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Guideline on the summary of product characteristics for antiparasitic veterinary medicinal products

Draft

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This guideline replaces the CVMP guideline on the summary of product characteristics for anthelmintics (EMEA/CVMP/EWP/170208/2005).

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	**antiparasitic, anthelmintic, ectoparasiticide, resistance, veterinary, SPC, product information**

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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Executive summary

The Summary of Product Characteristics (SPC) is an essential communication tool, which can be used in particular to promote effective and responsible use of antiparasitic Veterinary Medicinal Products (VMPs) in the face of an evolving resistance situation. Accordingly, the aim of this document is to provide guidance as to the information and recommendations to be included in the different SPC sections mainly in relation to antiparasitic resistance, and to propose standard text where appropriate.

This is the first revision of the *Guideline on the summary of product characteristics for anthelmintics*, which initially came into effect in February 2008. The main aim of the revision is to take into account the evolution of antiparasitic resistance in the EU and the scientific knowledge on the factors that significantly influence resistance development.

These issues have been reviewed in the Reflection paper on anthelmintic resistance in the EU [1], adopted by the CVMP in April 2017. Moreover, with the new Regulation (EU) 2019/6 on Veterinary Medicinal Products [2] in force, more emphasis is now placed on the need to limit the development of antiparasitic resistance. A draft Reflection paper on resistance in ectoparasites has also been developed [3], which highlights that resistance is of concern in ectoparasites as well and should be addressed through appropriate risk mitigation measures.

This has led to the decision to extend the scope of the revision of the existing guideline on the SPC for anthelmintics to also include other antiparasitic veterinary medicinal products. The scope was further extended to host species other than ruminants and horses, e.g. pigs, poultry and companion animals. The revision takes into account, in particular, the need to shift from systematic to more targeted and medically justified antiparasitic treatment, specific issues in relation to combination products, and the necessity for an accurate dosing. Besides, recommendations as to the justification of pack sizes are included. The guideline intends to be sufficiently flexible, keeping in mind the variability in host and parasite species, in product formulations and in treatment objectives.

1. Introduction (background)

For the purpose of this guideline, antiparasitic resistance is defined as the genetically transmitted loss of susceptibility in a population of parasites that were previously susceptible to the same substance when used according to label recommendations.

Traditionally, the use of veterinary medicinal products (VMPs) intended for antiparasitic treatment has largely been based on systematic mass treatment or prophylactic schedules. Approaches of this type may be appropriate in some situations, but are currently challenged by emerging concerns, which include, alongside environmental issues, the impairment of antiparasitic immunity and the increasing development and spread of antiparasitic resistance.

While the use of any antiparasitic active substance may eventually result in selection for resistance, the spread and practical impact of resistance is extremely variable depending on the host-parasite system involved and the concerned geographical location. For example, in gastro-intestinal nematodes of ruminants, the considerable extent of anthelmintic resistance in some European regions has resulted in treatment failures and in a problematic limitation of the therapeutic options, and in significant economic impact on livestock farming. As antiparasitic resistance issues are overall increasingly reported it should be considered for all domestic animal species, in order to limit future health and economic consequences.

Scientific evidence shows that resistance development can be mitigated by optimizing exposure to antiparasitics, at the level of product formulation and dosing, and through parasite management

practices oriented towards targeted treatment and integrated control mechanisms. Promoting better use through the product literature of antiparasitic products, in accordance with specific product properties, contributes to the objective of delaying the emergence and spread of antiparasitic resistance and thereby, to preserve the efficacy of antiparasitic VMPs as long as possible.

This guidance has been developed based on the current knowledge of the factors that may drive antiparasitic resistance, and also following experience gained from previous marketing authorisation procedures. Its intention is to eventually provide harmonized, effective and practicable advice.

2. Scope

This revised guideline applies to the SPC of VMPs containing antiparasitic substances as defined in Regulation (EU) 2019/6 (see Article 4, Definitions). It concerns any target animal species.

The definition of antiparasitic substances as provided by Regulation (EU) 2019/6, does not cover antifungal and antiprotozoal active substances, which are included under the definition of antimicrobial substances. Nevertheless, the resistance profile of protozoa may bear more similarity to antiparasitics than to antimicrobials, and therefore, in certain cases, the present guideline could be applied to some extent to products used for their antiprotozoal (e.g. anticoccidial) activity. However, this should not take precedence over guidance applying specifically to these products.

