

A marketing authorisation for a limited market under Article 23, once issued, shall be valid for a period of five years.

In order to address the requirements of Article 24, a re-examination procedure will be elaborated by the Agency in the case of products authorised via the centralised procedure and by Member States in the case of products authorised via national procedures. A decision to extend the validity of the marketing authorisation will be based on the following considerations:

- the acceptability of the safety profile, including any information received relating to reports of lack of expected efficacy (pharmacovigilance data, including information from the published literature);
- does the product continue to satisfy the criteria for classification as a limited market; and
- a specific medical need.

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.

If, at the time of re-examination:

- no concerns relating to the safety and efficacy of the Article 23 authorised product (and continued sales of the product) have been documented, and
- the product continues to satisfy the criteria for classification as a limited market, and
- there is an unmet medical need,

it will be considered that the conditions referred to in Article 23(1) continue to be fulfilled. In this case, the marketing authorisation for the Article 23 authorised product will be renewed, valid for a period of five years.

5. Procedures for marketing authorisations for limited markets

The procedural documents mentioned in this section as well as documents which are still to be developed or may be established as experiences with marketing authorisations for limited markets evolve are published on the EMA website at a dedicated location.

5.1. Procedure for classifying an indication/product as a 'limited market' and/or for determining eligibility for Article 23

A CVMP confirmation on classification of a product as a limited market in accordance with Article 4(29) 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. The period of validity will be renewable.

The procedure set up by the Agency consists of 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)).

5.2. Procedure according to Article 24(6)

Article 24(6) of Regulation 2019/6 allows for the possibility for the marketing authorisation holder to submit the missing data on safety and efficacy as referred to in the established data gaps. Provided that all missing data are submitted, and the B/R balance is confirmed to be positive, the Commission or the competent authority may at any time grant a marketing authorisation (MA) valid for an unlimited period of time.

The submission of missing data to fill identified gaps is voluntary, but it will remove the obligation for the marketing authorisation holder for a five-yearly re-examination of the MA. The granting of the marketing authorisation for an unlimited period of time is accompanied with the change of the legal basis of the marketing authorisation from an Article 23 MA to a 'standard' MA according to Article 8.

The submission of missing data and the 'switch' of the legal basis of the MA will be dealt with according to the following principles:

- submission of data in order to fill the identified gaps via variations requiring assessment (VRAs)

- data can be submitted preferably in one step when all data to fill all identified gaps are available, or as data become available, requiring separate, sequential VRAs

- the switch in legal basis takes place when the VRA procedure is closed in accordance with Article 67 of Regulation 2019/6.

References

The following legislation, guidelines and notes for guidance are relevant to this reflection paper:

1. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN
2. Commission Delegated Regulation (EU) 2021/805 of 8 March 2021 amending Annex II to Regulation (EU) 2019/6 of the European Parliament and of the Council https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32021R0805&from=EN
3. Guideline on data requirements for applications for immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 - (EMA/CVMP/59531/2020)
4. Guideline on efficacy and target animal safety data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 - (EMA/CVMP/52665/2020)
5. Guideline on safety and residue data requirements for applications for non-immunological veterinary medicinal products intended for limited markets submitted under Article 23 of the Regulation (EU) 2019/6 - (EMA/CVMP/345237/2020)

Annex 1 - Centrally authorised products that benefited from MUMS/limited market scheme

- **Arti-Cell Forte** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/arti-cell-forte)
- **Advocate** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/advocate)
- **Aivlosin** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/aivlosin)
- **Aservo Equihaler** (https://www.ema.europa.eu/en/documents/assessment-report/aservo-equihaler-epar-public-assessment-report_en.pdf)
- **Broadline** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/broadline)
- **CaniLeish** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/canileish)
- **Clevor** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/clevor)
- **Clynav** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/clynav)
- **Coxevac** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/coxevac)
- **Dany's BienenWohl** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/danys-bienenwohl)
- **Econor** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/econor)
- **Equisolon** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/equisolon)
- **Eravac** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/eravac)
- **Fungitraxx** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/fungitraxx)
- **HorStem** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/horstem)
- **Letifend** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/letifend)
- **Metacam** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/metacam)
- **MS-H vaccine** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/ms-h-vaccine)
- **Nobivac Myxo RHD** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/nobivac-myxo-rhd)
- **Nobivac Myxo RHD Plus** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/nobivac-myxo-rhd-plus)
- **Oncept IL-2** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/oncept-il-2)
- **Oxybee** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/oxybee)
- **Poulvac E. Coli** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/poulvac-e-coli)
- **Profender** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/profender)
- **Rabitec** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/rabitec)
- **Suprelorin** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/suprelorin)
- ***TruScient – withdrawn*** *(https://www.ema.europa.eu/en/medicines/veterinary/EPAR/truscient)*
- **VarroMed** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/varromed)
- **Zulvac SBV** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/zulvac-sbv)
- **Zycortal** (https://www.ema.europa.eu/en/medicines/veterinary/EPAR/zycortal)

Annex 2 – Understanding the limited market provision compared to current application of MUMS policy/guidance:

	Current application of MUMS	Future 'limited market' provision	Comments
Legal basis	None.	Regulation 2019/6, Articles 23-24	
Definition	No legal definition for minor use. Major species are defined in Regulation 2017/880 as cattle, sheep for meat, pigs, chicken including eggs, and Salmonidae. By default, all others are minor.	(29) 'limited market' means a market for one of the following medicinal product types: (a) veterinary medicinal products for the treatment or prevention of diseases that occur infrequently or in limited geographical areas; (b) veterinary medicinal products for animal species other than cattle, sheep for meat production, pigs, chickens, dogs and cats.	The limited market definition is very similar to what is used when considering MUMS classification requests, with the exception that salmon (all fish) will be classified as minor species.
Eligibility	If the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.	If the following conditions are met: (a) 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; (b) the applicant provides the evidence that the veterinary medicinal product is intended for a limited market.	Regarding Article 23(1)(b), an approach (criteria) has been developed for interpretation of "diseases that occur infrequently or in limited geographical areas". Article 23(1)(a) is an additional consideration over and above what is required for MUMS classification currently. As a consequence, all products that satisfy criteria to be classified as 'intended for a limited market' are not automatically eligible for consideration under Article 23. 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'

	Current application of MUMS	Future 'limited market' provision	Comments
Standard applied	Data requirements presented in accordance with MUMS guidance. - Satisfactory quality. - Safety adequately characterised. - Proof of efficacy.	Quality requirements as detailed in Annex II. Not required to provide the comprehensive safety or efficacy documentation required in accordance with Annex II.	No reduction in quality requirements according to the limited markets provision. Article 23 allows for authorisation in the absence of a 'comprehensive' safety and efficacy dataset. That is, at the end of the assessment procedure, a clear gap (vis-à-vis the data elements required by Annex II) in the safety and/or efficacy dataset should be identifiable.
Marketing authorisation status	Not recognised as any different to standard MA.	Will be labelled as limited market product to differentiate it from a standard MA considered to meet Annex II requirements. Article 23(2) states: "where a veterinary medicinal product has been granted a marketing authorisation in accordance with this Article, the SPC shall clearly state that only a limited assessment of safety or efficacy has been conducted due to the lack of comprehensive safety or efficacy data."	Products authorised in accordance with the limited markets provision should be recognised as different (in some cases requiring a different data requirement threshold) compared to products authorised currently according to MUMS policy and guidance. The concept of conditional marketing authorisation is not envisaged. 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.

	Current application of MUMS	Future 'limited market' provision	Comments
Post-authorisation requirements	Not recognised as any different to standard MA.	- Valid for a period of five years, which can be renewed. - The re-examination shall include an updated benefit-risk assessment. - The application for re-examination shall be limited to demonstrating that the conditions referred to in Article 23(1) continue to be fulfilled. - If the benefit-risk balance remains positive, the validity of the marketing authorisation shall be extended by additional periods of five years. - A marketing authorisation valid for an unlimited period of time may be granted, provided that the MAH submits the missing data on safety or efficacy referred to in Article 23(1). It should be noted that, with the exception of the requirement for re-examination, the same post-authorisation requirements (e.g. pharmacovigilance) apply as for standard marketing authorisations.	At the five-year time point, the conditions for 'eligibility' should continue to be met. The principle questions at that time will be "does the continued 'benefit of availability' continue to outweigh the absence of a comprehensive dataset" and are there any safety signals from PhV data? The legislation does not foresee an evaluation of new data at this time point. The documentation to be submitted is that the data required to 'complete' Annex II requirements. This is a 'may' provision – that is, there is no obligation on the MAH to address the data gaps once the authorisation has been issued. In view of this, the starting point for determination of data requirements should be Annex II and not the MUMS guidance.
Protection of technical documentation	Not recognised as any different to standard MA.	Not recognised as any different to standard MA. However, Article 18 (generics) is a derogation from point (b) of Article 8(1), which outlines the requirement for technical documentation according to Annex II (that is, 'full' dossier).	Given that, Article 18 does not reference to Article 23 and that Article 23 is, itself, a derogation from point (b) of Article 8(1), it follows that it is not possible to apply for a generic of a product authorised in accordance with Article 23. In case a validity for an unlimited period is granted for a MA according to Art. 24(6) the product benefits from protection of technical documentation for a period defined in Art. 39 of Regulation 2019/6 starting on the date the MA of unlimited validity is granted.

Annex 3 - Sources of animal population data

Whenever possible, reference should be made to official EU data, namely number of animals as collected by EUROSTAT[10]. When those data are not available, or not of the sufficient detail, other sources like FAOSTAT[11] might be used as the reference data for EU animal population. When the above-mentioned source of data does not provide adequate data, statistics provided by e.g. associations of animal producers might provide valuable information.

For companion animals no data are available currently from official sources at the EU level, as an example, the figures of the European Pet Food Industry could be used[12] as a reference. National statistical databases of MS can also be used to complete missing data.

[10] Living (food-producing) animals Eurostat: https://ec.europa.eu/eurostat/data/database >Data navigation tree > Database by themes > Agriculture, forestry and fisheries >Agriculture > Agricultural production > Animal production >Livestock and meat > Livestock (apro_mt_ls):
[11] Living animals FAOSTAT database: http://www.fao.org/faostat/en/#data > Production > Live Animals or for food-producing rabbits, turkey (produced) > Livestock Primary
[12] http://www.fediaf.org/images/FEDIAF_Facts__and_Figures_2018_ONLINE_final.pdf