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Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances

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This guideline replaces the current CVMP guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005) and the Question 2 of the question & answer document (EMA/CVMP/414812/2011-Rev.2).

Keywords	Antimicrobial, antibiotic, summary product characteristics, SPC, veterinary medicinal products, responsible use, resistance, susceptibility testing, breakpoints

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Guideline on the summary of product characteristics (SPC) for veterinary medicinal products containing antimicrobial substances

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Executive summary

This revision provides updated guidance on the information to be included in the summary of product characteristics (SPC) of veterinary medicinal products (VMPs) containing antimicrobial substances. It replaces the current guideline on the SPC for antimicrobial products (EMEA/CVMP/SAGAM/383441/2005), which came into effect in May 2008. Since then there have been significant developments in principles of therapy in regard to antimicrobial resistance and various regulatory initiatives have been undertaken by CVMP [1-6], including publication of the CVMP's strategy on antimicrobials 2016-2020, updated to 2021-2025 (EMA/CVMP/179874/2020) [7]. According to these initiatives, recommendations from other CVMP reflection papers and referral procedures, and based on experience gained from marketing authorisation procedures, further guidance is provided on information to be included in the SPC in order to encourage optimal use and to minimise selection of antimicrobial resistance. Warnings and guidance have been included in accordance with Regulation (EU) 2019/6 on veterinary medicinal products [8] such as restrictions on use and risk mitigation measures to limit the development of resistance. This revision of the guideline should also serve to improve consistency of the SPCs for antimicrobial products in the EU Member States.

1. Introduction (background)

The SPC is the key means of communication with the prescriber. It should contain the necessary information making it possible to use the antimicrobial VMP effectively and safely while at the same time minimising the risk of selection of antimicrobial resistance. Responsible use warnings and recommendations for the specific VMP should be included in the product information, and for this purpose examples of relevant phrases for drafting an SPC are presented in this guideline. However, warnings already covered routinely by good veterinary practice in relation to responsible antimicrobial use should not be part of the product information. An SPC drafted in accordance with this guideline should provide product-specific information that facilitates the development of treatment guidelines and responsible antimicrobial prescribing [7].

In the context of this guideline and in line with the definitions in Regulation (EU) 2019/6, an antimicrobial is defined as 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. An antibiotic is defined as a substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.

2. Scope

This revised guideline provides instructions about specific information that should be included in the SPC of VMPs containing antimicrobial substances. Defining a harmonised approach for the presentation of the necessary information is considered useful for national and EU regulatory procedures. The guideline has been developed primarily with antibiotic substances in mind, but in principle could be applied at high level to other types of antimicrobial substances.

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) and variation applications that require a reconsideration of the overall benefit-risk balance: for such procedures, it applies only to those 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 the Regulation (EU) 2019/6 [8] and other relevant EU and VICH guidelines. These include, but are not limited to:

- the CVMP Guideline for the demonstration of efficacy for VMPs containing antimicrobial substances (EMA/CVMP/627/2001) [1],
- the CVMP Guideline on the conduct of efficacy studies for intramammary products for use in cattle (EMA/CVMP/344/1999) [10],
- VICH GL27 Guidance on pre-approval information for registration of new VMPs for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL) [11],
- Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antimicrobial veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013) [12].

4. General considerations for the preparation of the SPC

The following headings refer to the respective sections of the SPC. This guideline does not include guidance on the sections of the SPC or aspects of the substance that do not relate directly to the antimicrobial properties of the VMP.

Section 3 Clinical Information

Section 3.2 Indications for use for each target species

The intended use of the product should be clearly worded in the indication, i.e. the clinical disease/signs to be treated. Indications for use must have defined target pathogen specie(s). General indications without named target pathogens or indications with claims that are not related to a clinical disease are not acceptable.

The target pathogens shall be listed for each target animal species and for each indication for use. Bacteria should be listed alphabetically in the following order: aerobic Gram-positive bacteria, aerobic Gram-negative bacteria, anaerobic bacteria, other micro-organisms.

Antimicrobial products should only be used when target pathogens are susceptible to the antimicrobial substance and, where feasible, in line with susceptibility testing according to guidance in section 3.5. Hence, indications should not routinely need to use the wording: "<target bacterial species> susceptible to <antibiotic>".

