EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 September 2018
EMA/CVMP/383441/2005-Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

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

Draft

Draft revised guideline agreed by Antimicrobials Working Party (AWP) and Efficacy Working Party (EWP-V)	November 2017
Adopted by CVMP for release for consultation	19 April 2018
Start of public consultation	27 April 2018
End of consultation (deadline for comments)	31 August 2019[1]

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

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

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

[1] In view of the suspension of guideline work from 1 October 2018, as part of the Agency's business continuity plan, the consultation period has been extended and will finish at the end of August 2019 when the CVMP working party activities are expected to resume.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

Table of contents

Executive summary

This second revision of the guideline on the Summary of Product Characteristics (SPC) for antimicrobial products provides updated guidance on the information to be included in the SPC of veterinary medicinal products (VMPs) containing antimicrobial substances. It replaces the first revision of the 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 antimicrobial therapy in regards to antimicrobial resistance and various regulatory initiatives have been undertaken by CVMP (1-4), including publication of the CVMP's strategy on antimicrobials to 2020 (5). 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. The second 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 VMPs 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 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 essential background information on authorised products for people compiling national and regional treatment guidelines (5).

In the context of this guideline, an antimicrobial is defined as a substance primarily acting against bacteria.

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.

This guideline applies to new marketing authorisation applications (where appropriate, depending on the legal basis of the application as defined in Directive 2001/82/EC) and renewal applications. It also applies to referrals 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 14 of the Directive 2001/82/EC (6) 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 (EMEA/CVMP/627/2001-Rev.1) (1),

- the CVMP Guideline on the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/EWP/344/1999-Rev.2) (7),

- the Guideline on the summary of product characteristics for pharmaceutical VMPs included in Volume 6C of the Rules Governing Medicinal Products in the European Union (8),

- 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) (9),

and any guideline(s) derived from this.

4. General considerations for the preparation of the SPC

The following headings refer to the respective sections of the SPC. Sections where specific guidance related to VMPs containing antimicrobial substances is not necessary do not appear in this guidance document.

Section 4 Clinical particulars

Section 4.2 Indications for use, specifying the 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 causative bacterial target 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 bacterial species 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, and other micro-organisms.

Antimicrobial products should only be used when bacteria are susceptible to the antimicrobial substance and, where feasible, in line with susceptibility testing according to guidance in section 4.5. Hence, indications should not routinely need to use the wording: "<target bacterial species> susceptible to <antimicrobial>".

The term "prevention" as a single and separate claim refers to the administration of an antimicrobial VMP to an individual healthy animal to prevent bacterial infection if the risk for infection is very high and the consequences are severe.

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

The term "metaphylaxis" refers to group treatment of all clinically healthy (but presumably infected) animals kept in close contact with animals showing clinical signs of a contagious disease. 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 4.3. Contraindications

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

animal population. This may also relate to off-label use: for example, for 3rd and 4th generation cephalosporins, the statement "Do not use in poultry" appears in section 4.3 following the assessment of the risk to public health (4).

Selective effects of the antimicrobial on the normal gut microbiota (flora) leading to disruption of the flora with serious consequences (e.g. use of colistin in foals and beta-lactams in rabbits and rodents) should be stated. Alternatively, a warning could be included in section 4.5 where the consequences are less serious but clinically relevant.

Section 4.4 Special warnings for each target species

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 bacterial target 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 in the same (sub)class / related class> in <target bacteria>. Use of the <product name/antimicrobial> should be carefully considered when antimicrobial 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 related 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 4.5 Special precautions for use

i) Special precautions for use in animals

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. Warning(s) may be needed if there are potential safety risks associated with the product in some situations.

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 accredited 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, inaccessibility of bacteriological sampling, impossibility of 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 bacteria 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 antimicrobial risk to public health, antimicrobials are categorised depending on the relative importance for their use in human medicine. These categories (AMEG, WHO) should be taken into account to define whether a product should be reserved for use when response to other antimicrobials is (expected to be) poor.

For certain substances in these categories, the CVMP has agreed to include specific precautionary phrases in the SPCs (4, 10, 11), see Annex I.

