The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

EMEA/CVMP/080/95-**FINAL**

COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

NOTE FOR GUIDANCE:

ADDITIONAL QUALITY REQUIREMENTS FOR PRODUCTS INTENDED FOR INCORPORATION INTO ANIMAL FEEDINGSTUFFS (MEDICATED PREMIXES)

ADOPTION BY CVMP	10 - 11 DECEMBER 1996
DATE FOR COMING INTO OPERATION	1 JULY 1997

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COMMITEE FOR VETERINARY MEDICINAL PRODUCTS

ADDITIONAL QUALITY REQUIREMENTS FOR PRODUCTS INTENDED FOR INCORPORATION INTO ANIMAL FEEDINGSTUFFS (MEDICATED PREMIXES)

1. INTRODUCTION

Medicated pre-mixes are intended for oral administration following incorporation in animal feedingstuffs. As a result of this, additional testing during the development pharmaceutics stage is required to study the quality of the medicated pre-mix during and after incorporation into the animal feedingstuff. The purpose of these tests is to provide information on which to propose a shelf-life for the medicated feedingstuff, to make recommendations to the feed compounder in respect of processing and compatibility, and to ensure that a homogeneous feedingstuff is produced. As far as possible, all studies in this section should be performed using production scale batches of medicated feedingstuffs. It is recognised that production scale batches may not be available during product development and relevant data may be generated using pilot scale batches (at least 10% of production scale and usually at least 50 kg). It is unlikely that adequate information for some studies can be provided from laboratory scale batches.

2. DEFINITIONS

Medicated pre-mix: any veterinary medicinal product which has been granted a marketing authorisation in accordance with Article 4 of Council Directive 81/851/EEC, prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

Medicated feedingstuff: any mixture of a veterinary medicinal product or products and feed or feeds which is ready prepared for marketing and intended to be fed to animals without any further processing.

Intermediate product: any mixture of a veterinary medicinal product or products and feed or feeds which is intended to be mixed or further processed to make a medicated feedingstuff. Such intermediate products may be authorised by Member States under Article 3 of Council Directive 90/167/EEC.

Complete feedingstuff: mixtures of feedingstuffs which, by reason of their composition, are sufficient for a daily ration.

Supplementary feedingstuffs: mixtures of feedingstuffs which have a high content of certain substances and which, by reason of their composition, are sufficient for a daily ration only if they are used in combination with other feedingstuffs.

3. INCORPORATION

The type, nature and quality of the feedingstuff into which the medicated pre-mix will be incorporated should be described. This might be a supplementary feedingstuff, an intermediate product, or a complete feedingstuff. The categories of animals to which it may be fed should be indicated.

The levels of incorporation of the medicated pre-mix in the feedingstuffs should be stated and in compliance with the European Pharmacopoeia monograph on Premixes for Medicated Feedingstuffs for Veterinary Use. The concentration of the active ingredient in the feedingstuff must be stated in terms of mg/kg feed and related to the dose in mg/kg bodyweight. Account should be taken of the requirement in the last paragraph of Article 4 (1) of Council Directive 90/167/EEC. This states that the daily dose of the medicated pre-mix must be contained in at least half the daily ration of the animals under treatment, or half the daily supplementary feed in the case of ruminants.

A description should be provided of how the medicated pre-mix is to be incorporated into the feedingstuff. Where the medicated pre-mix is intended for inclusion in an intermediate product this must be clearly stated. A diagrammatic representation showing the stages from medicated pre-mix to final feedingstuff may be useful.

4. HOMOGENEITY

Evidence should be presented to demonstrate that adequate mixing of the active ingredient in the final feed is likely to be achieved. The composition of the final feed used for these studies must be stated and should be representative of the feed used for the target species for which the medicated pre-mix is intended. Both the precision of the analytical method and the size of the sample taken for analysis are critical in determining homogeneity. Sufficient samples must be taken from the top, middle and bottom of the mix. The size of samples taken for homogeneity studies should reflect the daily intake of the target species but need not be greater than 50 g.

Discussion of the results from this study should include consideration of factors such as particle size, electrostatic properties, type of mixing machinery, and mixing in stages or trituration. Specific mixing instructions to appear on product literature should be proposed.

The higher and lower levels of active ingredient in the usual final feed which are considered acceptable with regard to safety and efficacy should be indicated. Batch analysis results should be presented to justify the proposed tolerances and results must be provided from those batches used in the safety and efficacy studies.

Details are required of the analytical methods used to identify and quantify the active ingredient in the medicated feedingstuff. Methods must be validated and where these are the same as those described in other parts of the dossier, reference to the relevant section should be made.

Medicated feeds are frequently transported over long distances by road or rail and unless otherwise justified a study should be carried out to demonstrate that there is no physical separation of the medicated pre-mix from the feedingstuff during transport which could result in loss of homogeneity.

5. COMPATIBILITY

Evidence should be presented to substantiate claims of biological or physico-chemical compatibility and substances should be listed with which the medicated pre-mix is known to be compatible or

incompatible. This is particularly important in known cases of incompatibility, e.g. the ionophore antibiotics used as additives and certain medicinal substances.

It is obviously impractical to test for all cases of possible incompatibility, but it should be taken into account that feedingstuffs contain additives, vitamins, minerals, trace elements, binders, and preservatives. Compatibility studies should be carried out with the usual feedingstuffs for the intended target species.

6. STABILITY

Evidence is required to demonstrate the stability of the medicated pre-mix after incorporation in a typical feedingstuff to which it is likely to be added. There are two aspects to be considered - the stability of the medicated pre-mix during manufacture and processing of the feed, and stability on storage. A shelf-life for the medicated feedingstuff must be proposed, based on the data presented.

During manufacture of the medicated feedingstuff, conditioning and pelleting are the main factors affecting stability of the medicated pre-mix. These processes can subject the medicated pre-mix to high temperatures (e.g. up to 85-110°C for 10 minutes to inactivate bacteria) and pressures which can cause degradation of materials such as antibiotics, and therefore the effects of such processing on the medicated pre-mix must be evaluated carefully. If a particular process or combination of conditions causes unacceptable degradation of the medicated pre-mix then this must be specifically contra-indicated on the product literature.

Preferably three batches of medicated feed likely to be used should be studied and these should be prepared from at least two different batches of the medicated pre-mix. Batch numbers, batch sizes, and date of manufacture for the medicated pre-mix and the medicated feedingstuff should be stated.

The composition, type and quality of feed (e.g. mash, crumbs, pellets) used must be stated. Feed for one category or age of animal may be substantially different in composition from that for another category or age and if the medicated pre-mix is intended for more than one species, stability in the different types of feed should be studied. If the medicated feedingstuff can be supplied both as mash or as pellets then studies on both types of feedingstuffs should be conducted. If a range of incorporation rates is proposed then studies must be carried out at the upper and lower levels of this range.

The time, temperature, humidity, light conditions etc. under which the medicated feedingstuff was stored should be stated. The nature and type of container in which the stability samples were stored must be stated and must be representative of the packaging in which the medicated feed will normally be stored.

Analytical procedures must be fully described and validated. Particular attention should be paid to recovery experiments because of interactions between active ingredients and macromolecules found in feedingstuffs.

Results should be tabulated and presented graphically where appropriate. A summary and discussion of the results should be given with the conclusions which have been drawn from the stability trials.

Storage conditions and a shelf-life for the medicated feedingstuff must be included on the product literature together with any specific instructions for incorporation of the medicated pre-mix into the feedingstuff.