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NOTICE TO APPLICANTS
VETERINARY MEDICINAL PRODUCTS

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Summary of the Product Characteristics

SPC - Pharmaceuticals

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GUIDELINE ON THE SUMMARY OF PRODUCT CHARACTERISTICS FOR PHARMACEUTICAL VETERINARY MEDICINAL PRODUCTS

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EXECUTIVE SUMMARY

In accordance with Article 14 of Directive 2001/82/EC[1] of the European Parliament and of the Council on the Community Code relating to veterinary medicinal products, as amended by Directive 2004/28/EC[2], and Article 31 of Regulation (EC) No. 726/2004 of the European Parliament and of the Council[3], any application for a marketing authorisation must be accompanied by the Summary of Product Characteristics (SPC) which is proposed by the applicant and approved by the competent authority.

This guideline provides guidance on how the SPC should be prepared.

I. INTRODUCTION

The SPC contains the information on the condition of use of a veterinary medicinal product as developed during the course of the assessment process. It is the common basis of communication between the competent authorities of all the Member States. As such the content cannot be changed by the authorisation holder except with the approval of the competent authorities.

The purpose of the summary of product characteristics is to provide a clear and unambiguous description of the approved conditions of use of a veterinary medicinal product in the European Community or Member State(s) concerned, presented in accordance with a single standardised layout.

The labelling, package leaflet and any data sheet must comply with the approved conditions of use set out in the SPC. The content of the package leaflet must be consistent with the SPC in a wording that can be easily understood by non-professionals as appropriate. The SPC is the basis of technical information for veterinarians on how to use the medicinal product safely and effectively. The SPC also provides an instrument for the control by the competent authorities, of promotional material provided by the authorisation holder.

At the Community level, the SPC provides a basis for comparing the approved conditions of use of a particular veterinary medicinal product in the different Member States. When using the Community centralised procedure, applicants must propose an identical SPC for all Member States. The Committee for Medicinal Products for Veterinary Use (CVMP) agrees on the SPC for the product, as part of its opinion. The SPC is annexed to the Commission decision granting marketing authorisation and will apply throughout the Community.

When using the Community mutual recognition or decentralised procedures, applicants must propose an identical SPC for all Member States concerned by the application. In the case of the mutual recognition procedure this SPC must also be identical with that approved by the Member State on whose authorisation the application is based.

The SPC is also used as a means of providing information to third countries about the conditions of use of a veterinary medicinal product within the Member States of the Community. In accordance with Article 93 of Directive 2001/82/EC as amended, the competent authorities of a Member State will, upon request, provide the authorities of a third country with a copy of the SPC for the product concerned.

Separate SPCs are required for each pharmaceutical form. The European Commission and certain Member States may require separate SPCs for each strength. Limited references to other strengths or pharmaceutical forms of the same veterinary medicinal product may be

[1] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-5/dir_2001_82/dir_2001_82_en.pdf
[2] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-5/dir_2004_28/dir_2004_28_en.pdf
[3] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf

necessary in an SPC, if the dosage regimen is based on the use of several strengths or pharmaceutical forms. For the purposes of advertising or of giving information to prescribers, the text contained in the SPC of different pharmaceutical forms and strengths may be combined for appropriate products within the same range.

II. SCOPE

The order of presentation of the SPC is specified in Article 14 of the Directive, and should always be followed. This guideline provides guidance on the information required in the different sections of the SPC for pharmaceutical products.

III. LEGAL BASIS

In accordance with Article 14 of Directive 2001/82/EC and Article 31 of Regulation (EC) No. 726/2004 any application for a marketing authorisation must be accompanied by the Summary of Product Characteristics (SPC) which is proposed by the applicant. Furthermore, Article 14 of Directive 2001/82/EC requires that the content must be approved by the competent authority. Thus the SPC forms an intrinsic and integral part of the marketing authorisation. The SPC is a publicly available document, which must be provided upon request.

IV. GENERAL CONSIDERATIONS FOR THE PREPARATION OF THE SPC

When preparing an SPC, it should be noted that the SPC is intended to provide detailed objective information on the conditions of authorisation of a veterinary medicinal product. The SPC is not a promotional document, nor is it intended to constitute a summary of the evaluation of the medicinal product by the competent authorities.

It follows that all the statements contained in the SPC must be justified by the contents of the application dossier which is submitted to the competent authority. Statements of a promotional nature such as "*x is the treatment of choice for y*" are not acceptable. Moreover, extraneous information such as the results of toxicity studies should not be included unless necessary to enable the practitioner to assess the benefits and risks of the use of the product in a particular case.

Particular care should be taken to ensure that clear and unambiguous language is used throughout the SPC. Attention should be given to the clear definition of the scope of the indications, contraindications, precautions for use and warning statements to ensure that these clearly identify the groups or sub-groups of animals concerned.