Taking into account the definition of prophylaxis provided in the Regulation and the restrictions around prophylactic use of antimicrobials laid down in Article 107(3), use for prophylaxis is restricted to the administration only in exceptional cases when the risk of an infection or of an infectious disease is very high and the consequences are likely to be severe. Prophylactic use of an antimicrobial VMP is further limited to the administration to an individual (antibiotic medicinal products) or a restricted number (other antimicrobial medicinal products) of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection.

The term "treatment" refers to the treatment of an individual animal or a group of animals showing clinical signs of an infectious disease.

The term "metaphylaxis" refers to the administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected. Metaphylaxis is always combined with the treatment of the diseased individuals and consequently a metaphylaxis claim will only be accepted in conjunction with a treatment claim. If metaphylaxis is part of the indication, the following sentence must be included:

> *"The presence of the disease in the <group> <flock> must be established before the product is used."*

Section 3.3 Contraindications

Information may be added in this section where there is specific scientific evidence of a serious risk to animal health demonstrating that the product must not be used in a particular (subgroup of the target) animal population.

Selective effects of an antibiotic on the normal gut microbiota (microflora) leading to disruption of the microflora with serious consequences (e.g. use of colistin in foals and beta-lactams in rabbits and rodents) should be stated for relevant species. Alternatively, a warning could be included in section 3.5 where the consequences are less serious but clinically relevant.

Section 3.4 Special warnings

The purpose of this section is to provide clear information on how to ensure the effective use of the product in the target animals. Warning(s) may be needed if there is potential lack of efficacy of the product in some situations.

Information on resistance should be included in cases where there may be an impact on the efficacy of the product, e.g. when target bacteria show a multimodal distribution profile indicating a proportion of isolates that may be clinically resistant and no clinical breakpoints are available, or when a significant proportion of the target pathogen population is resistant in several geographical locations.

In case cross-resistance of a target pathogen(s) against member(s) of the same antimicrobial class or related classes has been identified, the following information should be included:

> *"Cross-resistance has been shown between <antimicrobial in the product> and <different antimicrobial(s) in the same (sub)class / related class> in <target pathogen(s)>. Use of the <product /antimicrobial> should be carefully considered when susceptibility testing has shown resistance to <antimicrobial(s)/classes of antimicrobials> because its effectiveness may be reduced."*

Information regarding the absence of bacterial eradication (e.g. in *Mycoplasma* spp. infections) or bacteriological cure (e.g. mastitis caused by *S. aureus*) may be included in this section.

For metaphylactic treatment, precise and thorough information should be provided about the epidemiological circumstances under which the product has been shown to be effective (e.g. the proportion of the group showing clinical signs at the start of treatment) and the extent of benefit demonstrated. Where necessary, information should be included to give the product user realistic expectations of the efficacy of the product and thereby reduce unnecessary antimicrobial use.

Information on clinical trials related to clinical efficacy may be included when such information is relevant for the effective use of the product and relates to the specific circumstances of the trial (e.g. the substance has been used as a second line treatment and according to Antimicrobial Advice Ad Hoc

Expert Group (AMEG) classification, and should therefore be reserved for use in certain situations only).

Section 3.5 Special precautions for use

Special precautions for safe use in the target species

Recommendations for responsible use

The purpose of this section is to provide clear information on how to ensure the safe use of the product in the target animals. Responsible use recommendations(s) or risk mitigation measures may be incorporated if there are potential safety risks to animal and/or public health related to antimicrobial resistance and associated with the use of the product.

One of the main requirements for the responsible use of antimicrobials is an accurate diagnosis before treatment. Diagnosis should be confirmed preferably on isolation of the causative bacterial pathogen, followed by antimicrobial susceptibility testing and use of validated interpretive criteria (breakpoints) aiming for a substantiated (calculated) therapy. This "gold standard" of good veterinary practice may not always be feasible because of, for example, the acuteness/severity of the disease, difficulty in sampling the site of the infection for bacteriology, impossibility of routine bacterial isolation/cultivation, the lack of methods for susceptibility testing or the lack of clinical breakpoints. Empirical therapy should then be based on local epidemiological information concerning susceptibility of target bacteria.