Depending on the target animal species, the pharmaceutical form and the type of use, additional recommendations on rational use may be necessary. Individual animal or group treatment will affect the extent of the use of a product. In group treatment, the overall exposure of an antimicrobial, and thus the potential to select for antimicrobial resistance, will be higher when compared to individual treatment. If relevant, specific improvements to management and strategies for eradication can be mentioned as further means to control particular infections where known to be effective. Inclusion of a warning to discourage routine use as part of herd health programme may be necessary:

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

The following warning may be incorporated:

> *"Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to <product name/antimicrobial>and may decrease the effectiveness of treatment."*

A warning should be included where it is known that use of the antimicrobial may lead to co-selection of resistance due to known associations between resistance mechanisms.(e.g. *Salmonella* Typhimurium DT104 is frequently resistant to ampicillin, chloramphenicol/florfenicol, streptomycin sulphonamides and tetracyclines).

For broad-spectrum antimicrobials e.g. extended-spectrum penicillins the following warning may be included, if relevant:

> *"Narrow spectrum antibacterial 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 antimicrobial 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 <antimicrobial> 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.*

Section 4.8 Interaction with other medicinal products and other forms of interaction

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 4.3.

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 4.4.

Section 4.9 Amounts to be administered and administration route

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 dosing, recommended intervals, 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 5 Pharmacological properties

The information submitted in this section 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 antimicrobial in order to allow a proper decision to be made on the use of the antimicrobial product, and to achieve an optimal antibacterial effect and minimise the potential for selection of resistance in a given situation.

Section 5.1 Pharmacodynamic properties

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 antibacterial spectrum relevant for the target animal species and approved indications should be stated. The order of the listed micro-organisms should be the same as used in section 4.2. 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), 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 may be necessary to section 4.4.

Antimicrobial susceptibility data for bacterial target species relevant to the clinical indications should be updated based on any on-going EU surveillance programmes or other relevant information which might influence the benefits and risks of the VMP.

Section 5.2 Pharmacokinetic particulars

Pharmacokinetic particulars of the product should be described in sufficient detail for clinical use. 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.

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 6.5 Nature and composition of immediate packaging

Full information about contents of the packaging, material in contact with the VMP, pack size(s) for the particular pharmaceutical form and strength(s) is required.

For the prescribing veterinarian, it is especially important that appropriate pack size(s) is (are) available for VMPs that may be administered by farmers/animal owners. These should be justified taking into account the risks that might arise from inappropriate pack sizes, e.g. efficacy concerns if pack size is too small or safety concerns if pack size is too large. In addition, of particular relevance to antimicrobial products, the risks associated with leftovers should be considered, e.g. prolongation of treatment duration or administration of the leftovers to other animals in the absence of veterinary support.

It is fully acknowledged that establishing appropriate pack size can be 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 between Member States. Some basic principles on how to determine appropriate pack sizes are as follows:

- For products intended for the treatment of individual animals, one pack size should be available and put on the market which is not larger than necessary to allow a full course of treatment of a single animal of average size. However, where there is a large weight range for individuals in the target population and/or there is more than one dosage regimen (different dose levels and/or treatment durations), a suitable number of different pack sizes may have to be supplied.
- For products intended for the treatment of groups of animals, a pack size should be available that does not contain more than the amount of product necessary to complete one treatment course in a mean sized group of animals of average body weight with the lowest recommended dose and shortest treatment duration. However, where the group size varies considerably within and/or between Member States and/or a product is intended for use in more than one target species and/or there are different indications with significantly different dosage regimens, different pack sizes might be needed.

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

Section 6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

It is recommended that the following statement is included:

> *"Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product must be disposed of in accordance with local requirements.*

Definitions

Antimicrobial: A naturally occurring, semi-synthetic or synthetic substance that exhibits antimicrobial activity (kill or inhibit the growth of micro-organisms) at concentrations attainable in vivo. Antiparasitics and substances classed as disinfectants or antiseptics are excluded from this definition (OIE Terrestrial Animal Health Code definition). In the context of this guideline, the focus is on compounds acting against bacteria.

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: Group treatment of all clinically healthy (but presumably infected) animals kept in close contact with animals showing clinical signs of a contagious disease. 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.

Prevention: Administration of a VMP to individual healthy animals to prevent infection if the risk for infection is very high and the consequences are severe.

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-Rev.1).
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 strategy on antimicrobials 2016-2020 (EMA/CVMP/209189/2015)
6. Directive 2001/82/EC of the European Parliament and of the Council, as amended. Official Journal L 311, 28/11/2001 P. 0001 - 0066.
7. CVMP Guideline for the conduct of efficacy studies for intramammary products for use in cattle (EMEA/CVMP/EWP/344/1999-Rev.2)
8. Guideline on the summary of product characteristics for pharmaceutical veterinary medicinal products included in Volume 6C of the Rules Governing Medicinal Products in the European Union (http://ec.europa.eu/health/files/eudralex/vol-6/c/spcpharmaceuticals_10-07-2006_en.pdf).
9. 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)
10. 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).
11. 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).