Guidance is provided on the content of the different SPC sections, mainly in relation to the management of antiparasitic resistance or the risk thereof. Where appropriate, standard statements are proposed.

This guideline applies to new marketing authorisation applications (where appropriate, depending on the legal basis of the application as defined in Regulation (EU) 2019/6). It also applies to referrals, re-examinations (Articles 24 and 27 of Regulation 2019/6), and to variation applications that require a reconsideration of the overall benefit-risk balance. For such variations, it applies only to the parts of the SPC that fall within the direct scope of the procedure.

3. Legal basis

The SPC should contain information in accordance with the requirements detailed in Article 35 of Regulation (EU) 2019/6 [2]. This guideline should be read in conjunction with other relevant EU and VICH guidelines. These include, but are not limited to:

- VICH guidelines on the efficacy requirements for anthelmintics [4-12],
- CVMP guidelines on the demonstration of efficacy of ectoparasiticides [13-15],
- CVMP guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats [16],
- CVMP 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 [17],
- CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005) [18]
- CVMP Question and Answer document on the information contained in section 5.1 of the SPC [19],
- QRD template [20].

4. General considerations

In accordance with the terminology used in the current VICH and CVMP guidelines on efficacy of anthelmintics and ectoparasiticides, and by most experts in the field, the term "*infection*" should preferably be used when referring to helminths, while "*infestation*" should relate to ectoparasites. When referring to both types of parasites, "*infection*" can be used.

The SPC should in principle provide product-specific information to facilitate the decision on whether the use of the product is appropriate, and provide practical guidance for prudent and effective treatment. Recommendations pertaining to general scientific knowledge or routine veterinary practice are generally regarded as superfluous and should be avoided. The SPC wording should be adapted to be fully relevant to the particular administration route, product formulation, target parasites and therapeutic indications under assessment.

In order to foster user compliance as far as possible, advice and warnings should generally remain brief, and repetition of content across several SPC sections should be avoided. No detailed study results or experimental details should be included in the SPC unless those are relevant for proper product use or are considered essential information for the user.

Antiparasitic treatments are often regularly repeated, either to maintain continuous protection against new infections/infestations, or to keep parasite burdens at a low level. This however is of concern in regard to resistance development, and therefore the frequency and number of re-treatments should be based on medical or epidemiological need rather than being applied systematically. In general, the following types of recommendations should not be included in the SPC, unless they are supported by sound clinical or epidemiological justifications:

- recommendations for whole-group use;
- advice for systematic use at defined intervals or times of the year;
- recommendations for routine long-term or continuous use.

Further recommendations in relation to re-treatment can be found under point 5 - SPC section 3.9.

Antiparasitic resistance is an evolving matter, and SPC recommendations should always be based on the most recent, evidence-based scientific views.

When drafting the package leaflet, in particular where VMPs are expected to be administered by the animal owner, applicants should reflect the SPC instructions in a user-friendly language, as necessary.

5. Recommendations per SPC section

The proposed standard sentences below should be used as a guide, and may be adapted to better fit any particular product property or intended use.

Section 3. Clinical information

Section 3.2. Indications for use for each target species

As a general rule, each indication should relate to a specific parasite defined by the species and stage, unless the species/stage cannot be distinguished in practice.

Indications will generally be approved based on the efficacy criteria defined in the relevant guidelines (see section 3). Efficacy claims with no universally agreed meaning, such as "*for the control of*", should be avoided.

This section should provide clear information on the duration of persistent efficacy established for a given parasite.

In accordance with good veterinary practice, a product should not be used to treat parasites known or likely to be resistant to the concerned product, and therefore, it is not considered appropriate to include the following wording in the indications: "*<target parasite species> susceptible to <antiparasitic substance>".*

In the case of fixed combination products, the wording of the indication should reflect precisely the specific situation(s) in which the combined use is indicated, in line with the requirements of the CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005).

Antiparasitic substances with different activity spectra are often combined in VMPs; in such cases, the SPC should be clear that the product should only be used when all active substances are indicated at the same time. The following wording can be used as a basis:

> *"For <target animal species> with, or at risk from mixed infections/infestations by <parasite groups or species targeted by each of the combined active substances>. The veterinary medicinal product is only indicated when use against <appropriate arrangement of parasite groups or species> is indicated at the same time."*

Claims of efficacy against parasites that are known to be resistant to *another* active substance are not accepted in this section. Such effect is considered to correspond to an absence of cross-resistance (or side-resistance) rather than to an indication, and should be reflected in sections 3.4 and 4.2 (see below).