Applicants should maintain the integrity of each section of the document by only including information in each section, which is relevant to the section heading. However, some issues may need to be addressed in more than one section of the SPC (e.g. contraindications plus interactions). In such situations, the individual statements may cross-refer to other sections when these contain relevant additional information.

For centralised, decentralised and mutual recognition procedures the SPC in English should always be included in the dossier and will form the basis of product discussion. For national applications and at the time of approval of European ((MRP, DCP, centralised) applications the SPC must always be presented in the national language or languages of the Member State(s) concerned by the application. Where the SPC has been translated from another language, particular care should be taken to ensure the accuracy of the translation and to ensure that appropriate terminology has been used in the different languages concerned.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

{(Invented) name of product strength pharmaceutical form <target animal species>}

In those sections of the SPC in which full information on the name of the medicinal product is specifically required, the name should include both the strength and the pharmaceutical form, even if there is only one strength and/or pharmaceutical form. However, when otherwise referring to the medicinal product throughout the text of the SPC, strength and pharmaceutical form do not have to be mentioned in the name. The International Non-proprietary Name (INN) or the usual common name of the active substance should be used when referring to properties of the active substance(s) rather than those of the product. The use of pronouns is encouraged where it improves the readability of the text. The target species should be added, if necessary, in order to avoid any confusion.

It must be noted that there are some situations where the expression of the strength or pharmaceutical form is not straightforward, e.g. fixed combination products containing more than two active substances and biotechnological medicinal products. In such cases, it may be acceptable not to include the strength and/or the pharmaceutical form.

The strength should be the relevant quantity for the identification and use of the product and should be consistent with the quantity stated in the quantitative composition and in the posology. Different strengths of the same medicinal product should be stated in the same way, for example 250 mg, 500 mg, 750 mg.

The pharmaceutical form should be described by the European Pharmacopoeia full standard term. If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms.

When selecting invented names, care should be taken to avoid the use of words or abbreviations, which may give rise to confusion. A guideline on the "Acceptability of invented names for veterinary medicinal products processed in the centralised procedure" has been published by the EMEA.[4]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The qualitative and quantitative composition should be stated for the active substance(s) and those excipients, where the knowledge is essential for the safe administration of the medicinal product. For example, preservatives should always be mentioned with their *« E »* numbers. Other excipients should not be mentioned here. A standard statement should be included at the end of the section: "For full list of excipients, see section 6.1".

If a diluent is part of the medicinal product, information should be included in the relevant sections, usually sections 3 (pharmaceutical form), 4.9 (Amounts to be administered), 6.1 (List of excipients) and 6.5 (composition of packaging).

Qualitative composition

The international non-proprietary name (INN) recommended by the World Health Organisation should be used, accompanied by its salt, derivative or hydrate form if relevant. If no INN exists, the European Pharmacopoeia name should be used, or failing this, one of the Pharmacopoeia of the Member States. If the substance is not in the Pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation

[4] http://www.emea.eu.int/pdfs/vet/regaffair/032898en.pdf

should be given. Substances without an INN or an exact scientific designation should be described by a statement of how and from what they were prepared. References to a pharmacopoeial quality should not be included.

Where the active substance is present in the form of the parent molecule, the standard terminology should be used (e.g. dexamethasone, levamisole).

Where the active substance is present as a salt, derivative or hydrate, this should be clearly stated e.g.: dexamethasone acetate, levamisole hydrochloride

Quantitative composition

The quantity of the active substance must be expressed per dosage, per unit volume, or per unit of weight.

Where the active substance is present in the form of a salt or hydrate, the quantitative composition should be expressed in terms of the mass (or biological activity in International (or other) Units where appropriate) of the active entity or entities (base, acid or anhydrous material) in the molecule (e.g. X mg levamisole as levamisole sulphate). However, in the cases of older compounds which have traditionally been expressed in the form of a salt or hydrate, it may in some cases be appropriate to indicate the quantitative composition in terms of both the parent molecule and the salt (e.g. : X mg levamisole equivalent to Y mg levamisole sulfate)

In the case of unit dose preparations, the quantitative composition should be stated per unit dose (e.g. X mg per tablet; Y mg per ampoule). In other cases, the quantitative composition should be stated in terms of mg per g or mg per ml. When the product is a powder to be reconstituted prior to administration, the quantity per ml after reconstitution should be stated.

3. PHARMACEUTICAL FORM

The pharmaceutical form should be described by the European Pharmacopoeia full standard term. If an appropriate standard term does not exist, a new term may be constructed from a combination of standard terms. The term used in this section should be the same as the term used in section 1.