For all antimicrobial products, the following should be included:

> *"Use of the product should be based on identification and susceptibility testing of the target pathogen(s). If this is not possible, therapy should be based on epidemiological information and knowledge of susceptibility of the target pathogens at farm level, or at local/regional level."*
>
> *"Use of the product should be in accordance with official, national and regional antimicrobial policies."*

With regard to the risk to public health from antimicrobial resistance due to the use of antibiotics in veterinary medicine, antibiotics are categorised depending on the relative importance for their use in human and veterinary medicine. These categories (AMEG Categories: A-D) [6] should be taken into account to define whether a product should be reserved for use when response to other antibiotics is (expected to be) poor.

For AMEG Category B and C antibiotics add:

> *"An antibiotic with a lower risk of antimicrobial resistance selection (lower AMEG category) should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach."*

For certain substances with higher importance to public health, the CVMP has agreed to include specific precautionary phrases in the SPCs [4, 12, 13].

In addition, for broad-spectrum antibiotics e.g. extended-spectrum penicillins the following warning may be included, if relevant:

> *"Narrow spectrum antibiotic therapy with a lower risk of antimicrobial resistance selection should be used for first line treatment where susceptibility testing suggests the likely efficacy of this approach."*

For products containing 3rd- and 4th-generation cephalosporins it is recommended to include:

"The <product /antimicrobial> selects for resistant strains such as bacteria carrying extended-spectrum beta-lactamases (ESBL) and may constitute a risk to human health if these strains disseminate to humans."

Depending on the target animal species, the pharmaceutical form and the type of use, additional recommendations on responsible use or risk mitigation measures may be necessary.

Individual animal or group treatment will affect the extent of the use of a product. In group treatment, the overall exposure to the antimicrobial, and thus the potential to select for antimicrobial resistance, will be higher when compared to individual treatment. If pertinent, restrictions from use as mass treatment for groups of animals (herd/flocks) may be required:

"Not for use for group treatment"

and/or treatment might solely be allowed in individual animals:

"The <product /antimicrobial> should only be used in individual animals"

Specific improvements to management and strategies for eradication can be mentioned, if relevant as further means to control particular infections where known to be effective. Inclusion of a recommendation to discourage use as part of a herd health programme may be necessary:

"The <product /antimicrobial> should not be used as part of herd health programmes."

Further precautionary measures arising from product-specific assessment may be necessary where prophylactic or metaphylactic use is not deemed justified in view of the definitions of the Regulation 2019/6 and is associated with a high risk to public health. In such situations warning(s) should be inserted:

"Not for use for <prophylaxis>/<metaphylaxis>" or *"Not for use for prophylaxis/metaphylaxis in case of …"*

The CVMP has agreed to include warnings on prophylactic use in the SPCs of products containing certain substances with high importance to public health [4, 13, 14].

For antibiotic products used in dairy cows for which a withdrawal period for milk is established the following warning should be included:

"The feeding of waste milk containing residues of <antibiotic> to calves should be avoided up to the end of the milk withdrawal period (except during the colostral phase), because it could select antimicrobial-resistant bacteria within the intestinal microbiota of the calf and increase the faecal shedding of these bacteria."

Fixed combination products containing more than one antimicrobial substance might represent a higher risk for selecting resistance. Thus, any unnecessary use in terms of active substance(s) that is(are) not needed to treat an infection should be avoided. Where applicable (e.g. systemically-acting products, intramammary-applied products), the following phrase should be included for fixed combination products:

'This antimicrobial combination should only be used where diagnostic testing has indicated the need for simultaneous administration of each of the active substances.'

Section 3.8 Interaction with other medicinal products and other forms of interaction

If available, information should be given about clinically relevant pharmacological interactions where the concurrent use of the substance with another one should be avoided. For example, polyvalent cations are known to limit the absorption of some tetracyclines due to the formation of complexes, or pleuromutilins have been shown to interact with ionophores with serious impacts on animal safety. Cross-reference may be necessary to section 3.3.

Where evidence of clinically relevant synergism or antagonism between antimicrobials for specific pathogens is available, this should be noted.

Information on cross-resistance should be indicated in section 3.4.

Section 3.9 Administration route and dosage

The recommended dose and duration of treatment included in this section of the SPC is based on the efficacy and safety data of the product and should be as explicit as possible, and reflect the product indications for the respective target species (production categories) and the route(s) of administration, accordingly. 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.