Section 3.3. Contraindications

It is generally not considered appropriate to contraindicate the use of the VMP in case of established or suspected resistance to the active substance for the approved indication(s).

However, if there is evidence of a serious risk to animal health from resistance due to the use of the VMP in a defined animal species or subgroup, this should be reflected in this section.

Section 3.4. Special warnings

This section should include information that complements the indications where relevant, e.g. in relation to the effects on arthropod feeding. It further aims to ensure effective use of the product while limiting resistance selection pressure and thus, the risk of future resistance development. Its content should comprise:

(i) **Recommendations for responsible use and advice on how to apply targeted treatment as appropriate**

An antiparasitic VMP should only be used if necessary from a medical and/or epidemiological point of view, based on parasitological diagnosis and/or assessment of factors such as the animal's environment and lifestyle, and the incurred zoonotic risk. This potentially limits the overall resistance selection pressure, and may also be beneficial from an environmental and economic perspective. Moreover, in some specific contexts such as the control of gastro-intestinal nematodes in grazing ruminants, it is recognised that purposely leaving parasites

unexposed (e.g. in untreated animals) within a herd as *refugia* can be useful to delay spread of resistance.

This should be reflected in warnings encouraging a proper identification of the parasitic species of concern and evaluation of the status of the group, i.e. which individual animals or subgroups require treatment based on their parasite burden or their clinical or physiological status.

The following standard text should generally be used:

"Unnecessary use of antiparasitics, or use deviating from the instructions given in the SPC, may increase the resistance selection pressure and lead to reduced efficacy. The decision to use the product should be based on confirmation of the parasitic species and burden, or of the risk of [infection/infestation] based on its epidemiological features, for each individual animal/herd/flock [depending on the target species]."

In the case of anthelmintic products intended for the treatment of gastro-intestinal (and respiratory) nematodes in grazing animals the following text should be added:

"Repeated use for an extended period, particularly when using the same class of substances, increases the risk of resistance development. Within a herd/flock, maintenance of susceptible refugia is essential to reduce that risk. Systematically-applied interval-based treatment and treatment of a whole herd/flock should be avoided. Instead, if feasible, only selected individual animals or subgroups should be treated (targeted selective treatment). This should be associated with appropriate husbandry and pasture management measures. Guidance for each specific herd should be sought from the responsible veterinarian."

More specific guidance can be given where methods for guiding targeted treatment have been established (e.g. through product-specific studies or literature data) for a given indication.

For fixed combination products extending the spectrum, the following sentence may be included:

"In the absence of risk of co-infection [specify which as appropriate]*, the use of a narrow spectrum product should be considered."*

This only applies if a suitable alternative is widely available. Where relevant, more specific information can be given on the possible alternatives and/or on typical situations where an alternative product would be indicated.

This statement can be used also for products containing a single broad-spectrum active substance (e.g. a substance active against both gastro-intestinal nematodes and liver fluke, or an endectocide), where significant resistance issues have been identified in the field in the concerned parasites.

(ii) **Advice on concomitant measures needed to optimize effectiveness**

Where available, evidence-based advice should be added in regard to associated measures necessary to avoid re-infection or likely to reduce significantly the use of antiparasitics. This may concern, for example, the treatment of parasitic stages in the animal's environment or habitat, the concomitant use of hygienic or non-chemical methods for reducing the parasite burden, or specific animal husbandry and pasture management.

In companion animals, where it can be appropriate in view of the indications to treat all animals in the same household, the following text should be used:

"The possibility that other animals in the same household can be a source of re-infection with [*concerned parasite group or species,* e.g. *fleas*] *should be considered, and these should be treated as necessary with an appropriate product."*

Additional instructions may be needed where sufficient exposure to the product is influenced by external factors (e.g. weather conditions or bathing).

(iii) **Up to date information on the prevalence of resistance to the active substance(s) in the indicated parasite(s) and in the EU**

The following standard sentence can be used as a basis:

"Resistance to <active(s) substance(s)/class(es) of antiparasitic> has been reported in <parasite species> in <target animal species>."