It is recommended that a visual description of the appearance of the product (e.g. colour, markings, clarity, shape) or other parameters such as pH is given, in a separate paragraph or line to the standard term, e.g.:

Examples:

- *'Tablet.*
  White, circular flat bevelled-edge tablets marked '100' on one side.'
- *"Solution for injection.*
  Pale yellow, clear solution for injection, pH 7.0"

No reference should be made to the route of administration or to the container unless these elements are part of the standard term.

If the product is not presented in the final pharmaceutical form intended for administration to animals, the final pharmaceutical form should also be stated, e.g. "powder and solvent for solution for injection".

In case of tablets, designed with a score line, a statement should be given whether or not reproducible halfing of the tablets has been shown.

Examples:

- *"The tablets can be divided into equal halves".*
- *"The scoreline is intended to facilitate ease of swallowing and not to divide into equal doses."*

4. CLINICAL PARTICULARS

4.1 Target species

The target species, and sub-category, when appropriate, should be indicated.

4.2 Indications for use, specifying the target species

The indications should be clearly defined for the target species. It should be clearly stated whether the treatment is for prophylactic, therapeutic or diagnostic purposes.

4.3 Contraindications

Situations, which arise from a set of circumstances where the veterinary medicinal product must not be used for target animal safety reasons, i.e. absolute contraindications, are the subject of this section. Contraindications may be linked with a target species or a sub-group of the target species, the administration of the product by a particular route or with administration in conjunction with other products. Furthermore, particular clinical diagnoses, concomitant diseases, age or sex may constitute contraindications. Other veterinary medicines or classes of medicine, which should be specifically avoided (i.e. contraindicated) for concomitant or consecutive use, should only be stated here, if such use has serious consequences (e.g. fatalities). Otherwise, this information should be mentioned under section 4.8 (Interactions).

Absolute contraindications must be unambiguously, comprehensively and clearly worded. It is not necessary to contraindicate species that are not included in the target species, unless studies indicate a particular risk with off-label use in a non-target species. Cross-reference to other sections may be made, if necessary e.g. to sections 4.7 (Use during pregnancy, lactation or lay) and 4.8. (Interactions).

Non-indications (e.g. 'this veterinary medicinal product is not indicated for...') should not be mentioned. Relative contraindications should be listed in section 4.5 (Special precautions for use).

Additionally, all information relating to consumer safety should only be given in 4.11 (withdrawal period).

The standard phrase to be used in listing of contraindication is: '*Do not use in*….'

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 target animals.

Information could include recommendations on the handling of animals, the proper use of the product or any other impact on the efficacy of the product.

Examples

- *"Although the product may be safely administered to… with …, it has no therapeutic effect against …; or "The efficacy of ... has not been established in dogs weighing less than ... or under ...of age", or "The efficacy of product has not been tested under certain conditions e.g. …." (Limitations of use, if adequate)*
- *"A second injection must not be given, even if clinical signs re-cur…"(Information about dose or duration)*
- *"Animals with acute infections and severely reduced feed intake should be treated with a suitable injection product first." (General recommendations for the proper use and about handling if appropriate).*
- *"Frequent shampooing or immersion of the animal in water after treatment may reduce the efficacy of the product" or "Animals may be bathed 2 hours after treatment without loss of efficacy" (Impact on efficacy)*

Information on resistance should be included in this section, if applicable, taken into consideration relevant guidelines.

4.5 Special precautions for use

i) Special precautions for use in animals

The purpose of this section is to provide clear information on how to ensure the safe use of the product in animals. The section should include information on relative contraindications. It should also contain information on class or drug-related effects in particular conditions such as renal, hepatic or cardiac failure, or in particular patient groups such as very old or very young animals or sensitive subpopulations.

Possible hypersensitivity reactions in the target species to any of the excipients, residues from the manufacturing process or the presence of certain excipients should be included.

Relative contraindications should be mentioned first. Situations in which use of the product is absolutely contraindicated should be mentioned under section 4.3 (Contraindications) only.

The information should include the following:

- The conditions under which the product could be used provided that special conditions for use are fulfilled (for example, relative contraindications).

  Examples:
  - *"The safety of … has not been established in dogs weighing less than … or under …of age",*
  - *"The safety of the product has not been tested under certain conditions e.g. …." (Limitations of use, if adequate such as Information on use in certain subgroups of animals)*

- Special animal groups likely to experience product or class related adverse reactions when the product is used as recommended e.g. specified age groups, animals with renal or hepatic impairment (including the degree of impairment, such as mild, moderate or severe) or cardiac disease (including the severity of the condition) or sensitive sub-populations e.g. ivermectin sensitive Collies.

Examples:

"Special care should be taken when administering the product to animals with <condition or disease>, since …."