All deviations from approved and well justified dose, dosing interval, and treatment duration of the antimicrobial product should be minimised. Further guidance such as recommendations on discontinuation of treatment or re-evaluation of the diagnosis if no clinical response is seen in the animal reflect good veterinary practice and should not be included in the SPC.

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 should include information on legal obligations arising from Article 107, in particular 107(6) of Regulation (EU) 2019/6, and from Delegated and Implementing Acts related to these Articles, and from Article 17(3) of Regulation (EU) 2019/4 [9].

In line with Regulation (EU) 2019/4 medicated feed containing antimicrobials shall not be used for prophylaxis and accordingly the warning:

"Do not use for prophylaxis"

should occur in the SPCs of products intended to be used for the preparation of medicated feed.

Any other (discretionary) precautions, warnings, contraindications originating from product-specific assessment that are not laid out in the aforementioned Articles should continue to be included under the respective sub-section within SPC section 3 'Clinical information'. For example, product-related information restricting prophylactic and metaphylactic use linked with Articles 107(3) and 107(4) should appear in section 3.5. Repetition of content across several SPC sections should be avoided.

Section 4 Pharmacological Information

The information should allow the prescriber to relate specific susceptibility data (animal, farm, region) on the bacterial isolates to the mode of action and the kinetic profile of the antibiotic. This would allow

a proper decision to be made on the use of the antibiotic product, and to achieve an optimal antibacterial effect and minimise the potential for selection of resistance in a given situation.

Section 4.2 Pharmacodynamics

General properties of the antimicrobial should be described here, e.g. classification and mode of action, if the substance is bactericidal or bacteriostatic, and if its effect is mainly time-dependent or concentration-dependent.

The antimicrobial spectrum relevant for the target animal species and approved indications should be stated. The order of the listed target bacteria and micro-organisms should be the same as used in section 3.2. If possible, MIC distribution data for the bacterial target pathogens should be provided, including information on the number of analysed isolates, their origin (animal species, clinical condition, production type, geographic area) and year when the isolates were collected. The epidemiological cut-off value (ECOFF) should be provided, if feasible, to indicate the population without acquired resistance. The reference for the ECOFF used should be given. If no ECOFF is available, MIC_{50}- and MIC_{90}-values should be provided. Intrinsically resistant bacterial species should be mentioned if they are relevant in view of the indicated use.

Clinical breakpoint(s) and MICs (µg/ml) relevant for the target animal species and approved indications, if available, should be used to categorise isolates as susceptible (S), intermediate (I) or resistant (R). The reference and the year of issue for the clinical breakpoint(s) used should be given.

Information on the resistance mechanism(s) and the molecular genetics of acquired resistance in the target pathogens should be included. The existence of any cross-resistance and co-resistance should also be stated. Cross-reference to section 3.4 may be necessary.

Antimicrobial susceptibility data for bacterial target species applicable to the clinical indications should be updated based on findings from relevant European surveillance and other information which might influence the benefits and risks of the VMP. These data should be from the relevant time period, i.e. isolates should not be older than 5 years.

Section 4.3 Pharmacokinetics

Pharmacokinetic particulars of the product should be described in sufficient detail for clinical use in the target species. Relevant pharmacokinetic parameters such as Vd, C_{max}, T_{max}, elimination half-life, clearance, bioavailability and area under the concentration curve (AUC) should be mentioned for the recommended route of administration and dosing regimen. The degree of protein binding of the substance in the plasma should be given. Information about the concentrations of the free antimicrobial at the site of infection should be provided, if available and where a relationship with efficacy is established.

Where established, the most appropriate PK-PD index for the antimicrobial substance against each pathogen may be indicated and also the magnitude of this index associated with clinical efficacy.

If different doses are proposed for different indications, concentrations in plasma should be mentioned at least for the lowest and the highest dose.

Information on the excretion of the substance or active metabolites via the intestinal tract following administration at the recommended dose should be given if available and if relevant to the approved conditions of use.

Section 5 Pharmaceutical Particulars

Section 5.4 Nature and composition of immediate packaging

Of particular relevance to antimicrobial products, appropriate pack size(s) should be available, since inappropriate pack sizes may jeopardize the antimicrobial's responsible use and promote the spread of resistance.

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

Definitions

Antibiotic: Any substance with a direct action on bacteria that is used for treatment or prevention of infections or infectious diseases.