Where applicable, this should be completed by more detailed information on the clinical impact of established side-resistance, cross-resistance or multiple resistance.

The result of clinical studies investigating efficacy in parasites resistant to *another* substance or class can be referred to in this section.

(iv) **Advice on how to assess and handle potential resistance in the animals to be treated**

In the case of parasite species for which clinical resistance to the active substance has been reported in the field, the following standard text should be used:

"The use of this product should take into account local information about susceptibility of the target parasites."

Where a practical means for the detection of acquired resistance is available, the following statement should be added:

"It is recommended to further investigate cases of suspected resistance, using an appropriate diagnostic method (e.g. [specify the appropriate method(s)]*).*

Confirmed resistance should be reported to the marketing authorisation holder or to the competent authorities."

Apart from the Faecal Egg Count Reduction Test (FECRT), there are currently few reliable and practicable antiparasitic resistance detection methods. The FECRT is generally the appropriate test in the case of anthelmintic products intended for the treatment of gastro-intestinal nematodes in ruminants or horses. However, other methods might be appropriate depending on the concerned active substance and parasite species, and future developments can be expected. Therefore, the judiciousness of recommending a specific resistance detection method in the SPC, with the adequate interpretation criteria if available, should be considered on a case-by-case basis.

Section 3.9 Administration route(s) and dosage

The main purpose of this section is to ensure correct dosing, and in particular to avoid underdosing, which is known to favour resistance selection. Where applicable, it should also include information on the number of administrations and the interval between administrations needed to ensure efficacy against target parasites.

The recommended dose should be expressed in mg active substance per kg bodyweight, and also as units of the pharmaceutical form of concern (per kg bodyweight or for given bodyweight bands, where applicable).

Ranges in dose level should be avoided, unless there is clear guidance for the user as to when to administer the product at the upper or lower limit of the range.

The following standard text should be included as appropriate:

> *"Underdosing precludes effective use and may favour resistance development".*

> *"To ensure a correct dosage, body weight should be determined as accurately as possible. If animals are to be treated collectively, reasonably homogeneous groups should be set up, and all animals of a group should be dosed at the rate corresponding to the heaviest one."*

> *"Accuracy of the dosing device should be thoroughly checked."*

As various administration methods and devices may exist, these statements may be tailored to particular products. More specific instructions as to the mode of administration and calibration of the dosing device can be added as deemed useful. Recommendations to avoid cross-contamination between treated and untreated animals after product administration should be included where relevant, e.g. for pour-on products.

The user should be clearly informed on the number of administrations and interval between administrations needed for appropriate treatment of an infection/infestation (based on the efficacy and safety data of the product), and of the need for follow-up diagnostics where applicable.

Where repeated administration of the product is required to ensure continuous protection against claimed parasite species, the following standard text may be included, as appropriate:

> *"For infestations/infections with [parasite(s)], the need for and frequency of re-treatment(s) should be based on professional advice and should take into account the local epidemiological situation and the animal's lifestyle."*

Recommending different dosing regimens for different parasite species is not acceptable when the concerned species are commonly present as mixed infections, or cannot be readily distinguished under field conditions.

Section 3.11. Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

This section includes restrictions and conditions for use arising directly from specific legal provisions in Regulation (EU) 2019/6 or its Implementing and Delegated Acts i.e. not originating from product-specific assessment, mainly for antimicrobial and immunological VMPs.

For antiparasitic VMPs, the contents of this section may principally derive from Article 106 of Regulation (EU) 2019/6, on 'Use of medicinal products', and the related Delegated Act foreseen by Article 106(6) on oral administration. For example, Article 106(4) provides the legal basis to classify a VMP for administration only by a veterinarian and a standard sentence to this effect is included in the QRD SPC template.

Section 4. Pharmacological information

Section 4.2 Pharmacodynamics

The classification and mode of action of the active substance(s) should be described in this section, together with the type of effect on the target parasite(s) (e.g., killing, repellence, disruption of the life cycle). Information in relation to the speed of kill also pertains to this section, in line with the CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats [16].

Where known, brief information on the mechanism(s) and genetic basis of acquired resistance in the target parasites should be included. It should also be explained how this could result in side-resistance or cross-resistance.

The wording of this section should follow the principles laid down in the Question and Answer document on the information contained within section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products [19].

