European Medicines Agency
Veterinary Medicines and Inspections

London, 15 April 2005
EMEA/CVMP/540/03 Rev 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE

(CVMP)

GUIDELINE ON

QUALITY ASPECTS OF PHARMACEUTICAL VETERINARY MEDICINES FOR ADMINISTRATION VIA DRINKING WATER

DISCUSSION IN THE QUALITY WORKING PARTY	April 2003
ADOPTION BY CVMP FOR RELEASE FOR CONSULTATION	24 July 2003
START OF CONSULTATION	July 2003
DEADLINE FOR COMMENTS	31 January 2004
DISCUSSION IN THE QUALITY WORKING PARTY	April 2004
ADOPTION BY CVMP	14 July 2004
DATE FOR COMING INTO OPERATION	15 January 2005

Notes:

1. Impact on already authorised products:
All elements of this Guideline apply to new veterinary medicinal products (containing both new and existing active substances). The sections concerning control of the finished product and the stability of the medicated drinking water are applicable to already authorised products. The SPC and product literature for already authorised products should follow the principles set out in this guideline. However, information statements (e.g. on solubility) can be adapted to take account of existing pharmaceutical development data.

2. The revision made in 2005 merely adds some information to Appendix I on how the two different types of test waters can be made. It has been adopted by CVMP at its April 2005 meeting.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int http://www.emea.eu.int

GUIDELINE ON QUALITY ASPECTS OF PHARMACEUTICAL VETERINARY MEDICINES FOR ADMINISTRATION VIA DRINKING WATER

TABLE OF CONTENTS

1. INTRODUCTION

A number of drugs, especially antimicrobial agents, are administered to animals via their drinking water. This route of administration is most commonly used in treating poultry and pigs housed in large productions units, although it is also used in other species such as cattle.

Veterinary medicines administered in drinking water present a number of different and sometimes difficult challenges, in comparison with other types of medicines.

This Guideline sets out the quality data requirements that are specific to veterinary medicinal products that are administered in drinking water of animals. Guidance is included for in-use stability testing of veterinary medicinal products administered in drinking water of animals. The relevant data may be presented in section IIQ of the dossier.

2. SCOPE

The Guideline applies to pharmaceutical veterinary medicinal products, which are administered in drinking water to either individual animals or to groups of animals. Immunological products are excluded from its scope. The types of pharmaceutical forms that are taken into account in this guideline include: emulsion for in drinking water use; granule for oral solution for in drinking water use; powder for oral solution for in drinking water use; concentrate for oral solution for in drinking water use; suspensions for oral solution for in drinking water use.

This guideline does not apply directly to those products which may be administered to individual animals in milk replacer, although some of the principles within this guideline are also relevant to such products e.g. solubility, measuring devices, in-use stability.

3. PART IIA COMPOSITION

Development Pharmaceutics

Reference is made to the following guidelines:

- CVMP Note for Guidance on Development Pharmaceutics for Veterinary Medicinal Products
- CVMP Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products

It is not usually considered justified to include an antimicrobial preservative in non-aqueous formulations or formulations presented as solids intended to prepare medicated drinking water.

For granules and powders, data to confirm solubility, and the rate of dissolution of the product (active substance and excipients), at the nominal concentration, in water of different qualities (such as pH and ion content) and temperatures should be presented. Appendix 1 includes two different water qualities that may be used for such studies. Where this is a range of nominal concentrations, e.g. according to the target species or the bodyweight of the animals, the highest nominal concentration should be studied. Where solubility is being investigated, it is not usually sufficient to solely rely on visual observations, chemical analysis should also be undertaken. However, where the solubility of **each** of the components of the product exceeds 1 g per 30 ml at 15 to 25°C, visual observations will suffice. For those products which may be added to header tanks to give concentrated solutions which are then diluted further with water as part of automatic water supply lines, in addition to confirming solubility at the (highest) nominal concentration in drinking water (as specified in the SPC and other product literature), the **maximum** solubility of the product in water of two different qualities (see Appendix 1) should also be determined and stated. The time taken for the product to fully dissolve in drinking water at the nominal in-use concentration should usually not exceed 10 minutes. If the time taken for the product to fully dissolve at the nominal in-use concentration exceeds 10 minutes at ~ 20°C and/or ~5°C, then the time required for complete dissolution must be clearly stated on the SPC and product literature. .