"Treated animals should be monitored for <clinical signs or analytical parameters>…"

"<Adverse effect> may occur when administering the product to <animals or specific condition>, in this case treatments should be < discontinued or dose should be reduced>.s

- Any measures which can be taken to identify animals at risk and to prevent the occurrence, or to detect early the onset or worsening of conditions. Also, any safety measures to minimise impact of the treatment to untreated animals should be mentioned.

Examples:

- *"Do not allow recently treated animals to groom each other …."*

- Where appropriate, information may also be provided about possible risks resulting from the off-label use of the product.

Information on prudent use recommendations should be included in this section, if applicable, taken into consideration relevant guidelines, e.g. Guideline on the SPC for Antimicrobial Products (EMEA/CVMP/612/01).

Descriptions of warning and precautions regarding pregnancy and lactation and other aspects of interactions should be dealt with in sections 4.7 (Use during pregnancy, lactation or lay) and 4.8 (Interactions) respectively.

Descriptions on general information for instance on handling and directions for proper use concerning the mode of administration should be dealt with in section 4.9 (Amounts to be administered) with cross reference to section 4.4 (Special warnings) e.g. "Do not administer more than 10 ml in each site of injection.

ii) Special precautions to be taken by the person administering the medicinal product to animals

Risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user should be stated here.

Possible hypersensitivity reactions in the user to any of the excipients or residues from the manufacturing process should be included.

If applicable, information should also be given for persons in close contact to the treated animal e.g. animal owner, children, immuno-compromised persons, and pregnant women.

Examples:

People with known hypersensitivity to XXX *should <avoid contact with the product >*

Women of child-bearing potential should avoid contact with, or wear disposable gloves when administering, the product.

Recommendations should be given to minimise the exposure of the user during administration or preparation of the product for administration.

Safety phrases given in International and European legislation should be used where possible e.g. the safety phrases given in the "Directive on Dangerous Substances" [Directive 67/548/EEC as amended].[5].

Examples:

Personal protective equipment consisting of XXX *should be worn when handling the product.*
Do not eat, drink or smoke while handling the product.

Guidance on action to be taken following accidental contact should also be given, where necessary.

Examples:

In the case of accidental self-injection / ingestion / spillage onto skin, seek medical advice immediately and show the package leaflet or the label to the physician.

The following statements, which are relevant for the product label and package leaflet, should not be included in the SPC:

'For animal treatment only.'
'Keep out of reach and sight of children.'

<iii) Other precautions>

Information should be included here regarding possible reactions of the product with its surrounding, e.g. impact on the environment or chemical reactions of the product with furniture or cloth.

Examples:

The solvent in this product may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials.

This product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

... should not be allowed to enter surface waters as it has harmful effects on aquatic organisms.

Do not allow treated animals to swim in water courses until at least ... hours/days after administration.

"*The long-term effects of* YY *on the population dynamics of dung beetles have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season*"

4.6 Adverse reactions (frequency and seriousness)

This section should include information on adverse drug reactions attributed to the product when used as recommended. The reactions listed should be based on an assessment of all observed adverse events and all facts relevant to their causality, severity and frequency. The

[5] http://europa.eu.int/eur-lex/lex/LexUriServ/LexUriServ.do?uri=CELEX:31967L0548:EN:HTML

main adverse reactions in the target species should be included in the SPC, if they are at least possibly causally related, based for example on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual reports. Adverse events, without at least a suspected causal relationship, should not be listed in the SPC. Data can be derived either from data submitted in an application dossier or from post-authorisation pharmacovigilance reports.

This section should also include information about any action that may be taken by the animal owner or the veterinarian in case of adverse reactions, for example immediate cessation of treatment or emergency resuscitation. If there is a need for awareness of clinical signs representing early warning of a serious adverse reaction, a statement should be included. Any need for specific clinical or laboratory monitoring should be stated.

Claims regarding the absence of specific adverse reactions, statements on lack of proof of causal association or comparative frequency statements other than those described below should not be included in this section.

In order to provide clear and readily accessed information, the section should be structured according to the following recommendations:

a) Description of the adverse reaction(s)
The information in this section must be consistent with the figures presented and should not contain general statements such as "*well tolerated*" etc.

The following information should be provided for each adverse reaction: a brief description of the nature of the reaction, the duration, reversibility and intensity of the reactions, the frequency of the reaction experienced in treated animals and any effect on the general state of health of the animal. In addition, it should be indicated whether certain species or breeds or types of individual are more susceptible to the undesirable effect concerned, or whether it is more frequent under certain types of husbandry conditions.

All adverse reactions should be ranked in “frequency groupings” with the most frequently occurring reactions listed first, using the following convention:

- Very common *(more than 1 in 10 animals displaying adverse reaction(s) during the course of one treatment)*
- Common *(more than 1 but less than 10 animals in 100 animals*)
- Uncommon *(more than 1 but less than 10 animals in 1,000 animals*)
- Rare *(more than 1 but less than 10 animals in 10,000 animals*)
- Very rare (*less than 1 animal in 10,000 animals*, including isolated reports).