Antimicrobial: 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.

Antimicrobial resistance: The ability of micro-organisms to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill micro-organisms of the same species.

Co-resistance: The presence of resistance to more than one class of antimicrobial in the same bacterial strain, as might occur when different resistance genes are found on the same plasmid.

Co-selection of resistance: The selection of multiple AMR genes when one of these is selected by the presence of a relevant antimicrobial. An example of this is the integron, which may carry a gene cassette(s) encoding AMR genes that is (are) under the control of a single promoter. As a result, these genes are expressed in a coordinated manner, although the furthest downstream gene may not be as efficiently expressed as the gene next to the promoter. These cassettes are commonly found in both Gram-positive and Gram-negative bacteria. Since they can be part of a transposon they can become a part of the bacterial chromosome or plasmid and can then be transmitted amongst different bacterial strains.

Cross-resistance: A single resistance mechanism confers resistance to an entire class of antimicrobials. An example is the aminoglycoside-modifying enzymes which may confer resistance to several members of the aminoglycoside family. Cross resistance can occur across different classes of agents - a result of either overlapping drug targets, as is the case with macrolides and lincosamides, or a drug efflux pump with a broad range of activity (*i.e.* capable of exporting different classes of drugs).

Metaphylaxis: The administration of a medicinal product to a group of animals after a diagnosis of clinical disease in part of the group has been established, with the aim of treating the clinically sick animals and controlling the spread of the disease to animals in close contact and at risk and which may already be subclinically infected.

Prophylaxis: The administration of a medicinal product to an animal or group of animals before clinical signs of a disease, in order to prevent the occurrence of disease or infection.

Treatment: A treatment claim refers to the administration of a VMP after the onset of clinical signs of disease and only clinically affected individuals are to be treated.

References

1. CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMA/CVMP/627/2001).
2. Question and answer on the CVMP guideline on the SPC for antimicrobial products (EMA/CVMP/414812/2011-Rev.2).
3. CVMP/CHMP Answers to the requests for scientific advice on the impact on public health and animal health of the use of antibiotics in animals (EMA/381884/2014).
4. Commission implementing decision of 13.1.2012 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing authorisations for veterinary medicinal products which contain the active substances "Cefquinome and Ceftiofur, C(2012)182 final.
5. CVMP/CHMP Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Preliminary risk profiling for new antimicrobial veterinary medicinal products (EMA/CVMP/CHMP/682199/2017).
6. CVMP/CHMP Answer to the request from the European Commission for updating the scientific advice on the impact on public health and animal health of the use of antibiotics in animals - Categorisation of antibiotics (EMA/CVMP/CHMP/682198/2017)
7. CVMP strategy on antimicrobials 2016-2020 (EMA/CVMP/209189/2015) and 2021-2025 (EMA/CVMP/179874/2020)
8. 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, PE/45/2018/REV/1, Official Journal L 4, 7.1.2019, p. 43–167
9. 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, PE/43/2018/REV/1, Official Journal L 4, 7.1.2019, p. 1–23
10. CVMP Guideline on the conduct of efficacy studies for intramammary products for use in cattle (EMA/CVMP/344/1999)
11. VICH GL27 Guidance on pre-approval information for registration of new veterinary medicinal products for food producing animals with respect to antimicrobial resistance (CVMP/VICH/644/01-FINAL)
12. Guideline on the assessment of the risk to public health from antimicrobial resistance due to the use of an antibiotic veterinary medicinal product in food-producing animals (EMA/CVMP/AWP/706442/2013)
13. CVMP Reflection paper on the use of fluoroquinolones in food producing animals - Precautions for use in the SPC regarding prudent use guidance (EMEA/CVMP/416168/2006-FINAL).
14. Commission implementing decision of 16.3.2015 concerning, in the framework of Article 35 of Directive 2001/82/EC of the European Parliament and of the Council, the marketing

authorisations for all veterinary medicinal products containing "Colistin" to be administered orally (C(2015) 1916 final).

15. 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
16. 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)

Annex - Recommendations on the pack sizes suitable for antimicrobial VMPs

In general, any veterinary medicinal product (VMP) should be made available in a suitable pack size to ensure the appropriate treatment of the intended target animal(s). For antimicrobial VMPs, adequate pack size(s) should be chosen with particular care as an additional consideration to support their prudent use.