For emulsions and suspensions, data on the dispersion of the product in water of two different qualities (see Appendix 1) should be presented. Where dispersion is being investigated, it is not sufficient to solely rely on visual observations; chemical analysis should also be undertaken.

The pH of the medicated drinking water (at the nominal concentration) should be indicated. If the veterinary medicinal product has been designed such that its use results in medicated drinking water of a specific pH, then the rationale for the selection of that pH, as well as a description of how the product's design enables this to be achieved, should be provided. The impact that the pH of the medicated drinking water has upon: the solubility of the active substance; the bioavailability of the active moiety; the stability of the active substance, and also on the integrity of the water system should be discussed.

It is not acceptable for the active substance to be in suspension in the medicated drinking water, as it would not be possible to ensure accurate dosing. Whilst it is preferable for the product to form a complete solution in drinking water, the formation of a fine suspension of one of more of the excipients may be acceptable where this has been fully justified. In such cases, it is essential that for at least 3 batches of the product, the ingredients which are present in suspension in the medicated drinking water are identified and their particle size distribution in the medicated drinking water is presented. It is important to demonstrate that the final suspension produced is consistent in terms of these characteristics. The information should be discussed, particularly with respect to the potential for blocking of commonly used equipment via which the medicated drinking water is likely to be passed e.g. header tanks, water supply lines, drinking nozzles, etc.

The proposed pack sizes should be discussed with reference to the number of animals likely to be treated on an individual farm. The practicality of the instructions for preparation of the medicated drinking water should be considered, taking into account the likely availability of suitably calibrated measuring equipment.

Where individual or small groups of animals are to be treated it is usually necessary to provide with each pack a suitable measuring device. For powders, the extremes of bulk density (tapped and untapped) should be taken into account when a volumetric measuring device is proposed. Where the bulk density of a product may differ significantly from batch to batch or where there is a significant difference between the untapped and tapped bulk density, the use of suitably calibrated weighing equipment should instead be recommended in the SPC and product literature. Where the use of a measuring device is appropriate for a solid such as a powder, the use of level rather than rounded scoops is preferred. A cross-reference to the specification and technical drawing for the measuring device in Section IIC(3) should be given , together with laboratory data generated using a batch of the proposed product (which complies with the proposed specification) which demonstrate its accuracy and precision. For measuring devices which are left *in-situ,* the need for stability data on the product with the measuring device *in-situ* should be considered.

In terms of the batches of the product used in clinical trials**,** and if relevant, any residues studies, the following information should be tabulated:

- Batch number
- Use of batch
- Formulation
- Assay of the medicated drinking water at the start of the study.
- The assay of the medicated drinking water following preparation of the final quantity of medicated drinking water, but only where the animals are medicated in the study for more than one day.

Assays may be performed using specific or non-specific methods such as titration or UV. The methods should be validated. The assay results do not need to be available before the animals in the clinical trial/residue study have access to the medicated drinking water. The results are intended to provide a retrospective confirmation that the correct concentration was achieved in the medicated drinking water used in the trials.
The significance of any differences between the batches used in clinical/residues studies versus those which will be marketed should be discussed.

4. PART IIB METHOD OF MANUFACTURE

Cross reference is made to the following guidelines:

- CVMP Note for Guidance on Manufacture of the Finished Dosage Form
- Joint CPMP/CVMP Note for Guidance on Process Validation

5. PART IIC CONTROL OF STARTING MATERIALS

Cross reference is made to the following guidelines:

- Joint CPMP/CVMP Note for Guidance on Summary of Requirements for Active Substances in the Quality Part of the Dossier
- CVMP Note for Guidance on Chemistry of the New Active Substance
- CVMP Note for Guidance on Excipients in the Dossier for Application for Marketing Authorisation for Veterinary Medicinal Products
- VICH guideline on Impurities in New Veterinary Drug Substances

If appropriate, consideration should be given to the desired polymorphic form of the active substance and its control.

For products which are presented as powders, the particle size of the active substance and the relevant excipients should be controlled in order to ensure the reproducibility of the blending process.