Annex I
Specific precautionary phrases to be included in section 4.5

Specific precautionary phrases that have been agreed by CVMP to be included in section 4.5 as recommendations for responsible use of fluoroquinolones, 3rd and 4th generation cephalosporins administered systemically, and colistin administered orally in food producing animals:

Fluoroquinolones (administered systemically)

All fluoroquinolone products

"Official and local antimicrobial policies should be taken into account when the product is used."

"Fluoroquinolones should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials."

"Whenever possible, fluoroquinolones should only be used based on susceptibility testing."

"Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the fluoroquinolones and may decrease the effectiveness of treatment with other quinolones due to the potential for cross resistance."

Quinolone products[2] (e.g. flumequine, oxolinic acid)

"Official and local antimicrobial policies should be taken into account when the product is used."

"Whenever possible, quinolones should only be used based on susceptibility testing"

"Use of the product deviating from the instructions given in the SPC may increase the prevalence of bacteria resistant to the quinolones and may decrease the effectiveness of treatment with other (fluoro-)quinolones due to the potential for cross resistance."

3rd and 4th generation cephalosporins (administered systemically)

Cefquinome, ceftiofur

Add, to all products:

"Product name (*to be completed nationally*)" 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 e.g. via food. For this reason, "*product name (to be completed nationally)*" should be reserved for the treatment of clinical conditions which have responded poorly, or are expected to respond poorly (refers to very acute cases when treatment must be initiated without bacteriological diagnosis) to first line treatment. Official, national and regional antimicrobial policies should be taken into account when the product is used. Increased use, including use of the product deviating from the instructions given in the SPC, may increase the prevalence of such resistance. Whenever possible, "*product name (to be completed nationally)*" should only be used based on susceptibility testing.

"*Product name (to be completed nationally)*" is intended for treatment of individual animals. Do not use for disease prevention or as a part of herd health programmes. Treatment of groups of animals should be strictly restricted to ongoing disease outbreaks according to the approved conditions of use.

Add, where applicable, for products indicated for bovine metritis:

Do not use as prophylaxis in case of retained placenta.

[2] Not required for decoquinate

Polymyxins:

Colistin (administered orally)

Add, to all products:

Do not use colistin as a substitute for good management practices.

Colistin is a last resort drug in human medicine for treatment of infections caused by certain multi-drug resistant bacteria. In order to minimise any potential risk associated with widespread use of colistin, its use should be limited to treatment or treatment and metaphylaxis of diseases, and should not be used for prophylaxis.

Whenever possible, colistin should only be used based on susceptibility testing.

Use of the product deviating from the instructions given in the SPC may lead to treatment failures and increase the prevalence of bacteria resistant to colistin.

Annex II
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 identified 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

Specific reference to pack sizes in the veterinary legislation is spare:

Annex I of Directive 2001/82/EC (as amended by 2009/9/EC; Art I, Part 2 A4 of Development pharmaceutics) states that "*An explanation shall be provided with regard to the choice of composition, constituents, immediate packaging, possible further packaging, outer packaging if relevant, the intended function of the excipients in the finished product and the method of manufacture of the finished product. This explanation shall be supported by scientific data on development pharmaceutics. ….*" Although the pack size is not specifically included in this paragraph of the Directive, the information regarding the choice of packaging is not limited to the type of material, but would also include considerations on e.g. the number of units in one pack or the fill volume of multidose or single dose vials.

Furthermore, reference to pack sizes is made in the Variation Regulation, in regard to a change in the pack size of the finished product (variation B.II.e.5). Conditions for such a change include that the new pack size should be consistent with the approved posology and treatment duration, and that the remaining presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the SPC.

Pursuant to Article 67 of Directive 2001/82/EC, as amended, *"Member States shall take all necessary measures to ensure that, in the case of medicinal products supplied only on prescription, the quantity prescribed and supplied shall be restricted to the minimum amount required for the treatment or therapy concerned."* This fully applies to antibiotics, since they are supplied only on prescription within the EU.

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, ideally 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 duration of treatment. The other pack size should cover the full course 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.

Livestock, herd sizes and diseases can vary across Member States, and Member States might therefore decide to apply individual measures in regard to the distribution/supply of certain pack size(s) in their country (subject to national legislation/implementation of Art. 67 of Directive 2001/82/EC).