More precise figures on the frequency of adverse reactions from clinical trials, e.g. XX% animals, are generally of limited value under conditions of market use and should only be included when it is of particular relevance to the animal owner or user of the product and/or prescriber to be informed of certain risks. In these cases it is preferable that the data should be based on pooled study results and/or large studies performed under actual market conditions and should refer to adverse reactions, not to unrelated adverse events.

This information can be presented in tabular format. Examples of acceptable statements are given below:

Examples:

“Commonly reported adverse reactions are gastrointestinal signs such as diarrhoea.”

"Adverse reactions are rare. At the beginning of therapy, colic, diarrhoea, or tremors may occur"

b) Measures to be taken to avoid specific adverse reactions should be mentioned under 4.5 (Special precautions) and cross-referenced here.
Any adverse reactions resulting directly from an interaction should be mentioned here and cross-referenced to Section 4.8 (Interactions).

c) Adverse reactions, which have been described for the active ingredient(s) or their pharmacological class and which are very rare or occur with delayed onset of clinical signs. These reactions may not have been observed in relation to the product, but are generally accepted as being attributable to the pharmacological class. The fact that this is a class attribution should be mentioned.

4.7 Use during pregnancy, lactation or lay

In order to ensure the safe use of the product, the user must be informed of the recommendations regarding the use of the product in pregnant/lactating animals or laying birds. Information about use of the product during pregnancy or lactation may have been provided in the sections dealing with contraindications or special precautions for use. In such cases, a cross-reference to the relevant section will be sufficient. Information on the reasons for the relevant recommendation should always be given.

<Pregnancy>

In the case where reproductive toxicity studies have shown evidence of teratogenic, foetotoxic or maternotoxic effects in the target species or in other animal species, the applicant should give further information.

Examples
- *"Can be used during pregnancy"(if the safety on pregnant animals has been shown in the target species)*
- *"The use is not recommended (during the whole or part of the pregnancy)" or "Do not use (during the whole or part of the pregnancy), because…"(if adverse reactions have been shown during pregnancy with the recommended dose in the target species, a case by case evaluation is needed and depending on the type of reaction)*
- *"The use is not recommended (during pregnancy), because…" or "Use only accordingly to the benefit/risk assessment by the responsible veterinarian, because… "(if there is no information available in the target species but an extrapolation to the target species is acceptable based on safety shown in laboratory studies or in other animal species:*
- *"Laboratory studies in < species> have not produced any evidence of a teratogenic , foetotoxic, maternotoxic effects".*
- *"Laboratory studies in < species> have shown evidence of teratogenic, foetotoxic, maternotoxic effects".*

<Lactation>

The tolerance of the product in lactating animals and suckling off-spring should be addressed here. Information in relation to consumer safety i.e. consequences of residues for the use of milk for human consumption should be given in section 4.11 (Withdrawal period).

Where possible, information on excretion of the active substance and/or its metabolite(s) in milk should be given. Where relevant, recommendation as to whether to stop or continue to feed (new-born) animals with milk obtained from the mother should be given, and the reason for the recommendation should be stated.

Examples:

- *"Can be used during lactation" (If the safe consumption of milk obtained from treated animals has been shown in the off spring in the target animal)*
- *"The use is not recommended during lactation, because…", "Do not use during lactation, because" or "New born calves/pigs..<species> should not be fed with milk from the treated animals, because…" (If adverse reactions have been shown in the off spring consuming milk from treated animals)*
- *If there is no information available in the target species but an extrapolation to the target species is acceptable based on safety shown in the laboratory animals: "The use is not recommended during lactation, because…."*
  or
  "Use during lactation only accordingly to the benefit/risk assessment by the responsible veterinarian, because …."

<Laying birds>

For chicken/avian products, it should be indicated if the product is unsuitable for laying birds.

Examples:

- *"Do not use in breeding birds and/or within 4 weeks before the onset of the laying period".*

If the product is not for use in laying birds, information about the consequences of residues for the use of eggs for human consumption should be given in section 4.11 (Withdrawal period).

<Fertility>

The following standard phrase should be used when applicable:

"Do not use in breeding animals"

Information regarding fertility in both males and females should be given in sections 4.3 (Contraindications), 4.4 (Special warnings) or 4.6 (Adverse reactions), as appropriate.

4.8 Interaction with other medicinal products and other forms of interaction

When known, information on the nature, mechanism and effects of pharmacological interactions and, where appropriate, corrective actions should be provided.

The words *'No data available'* should be used if no information about interactions exists in the data provided.