Where the active substance will be in suspension in the finished product, control of particle size in the active substance and/or finished product should be addressed in the development pharmaceutics sections, and if necessary limits to control particle size distribution of the active substance should be proposed together with details of the proposed method. The control of particle size of the active substance may also be necessary for products presented as powders or granules, particularly where the dissolution rate in the drinking water is slow.

If an excipient will be present as a fine suspension in the medicated drinking water then particle size control of the excipient should be detailed.

A specification and technical drawing for any measuring device should be presented.

6. PART IID SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Cross reference is made to the following guideline:

- CPMP/CVMP Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products

7. PART IIE CONTROL OF THE INTERMEDIATE PRODUCT

This section is not usually relevant for such products. However, if there is an intermediate product, it should be described and its specification, test methods and the supporting validation data should be presented.

8. PART IIF CONTROL OF THE FINISHED PRODUCT.

Cross reference is made to the following guidelines:

- CVMP Note for Guidance on Specifications and Control Tests on the Finished Product
- VICH guideline on Validation of Analytical Procedures: Definition and Terminology
- VICH guideline on Validation of Analytical Procedures: Methodology
- VICH guideline on Impurities in New Veterinary Medicinal Products.

Where appropriate, limits and methods to control the particle size distribution and dissolution time, in water of a specified quality, of granules, powders and suspensions should be presented.

Where appropriate, limits and a method to control dispersion time, in water of a specified quality, for emulsions should be presented.

Where solid products are measured volumetrically (e.g. by means of a measuring scoop), the bulk density of the product should be controlled.

Where pack sizes of the product and instructions are such that the total contents of a pack will be used in the preparation of the medicated drinking water, lower and upper limits for fill weight are required. In such cases the limits should not usually be wider than 98 - 102% of the declared weight of contents, unless otherwise justified.

9. PART IIG STABILITY

Cross reference is made to the following guidelines:

- VICH guideline on Stability Testing of New Veterinary Drug Substances and Medicinal Products
- VICH guideline on Stability Testing for New Veterinary Dosage Forms
- VICH guideline on Stability Testing: Photostability of New Veterinary Drug Substances and Medicinal Products
- CVMP Note for Guidance on Stability Testing of Existing Active Substances and Related Finished Products
- CVMP Note for Guidance on In-Use Stability Testing of Veterinary Medicinal Products (excluding Immunological Veterinary Products).

The stability of medicated drinking water at the lowest nominal concentration that is to be specified in the SPC and product information should be fully investigated. The initial data submission should include stability results generated on one recently manufactured batch of the product and one batch of the product which has been stored at 25°C/60%RH for at least 6 months. Unless, the stability data for the product indicate that significant changes are likely to occur under real time storage conditions, the provision of stability results for medicated drinking water prepared using one batch of the product at the end of its shelf-life, will usually be acceptable post-authorisation. Each batch of product should be used to prepare two sub-lots of medicated drinking water. Two different qualities of drinking water should be used to prepare the sub-lots of medicated drinking water. Appendix 1 includes two different water qualities that may be used for such studies. Samples of the medicated drinking water should be stored at 25°C. The storage vessel used should simulate the container(s)/contact parts of the water supply system likely to be present during administration of the product e.g. plastic bucket, metal pipework. Physical and chemical properties (such as appearance, assay and levels of degradation products) of the medicated drinking water should be studied.

If the finished product and/or the corresponding active substance have been shown to be sensitive to light (see VICH Topic GL5), the stability of medicated drinking water exposed to light should be investigated and these data should be presented.

A specification for the medicated drinking water should be proposed and justified.

The shelf-life of the medicated drinking water should not exceed 24 hours (Ref: CVMP position paper on maximum in-use shelf-life for medicated drinking water - EMEA/CVMP/1090/02).

On the basis of the in-use stability data and the proposed specification for medicated drinking water, a maximum shelf-life for medicated drinking water should be proposed.

10. SPC AND PRODUCT LITERATURE

In the SPC and product literature (labelling and package insert), clear instructions should be given on how the required quantity of product should be measured. For example, it might be specified that suitably calibrated weighing equipment should be used. Another example might be that the use of a measuring scoop is specified. In such cases it must be clear whether level or rounded scoops of the product should be used.

