8 December 2022
EMA/CVMP/QWP/711629/2022
Committee for Veterinary Medicinal Products (CVMP)

Guideline on additional Quality requirements for products intended for incorporation into animal feed

Adopted by CVMP	10-11 December 1996
Date for coming into effect (OPERATION)	01 July 1997
Revision 1*	
Agreed by Quality Working Party	23 November 2022
Adopted by CVMP	8 December 2022
Date for coming into effect	17 February 2023

*The current revision consists of administrative changes made in order to align the guideline with Regulation (EU) 2019/6, as amended, and 2019/4 and to align with the current EMA template for Guidance. The references to the legislation applicable and other scientific guidelines have also been updated as appropriate. As no changes were made to the scientific content, no concept paper and no public consultation were deemed necessary. The document reference number is changed to ensure correct document management. The former document reference number is EMEA/CVMP/080/95.

Keywords	***Quality requirements, incorporation, animal feed***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

There are veterinary medicinal products intended for oral administration following incorporation in animal feed. As a result of this, additional testing during the product development stage is required to study the quality of such veterinary medicinal product during and after incorporation into the animal feed. The purpose of these tests is to provide information on which to propose a shelf-life for the medicated feed, to make recommendations to the feed compounder in respect of processing and compatibility, and to ensure that a homogeneous medicated feed is produced. As far as possible, all studies in this section should be performed using production scale batches of medicated feed. 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.

This guideline applies only to veterinary medicinal products defined in Directive 2001/82/EC as pre-mix for medicated feedingstuffs, i.e. any veterinary medicinal product prepared in advance with a view to the subsequent manufacture of medicated feedingstuffs.

2. Definitions

Medicated feed: a feed, which is ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products or intermediate products with feed materials or compound feed.

Feed Materials: products of vegetable or animal origin, whose principal purpose is to meet animals' nutritional needs, in their natural state, fresh or preserved, and products derived from the industrial processing thereof, and organic or inorganic substances, whether or not containing feed additives, which are intended for use in oral animal-feeding either directly as such, or after processing, or in the preparation of compound feed, or as carrier of premixtures.

Compound feed: a mixture of at least two feed materials, whether or not containing feed additives, for oral animal-feeding in the form of complete or complementary feed.

Intermediate product: a feed, which is not ready to be directly fed to animals without further processing, consisting of a homogenous mixture of one or more veterinary medicinal products with feed materials or compound feed, exclusively intended to be used for the manufacture of medicated feed.

Complete feed: compound feed which, by reason of their composition, are sufficient for a daily ration.

Complementary feed: compound feed which has 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 feed.

3. Incorporation

The type, nature and quality of the feed into which the veterinary medicinal product will be incorporated should be described. This might be a complementary feed, an intermediate product, or a complete feed. The categories of animals to which it may be fed should be indicated.

The levels of incorporation of the veterinary medicinal product in the feed 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 feed 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 Regulation (EC) 2019/4 Article 16, paragraph 10 (c) which states "ensure that the medicated feed containing the dosage of the veterinary medicinal product corresponds to at least 50% of the daily feed ration on a dry matter basis and that, for ruminants, the daily dose of the veterinary medicinal product is contained in at least 50% of the complementary feed except for mineral feed".

A description should be provided of how the veterinary medicinal product is to be incorporated into the feed. Where the veterinary medicinal product is intended for inclusion in an intermediate product this must be clearly stated. A diagrammatic representation showing the stages from veterinary medicinal product to final medicated feed 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 veterinary medicinal product 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 feed. 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 veterinary medicinal product from the feed 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 veterinary medicinal product 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 feeds contain additives, vitamins, minerals, trace elements, binders, and preservatives. Compatibility studies should be carried out with the usual feeds for the intended target species.

6. Stability

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

During manufacture of the medicated feed, conditioning and pelleting are the main factors affecting stability of the veterinary medicinal product. These processes can subject the veterinary medicinal product 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 veterinary medicinal product must be evaluated carefully. If a particular process or combination of conditions causes unacceptable degradation of the veterinary medicinal product 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 veterinary medicinal product. Batch numbers, batch sizes, and date of manufacture for the veterinary medicinal product and the medicated feed 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 veterinary medicinal product is intended for more than one species, stability in the different types of feed should be studied. If the medicated feed can be supplied both as mash or as pellets then studies on both types of feeds 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 feed 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 feeds.

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 feed must be included on the product literature together with any specific instructions for incorporation of the veterinary medicinal product into the feed.