The words '*None known'* should be used where investigation or clinical field trial / pharmacovigilance data show no evidence of interactions.

In other cases it is necessary to specify substance or class interactions, to identify the relevance for the product user and to provide an appropriate cross-reference to the advice given under Contraindications. Clinically relevant interactions where, in general, the concurrent use of the product with another one should be avoided (relative contraindication) should also be mentioned here.

4.9 Amount(s) to be administered and administration route

The dosage has to be specified for each target species, route of administration and indication.

The dosage should be given per kg bodyweight in the first place, where appropriate, as well as in terms of the amount to be administered to the animal (*ml* or *tablets /xx kg BW*).

The method, including route and site of administration including directions for proper use by the veterinarian, farmer or owner should be given. Any special equipment needed for administration of the product should be mentioned. Where the product is to be administered via the feed or water, any dosage adjustment for inappetent animals should be specified, if justified from the data available.

Other terms can be added in order to provide guidance on the proper use of the product**.** SI units should be used. The frequency and duration of treatment should be specified in hours, days or weeks.

For products to be administered via drinking water, important additional information should be added here:

- The following statement should also be included: "Medicated drinking water should be refreshed or replaced every "X" hours."
- For this and other information to be added here, reference should be made to section 10 of the Guideline on Quality Aspects of Pharmaceutical Veterinary Medicinal Products for Administration via Drinking Water (EMEA/CVMP/540/03).

For premixes for medicated feeding stuff, clear instructions for the proper preparation of the medicated feed e.g. pelleting instructions and mixing equipment, and the amount of premix for the incorporation should be provided. Also, information on the feeding stuff(s) to be used should be included. If necessary, the use of a pre-mixture should be recommended.

For products to be reconstituted, information on the solvent to use and its volume should be given.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

The purpose of overdose studies is to detect signs of possible adverse reactions and to identify the dose at which they occur, in order to establish a safety margin.

Signs observed at higher dose levels than the recommended one should be mentioned. If no clinical signs were observed this should be mentioned as well. The following information should be provided, if available:

- Clinical signs, nature, evolution, seriousness, duration. It should also be indicated at what doses the overdosage signs were observed.
- Available symptomatic treatments
- Emergency procedures
- Antidote

Examples:

- *"Signs as <description> may occur in <target specie> when the dose is exceeded. Do not exceed the recommended dose." (Effects which do not occur under normal treatment)*"

4.11 Withdrawal period(s)

In Community legislation, the withdrawal period is defined as the period between the last administration of the veterinary medicinal product to animals and the production of foodstuffs from such animals. Where all foodstuffs may be used for human consumption during the treatment period and immediately after the last administration of a veterinary medicinal product, a withdrawal of "zero days" should be indicated.

If necessary, withdrawal periods should be stated for meat and offal, milk, eggs or honey. Withdrawal periods should be indicated in whole days, using Arabic numerals, except for milk withdrawal periods, which may be more appropriately expressed in whole hours. A zero withdrawal period should be expressed as *'Zero hours/days'*.

However, for fish, the withdrawal period should be stated in degree-days. The number of degree-days is divided by the average water temperature, in °C, to give the withdrawal period in days.

When expressing the withdrawal period, the method of treatment must be taken into account:

- In the case of single administration only, the withdrawal period starts from the time of treatment.
- In the case of two or more administrations, the time of the last treatment is defined as the start of the withdrawal period.
- If a product is removed at the end of the treatment (e.g. implants), the time of the removal of the product is defined as the start of the withdrawal period.
- In the case of intra-mammary products administered during the dry period, the withdrawal period for animal slaughter for meat starts from the date of treatment; for milk, however, the withdrawal period is determined by the date of subsequent calving.

For veterinary medicinal products for food producing species, which contain pharmacologically active substances without MRLs (e.g. for milk/eggs), relevant information should be given.

Examples:

- *"Not applicable" (For non-food producing species)*
- *"Zero days" (For food producing species where no withdrawal period is necessary)*
- *"XX hours, days or degree-days" (For food producing species where a withdrawal period is necessary)*
- *"The product is not authorised for use in lactating animals producing milk for human consumption" or*
- *"Not authorised for use in laying birds producing eggs for human consumption"*
- *"Do not use in pregnant animals, which are intended to produce milk for human consumption, within x months of expected parturition" (For food producing species where no MRL exists for milk)*
- *"Do not use within x weeks of onset of the laying" (For food producing species where no MRL exists for eggs).*

5. PHARMACOLOGICAL PROPERTIES

The section should begin stating the therapeutic group, according to the ATCvet classification system and the group of substances to which it belongs (ATCvet code).

5.1 Pharmacodynamic properties

The pharmacodynamic activity of the active substance(s) should be specified, together with the mechanism of the action, on the basis of the information contained in the application dossier. Also, information on resistance should be included in this section, if appropriate.