Section 4.3 Pharmacokinetics

This section should present the pharmacokinetic parameters which underlie efficacy of the proposed formulation, when using the recommended route(s) and dosing regimen in each of the proposed target species.

The profile of each active substance (or active metabolite) with systemic availability, should be described using appropriate pharmacokinetic parameters.

The distribution to particular sites (e.g. hair coat, skin, gastro-intestinal lumen,…) should be described if relevant.

Parameters in relation to the elimination kinetics should be included, however, care should be taken that this is not misleading in regard to the persistent antiparasitic efficacy; for instance, phrases such as "*…can still be detected in ...after… weeks post-treatment*" should be avoided.

Appropriate measures of central tendency for pharmacokinetic parameters should be used, and associated with an appropriate measure of variability.

Section 5.4. Nature and composition of immediate packaging

The availability of appropriate pack sizes is likely to have a significant impact on appropriate dosing and on the implementation of targeted treatment, as well as on the appropriate disposal of unused product. Hence, the selection of appropriate pack size(s) should be part of the efforts to delay resistance development.

More information on the suitable pack sizes is provided in Annex I.

Definitions

Antimicrobial: in accordance with Regulation 2019/6, means any substance with a direct action on micro-organisms used for treatment or prevention of infections or infectious diseases, including antibiotics, antivirals, antifungals and anti-protozoals.

Antiparasitic: in accordance with Regulation 2019/6, means a substance that kills or interrupts the development of parasites, used for the purpose of treating or preventing an infection, infestation or disease caused or transmitted by parasites, including substances with a repelling activity.

Antiparasitic resistance: for the purpose of this document, antiparasitic resistance is defined as the genetically transmitted loss of susceptibility in a population of parasites that were previously susceptible to the same substance when used according to label recommendations.

Cross-resistance: resistance against two active substances belonging to different antiparasitic classes.

Multiple resistance: resistance to several antiparasitic substances, generally to most or all of the main classes available against the concerned parasite.

Refugia (a *refugium*): areas in which a population of organisms can survive through a period of unfavourable conditions. In the context of drug resistance in animal parasites, a refugium refers to untreated hosts or an environment that allow the maintenance of drug-sensitive parasites in the face of drug exposure. In practice, this frequently relies upon treatment of only a proportion of animals, rather than the whole group, leaving some part of the parasite population untreated and thus free from the selection pressure applied by exposure to drug (from Hodgkinson *et al.*, 2019, IJP: Drugs and Drug Resistance 10: 51–57).

Side-resistance: resistance to an antiparasitic compound conferred by resistance to another compound of the same chemical class.

Targeted selective treatment: Specific targeted treatment strategy aiming to leave untreated a proportion of animals (and therefore, of parasites) in a herd or flock. The individual animals that will benefit most from treatment are selected based on specific parasitological or physiological indicators and criteria. This concept is primarily applied in relation to gastro-intestinal nematodes of ruminants.

Targeted treatment: product administration to an individual animal or a defined animal subgroup, following appropriate parasitological, clinical and/or epidemiological assessment. This is opposed to fixed-interval and/or whole-herd treatment strategies. In the framework of this guideline, this phrase is used in a general manner, for all target species and parasitic infections or infestations.

References

[1] CVMP Reflection paper on anthelmintic resistance (EMA/CVMP/EWP/573536/2013).

[2] Regulation (EU) 2019/6 of the European Parliament and the of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC, Official Journal of the European Union L 4, 7.1.2019, p. 43–167.

[3] Draft CVMP Reflection paper on resistance in ectoparasites (EMA/CVMP/EWP/310225/2014).

[4] VICH GL7: Efficacy requirements for anthelmintics: overall guidelines (CVMP/VICH/832/99).

[5] VICH GL15: Efficacy of anthelmintics: specific recommendations for equines (CVMP/VICH/833/99).

[6] VICH GL12: Efficacy of anthelmintics: specific recommendations for bovines (CVMP/VICH/839/99).

[7] VICH GL13: Efficacy of anthelmintics: specific recommendations for ovines (CVMP/VICH/840/99).

[8] VICH GL14: Efficacy of anthelmintics: specific recommendations for caprines (CVMP/VICH/841/99).

[9] VICH GL16: Efficacy of anthelmintics: specific requirements for porcines (CVMP/VICH/834/99).