In the SPC and product literature (labelling and package insert), for suspensions and powders with a relatively long dissolution time (> 10 minutes), there should be a warning that complete dissolution may take up to “X” minutes depending on the temperature and that the medicated drinking water should be stirred for at least “X” minutes to ensure that dissolution is complete before the product is administered. “X” should be justified based on the development pharmaceutics data.

In the SPC and product literature (labelling and package insert) for those products which form a fine suspension of excipients when added to drinking water, a warning should be included to indicate that a fine suspension of excipients is formed.

In the SPC and product literature there should be a statement that only sufficient medicated drinking water should be prepared to cover the daily requirements.

In the SPC and product literature (labelling and package insert), the shelf-life of the medicated drinking water should be stated. This may not exceed 24 hours. The following statement should also be included:
"Medicated drinking water should be refreshed or replaced every "X" hours".

In the SPC and package insert, where relevant, information on the maximum solubility of the product in specified qualities of water at 4°C and 20°C should be given.

APPENDIX 1

General remarks:

The following two qualities of water may be used in the development pharmaceutics and stability studies:

- Soft water/low pH with a pH range from 5.0 to 7.0 and 60 mg/L or less of calcium carbonate
- Hard water/high pH with a pH range from 8.0 to 9.0 and 180 to 350 mg/L of calcium carbonate

Principle of the preparation of standard waters:

Since calcium carbonate is a poorly soluble substance (circa. 14 mg/L in water of 20°C) the concentrations mentioned in the guideline must be considered as pure arithmetical values. Therefore artificial standard waters have to be prepared consisting of an aqueous solution of calcium chloride and sodium bicarbonate, dissolved consecutively in distilled water. The formed calcium bicarbonate solutions resemble natural water qualities. The counter-ions sodium and chloride form a very diluted sodium chloride solution and can therefore be considered as inert. The corresponding chemical conversion can be formulated as follows:

$$CaCl_2 + 2\ NaHCO_3 \rightarrow Ca(HCO_3)_2 + 2\ NaCl$$

$CaCl_2$:	calcium chloride;	formula weight of anhydrous substance;	MW = 110.99
		formula weight of dihydrate;	MW = 147.02
$NaHCO_3$:	sodium bicarbonate;	formula weight (anhydrous substance);	MW = 84.01
$CaCO_3$:	calcium carbonate;	formula weight (theoretical);	MW = 100.09

1.469 mg calcium chloride dihydrate corresponds to 1.000 mg calcium carbonate.

Proposal for preparation of standard "soft water/low pH":

Either use CIPAC* water A (20mg/L at pH 6 - 7) or a method of preparation equivalent to the following:

29.33 mg of calcium chloride dihydrate (corresponding to 20 mg/L of calcium carbonate) are dissolved in 1L of distilled water** and the pH is measured subsequently. The pH of the solution will be between 5.0 and 7.0, i.e. within range, so sodium bicarbonate 0.1M solution should only be added gradually and mixed with stirring, if necessary.

The theoretical calcium carbonate content and the determined pH should be stated in the relevant study report.

Proposal for preparation of standard "hard water/high pH":

Either use CIPAC* water D (342mg/L at pH 6 - 7) and adjust the pH to 8.0 - 9.0 using sodium bicarbonate 0.1M solution, or a method of preparation equivalent to the following:

264.4 – 514.1 mg of calcium chloride dihydrate (corresponding to 180 – 350 mg/L of calcium carbonate; e.g. 502.4 mg calcium chloride dihydrate corresponds to 342 mg calcium carbonate) are dissolved in 1L of distilled water** and the pH is measured subsequently. Sodium bicarbonate 0.1M solution (around 20 ml) is then added gradually and mixed with stirring until the pH reaches the given value between 8.0 and 9.0.

The theoretical calcium carbonate content and the determined pH should be stated in the relevant study report.

Notes:

***** CIPAC = Collaborative International Pesticides Analytical Council. These standard waters can be purchased from reagent suppliers. The methods of preparation of the CIPAC standard waters are described in the CIPAC Handbook. For more information on how to order this handbook see http://www.cipac.org/

****** Since a number of water purifying systems yield demineralised water with a pH varying significantly from the theoretical value of 7.0 it is favourable to use distilled water or purified water for pharmaceutical use as starting material for preparing the standard waters. Note that the pH of water kept in open containers can decrease gradually due to the absorption of carbon dioxide from the surrounding air.