5.2 Pharmacokinetic particulars

Information, relevant for the proposed use of the product should be provided on the absorption, distribution, biotransformation and elimination of the active substance in each of the target species, for example:

Absorption:

- Percentage of the dose absorbed by the recommended route of administration, e.g. oral or dermal route;
- Time necessary to obtain the maximum concentration (Tmax);
- The maximum concentration (Cmax);
- Influence of feeding regime for absorption by the oral route;
- Quantity or percentage of the dose applied absorbed after topical administration.

Distribution:

- Existence of possible linearity between the concentrations obtained and the dose administered;
- Degree of protein binding;
- Tissue distribution
- Apparent volume of distribution

Biotransformation

- Information relating to metabolism.
- Activity of metabolites
- Percentage of the substance metabolised if known

Elimination

- Half life;
- Principal routes of excretion. Also, if relevant from an environmental point of view, information on secondary excretion routes might be included (e.g. main excretion route via urine; however, some active metabolites with impact on the environment might also be excreted via faeces).

For products intended for multiple administrations information on kinetic properties after repeated dosage should be given. Additionally, information on steady state levels, possible changes in absorption, distribution, metabolism and elimination between the pharmacokinetic particulars after a single administration and those after multiple administrations should be taken into consideration.

Environmental properties

For products, which might enter the environment directly e.g. medicines for fish or via manure, general information on environmental effects should be provided. The impact of the active substance or relevant metabolites excreted into the environment should be addressed. Information on degradation and factors influencing this (e.g. light, pH, temperature) and other

ways of deactivation (e.g. binding to organic matter) should be given. Possible accumulation in the environment should be addressed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, even those present in small amounts, should be included. The active substance itself, residues of substances used during manufacture of the finished product (for example, solvents or head-space gases), and lubricants for pre-filled syringes should not be included. At the top of the list, those excipients that should also be named on the product literature should appear. Unless specified in section 2, it is not necessary to give the quantitative details of these excipients on the product literature. Excipients that should usually be included on the product literature include preservatives, colorants and premix carriers.

Excipients should be referred to by their recommended INN, if one exists, accompanied by the salt or hydrate form, if relevant, or by their European Pharmacopoeia name. If an excipient has neither an INN nor a Ph.Eur. name, it should be described by its usual common name. References to the pharmacopoeial quality should not be included. E numbers should be given where they exist if the excipient has a recognised action or effect, for example preservatives and colouring matters, along with the common name of the excipient.

Flavours or fragrances may be declared in general terms (e.g. ‘orange flavour’, ‘citrus perfume’). However, any of the components, which have a recognised action or effect, must be included.

Modified excipients should be declared in such a way as to avoid confusion with the unmodified excipients, e.g. ‘pregelatinised starch’.

For clarity, it is recommended that each excipient be listed on a separate line.

Abbreviations for excipients should not be used. However, where justified for space considerations, abbreviations for excipient names may appear on the labelling, on condition that these abbreviations are also included in this section together with the full name.

Ingredients that may or may not be added for pH-adjustment should be followed by the parenthesis “*(for pH adjustment)*”.

In the case of premixes for medicated feeding-stuffs, the main carriers in brackets should be indicated...

6.2 Incompatibilities

In this section information should be given about physical or chemical incompatibilities of the product with other products with which it is likely to be diluted, mixed or co-administered. Major incompatibilities observed from compatibility studies should be included here.

- For products to be diluted before parenteral administration: significant problems of adsorption of product to syringes, large volume parenteral containers etc. should be stated.
- In the case of premixes for medicated feeding-stuffs: any restriction on the range or the type of feed which may be used for the preparation of the final feed should be indicated. If specific mixing or pelleting instructions are needed, this should be mentioned in section 4.9 and include details of the amounts to be administered and the administration route.

- Where incompatibility studies have not been carried out, and if appropriate for the product, a warning should be included <*not to mix the product with other medicinal products*> (e.g. for parenterals or premixe for medicated feeding stuffs).

In other cases, the standard term <*None known*> is used.

If incompatibility is not a concern due to pharmaceutical form of the product, e.g. solid oral pharmaceutical forms, the term used is <*Not applicable*>.

6.3 Shelf-life

- Shelf-life of the veterinary medicinal product as packaged for sale
- Shelf-life after first opening the immediate packaging (where relevant)
- Shelf-life after dilution or reconstitution according to directions (where relevant)
- Shelf-life after incorporation into meal or pelleted feed

The shelf-life should be expressed in Arabic numerals as a number of years or months:
e.g. 6 months/ 1 year/ 18 months/ 2 years/ 30 months/ 3 years

In the case of multi-dose preparations presented in sealed containers, the shelf-life of the broached or opened container should also be stated. Similarly, in the case of premixes for medicated feeding-stuffs, the shelf-life should be indicated for the premix, and after incorporation into the medicated feed, e.g. meal or pelleted feed. For medicated drinking water, the shelf life should be stated and may not exceed 24 hours.