A suitable number of different pack sizes may have to be supplied to allow dosing of individual animals of different sizes, or different numbers of animals within a group. A reasonable balance has to be achieved between the need for different pack sizes to allow correct dosing without a significant amount of leftovers, and the practical and economic difficulties that could be connected to the supply of many different packages.

Legal basis

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". This fully applies to antimicrobial VMPs, since they are only supplied on veterinary prescription in the EU (as per Article 34 (1.c)).

Specific reference to pack sizes for VMPs containing antimicrobial substances is made in Annex II to Regulation (EC) No 2019/6, Section II *Requirements for veterinary medicinal products other than biological veterinary medicinal products*, subsection II.2A2 *Product development*: "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* [15], 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) [16] 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.

Justification for the pack sizes

Any pack size(s) for an application for marketing authorisation should be justified, taking into account the risks that might arise from inadequate pack sizes (e.g. safety concerns in case of too large packs, or efficacy concerns for too small pack sizes). It is particularly important that appropriate pack size(s) is (are) available for VMPs that may be administered by the farmers/animal owners. Such products are mainly formulations for oral administrations, but in some Member States injectable products can also

be administered by the animal owner under the responsibility of a veterinarian. If the pack size is too large in regard to the animal(s) to be treated and/or the recommended treatment period, leftovers may be misused, e.g. by prolonging the treatment period or by administration to other animals without veterinary support.

It is fully acknowledged that establishing the appropriate pack size is very difficult. Several factors e.g. species, herd sizes and husbandry practices affect what can be regarded as an appropriate pack size, and these factors can vary to a great extent both within and among Member States. Notwithstanding these difficulties, some basic principles on how to determine an appropriate pack size are given in this document. The principles for determining a suitable pack size differs substantially between the situation when only one animal is to be treated, or when group treatment is applied. For this reason, advice is given separately for packages intended for individual treatment and for group treatment.

Individual treatment

For products intended for individual treatment, the dosage, treatment duration, and the average bodyweight of the animal species for which it is indicated will define the minimum amount required for one treatment course. As a basic requirement, one package should be available which is not larger than necessary to allow the full course of the treatment of one single animal of average size. When the total amount needed to complete a full course of treatment varies considerably due to e.g. different sizes of the animals, dosages or duration of administration, different pack sizes should be made available.

Any additional pack size which is larger than necessary to treat one single animal would have to be carefully justified. In case of multi-dose packages, e.g. vials for injectables intended to be used by a veterinarian to treat several animals, the amount of VMP per vial would have to be justified taking into in account of the disease and species to be treated. In some EU countries, the veterinarian may provide vials to the animal owner to complete a treatment episode. The size of the multi-dose vial would have to be adapted taking into in account of such use to ensure that it would not result in substantial amounts of left-overs.

Group treatment

The definition of appropriate pack size(s) for products intended for group treatment, would have to include an estimation of the average number and weight of the animals that will be concomitantly treated for the particular disease, within the intended area(s)/country(ies). Since these parameters vary considerably among Member States and between diseases, acceptable figures cannot be given in this document.

As a general rule, and in account of what is mentioned above one pack size should be made available that contains not more than the amount necessary to complete one treatment course in a mean size group of animals of an average body weight with the lowest recommended dose and shortest treatment duration. 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.

When a product is intended for use in more than one target species or different indications with significantly different recommended dosages and duration of administration, different pack sizes should be made available. Any pack size which differs from the one ensuring the minimum amount necessary - established according to the principles above - should be carefully justified by the applicant.

Individual and group treatment

If a product is intended for both group and individual treatment, at least two pack sizes should be made available. One should allow the full course of one treatment of one single animal, with the smallest recommended dose and the shortest duration of treatment. The other pack size(s) should cover the full course(s) of one treatment of a group of animals according to the principles outlined under "Group treatment". Any pack size which differs from the ones ensuring the minimum amount required - established according to the principles above - should be carefully justified by the applicant.

Overall conclusions

A minimum pack size that would allow the completion of one treatment course in an individual animal or in a mean size group of the target animals, of an average body weight with the lowest recommended dose and shortest treatment duration should always be supplied.

A justification for the pack sizes presented in connection to an application for marketing authorisation should always be provided, in particular any pack size(s) which differs from the one ensuring the minimum amount necessary.