[10] VICH GL19: Efficacy of anthelmintics: specific recommendations for canines (CVMP/VICH/835/99).

[11] VICH GL20: Efficacy of anthelmintics: specific recommendations for felines (CVMP/VICH/545/00).

[12] VICH GL21: Efficacy of anthelmintics: specific recommendations for poultry (CVMP/VICH/546/00).

[13] Demonstration of efficacy of ectoparasiticides (7AE17a, 1994).

[14] CVMP Guideline on specific efficacy requirements for ectoparasiticides in cattle (EMEA/CVMP/625/2003).

[15] CVMP Guidelines on specific efficacy requirements for ectoparasiticides in sheep (EMEA/CVMP/411/2001).

[16] CVMP Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats (EMEA/CVMP/EWP/005/2000).

[17] CVMP 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).

[18] CVMP guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005)

[19] CVMP Question and Answer document on the information contained within section 5.1 of the SPC on pharmacodynamic properties for pharmaceutical products (EMA/CVMP/757903/2016).

[20] Veterinary Product Information Templates

[21] Regulation (EU) 2019/4 of the European Parliament and of the Council of 11 December 2018 on the manufacture, placing on the market and use of medicated feed, amending Regulation (EC) No 183/2005 of the European Parliament and of the Council and repealing Council Directive 90/167/EEC, Official Journal of the European Union L 4, 7.1.2019, p. 1–23.

Annex I

Recommendations on the pack sizes suitable for antiparasitic VMPs

Recital 47 of Regulation (EU) 2019/6 indicates that "the supply of veterinary medicinal products by veterinarians should be restricted to the amount required for treatment of the animals under their care". Furthermore, pursuant to Article 105(6) of Regulation (EU) 2019/6, "the quantity of the medicinal products prescribed shall be limited to the amount required for the treatment or therapy concerned".

Annex II of EU Regulation (EU) 2019/6, Section II *Requirements for veterinary medicinal products other than biological veterinary medicinal products*, subsection II.2A2, states the following: "The proposed pack sizes shall be justified in relation to the proposed route of administration, the posology and the target species in particular for antimicrobial (active) substances."

In addition, reference to pack sizes is made in the *Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council*, in regard to deletion of pack size(s) of the finished product (variation B.3.r) and changes in pack size (number of units e.g. tablets, ampoules, etc. in a pack) within the range of the currently approved pack sizes (variation B.38). Conditions for such changes include that the remaining pack sizes (in case of deletion of pack sizes) and the new pack size (in case of changes in pack size) shall be consistent with the posology and treatment duration as approved in the SPC. Furthermore, the *Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations* (EMA/CMDv/7381/2021) sets the conditions for changes in pack size of the finished product where those changes are considered to be variations requiring assessment (variation F.II.e.5). In these cases, justification for the new pack size is to be provided, showing that the new size is consistent with the dosage regimen and duration of treatment as approved in the SPC.

The different pack sizes to be marketed should be justified, and should be defined with as main purpose to ensure that an adequate pack size is available which covers a complete treatment course (individual, or grouped where appropriate) in most practical cases, while avoiding systematic and important leftovers which could be misused, by prolonging the treatment or treating other animals in the absence of veterinary support.

It is acknowledged that establishing appropriate pack sizes can be difficult given the variability between species, indications, herd sizes and husbandry practices; nevertheless, the available pack size(s) must be justified based on the following basic principles:

- For products primarily intended for animals kept individually, in principle the smallest pack size available should correspond to one single antiparasitic treatment (of an animal of average size, where applicable), unless otherwise justified. Additional, larger pack size(s) may be made available where it is usually necessary to repeat treatment. In such cases, all substances combined within a product should be considered when assessing the likely necessity for repeated administration.

- For products primarily intended for animals kept in groups, the minimum pack size should correspond to one single antiparasitic treatment in a subgroup of reasonable size, taking into account the indications and host species, and the realistic minimum proportion of animals which would require administration in a context of targeted treatment. This would require an estimation of the typical number of animals to treat, in view of the current best practice

recommendations. Additional, larger pack sizes may be justified in the same way for other indications or host species. The maximum pack size should not be larger than necessary to allow one antiparasitic treatment of a whole group of a typical size (based on the average expected bodyweight of animals). If the size of a group of the target population varies considerably within or between Member States, several pack sizes might need to be made available accordingly.