No storage conditions should be included here. They are given in SPC point 6.4 (Special precautions for storage).

6.4 Special precautions for storage

This section contains the information necessary for the correct storage of the product: temperature, light and humidity. Storage conditions for veterinary medicinal products should be made according the "Note for guidance on Declaration of Storage Conditions of Veterinary Medicinal Products"[6]. If no storage warning is required, state <*No special precautions for storage*>.

6.5 Nature and composition of immediate packaging

A short but complete description of the container used for (and the contents of) the final sales presentation should be provided, including:

- Fill-volume/weight of the container, if appropriate
- Type of the container
- Material of the primary container
- Devices supplied - only if authorised during the procedure and included in the package
- Package size(s). All pack sizes should be listed. Pack sizes mentioned should include the number of units, number of doses total weight or volume of the immediate container, as appropriate, and the number of containers present in any outer carton. If appropriate, a standard statement, 'Not all pack sizes may be marketed', should be included, in order to alert veterinarians to the fact that not all listed pack sizes may be available for prescribing or dispensing.

[6] http://www.emea.eu.int/pdfs/vet/qwp/042299en.pdf

Multiple unit packs for distribution purposes only do not constitute new pack sizes for marketing of the product and should therefore not be included in this section.

The Ph- Eur. standard terms should always be used. Some examples are:

> *"Cardboard box with 1 amber glass vial of 1, 5, 10, 25 or 50 ml with a bromobutyl rubber stopper and aluminium cap".*
> *"Card envelope containing three translucent plastic unit dose pipettes of 0.50 ml in an aluminium/aluminium blister overwrap".*
> *" White HDPE bottle containing 30 tablets with cotton coil, desiccant bag, child proof closure and sealing disc",*
> *"PVC /aluminium heat sealed blisters with 10 tablets/blister. Cardboard box with 2 blisters".*

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

This section should include information necessary for the safe disposal of unused product, and the equipment used for the administration of the product to animals. In addition, reference should be made to any restrictions on the disposal of waste products from treated animals.

Where the requirements for disposal differ between Member States, the disposal advice on the package leaflet and labelling must conform to the requirements in the particular Member State where the veterinary medicinal product is to be authorised.

The following phrase may be used:

> *<Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements>*
> *<Dispose of waste material by boiling, incineration or immersion in an appropriate disinfectant approved for use by the competent authorities.>*

In particular cases there may be a need for specific warnings due to the environmental features of the active substance/metabolites, for example:

> ”XX *should not come into water courses as this may be dangerous for fish and other aquatic organisms”*

7. MARKETING AUTHORISATION HOLDER

The name and permanent address or registered place of business of the marketing authorisation holder (including electronic mail address, if appropriate) should be included here. References to web-sites on the Internet should not be included.

8. MARKETING AUTHORISATION NUMBER(S)

Item to be completed by the competent authority or by the marketing authorisation holder once the marketing authorisation has been granted. For veterinary medicinal products for which the European Commission is the competent authority, the number to be included in this section is the number in the Community Register.

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Item to be completed by the competent authority or by the marketing authorisation holder once the marketing authorisation has been granted or renewed. The date of first authorisation and the date of renewal, if applicable, should be indicated.

10. DATE OF REVISION OF THE TEXT

Leave blank in case of a first authorisation. In case of changes to the product literature affecting the SPC, the date of approval by the Competent Authority should be indicated.

For veterinary medicinal products for which the European Commission is the competent authority: date of the latest Commission Decision or date of EMEA approval, if applicable.

For products for which Member States are the competent authorities: date of approval of latest variation or implementation date of the urgent safety restriction resulting in a revision of the SPC.

Item to be completed by the competent authority or by the marketing authorisation holder.

Prohibition of sale, supply and/or use

If there are national restrictions for minimum inclusion rates of premixes in the national legislation on medicated feeding stuffs following standard sentences should be used:

Examples:

"Consideration should be given to official guidance from the National Authorities on the incorporation of medicated premixes into final feeds."

"Not applicable"

REFERENCES (scientific and / or legal)

Directive 2001/82/EC, as amended by Directive 2004/28/EC

Regulation (EC) No. 726/2004

Guideline on the "Acceptability of invented names for veterinary medicinal products processed in the centralised procedure"

Note for guidance on Declaration of Storage Conditions for Veterinary Medicinal Products

SPC guideline for antimicrobials

Directive on Dangerous Substances (Directive 67/548/EEC as amended)