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VICH GL8(R) Stability testing for medicated premixes

Draft

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

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International Cooperation on Harmonisation of Technical Requirements
for Registration of Veterinary Medicinal Products

VICH GL8 (STABILITY PREMIXES)
November 2024
Revision 1 at Step 9
For consultation at Step 4

STABILITY TESTING FOR MEDICATED PREMIXES (REVISION 1)

Revision at Step 9

Recommended for Consultation at Step 4 of the VICH Process
in November 2024
by the VICH Steering Committee

This Guideline has been developed and revised by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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1. General

The VICH Guideline covering the Stability Testing of New Veterinary Drug Substances and Medicinal Products (VICH GL3(R)), hereafter referred to as the parent guideline, references additional guidance for Medicated Premixes (VICH GL8). This document is an annex to the parent guideline (VICH GL3(R)) and addresses the recommendations for stability testing of new Medicated Premixes. The parent guideline provides a general indication of the information on product stability generated, but the annex for Medicated Premixes leaves sufficient flexibility to encompass a variety of different practical and scientific considerations that are specific to the characteristics of the veterinary medicinal products being evaluated. Specific requirements for other stability studies which are important to consider for medicated premixes, such as segregation and homogeneity studies and analytical method validation are (to be) covered in a separate guideline.

2. Preamble

The guideline primarily addresses the generation of acceptable stability information for submission in Registration Applications for new medicated premixes. Medicated Premixes are intended for oral administration following incorporation into animal feed. The guideline only pertains to Medicated Premixes and does not cover information for medicated feeds manufactured from medicated premixes. Although this guideline does not seek to cover information required for the actual registration of medicated feeds manufactured from medicated premixes, the regulatory requirements for a medicated premix include demonstration of its being fit for the purpose of manufacturing medicated feed.
Stability studies carried out with a medicated premix should be in line with the parent guideline. However, the application of the parent guideline may be limited insome instances. This guideline therefore describes those areas where there may be differences in the stability data package for medicated premixes.
Whereas the parent guideline (VICH GL3(R)), and this guideline (VICH GL8(R1)), refer to the stability of new veterinary drug substances and medicinal products, the competent authorities can decide to allow a broader use of this guideline in their own jurisdiction for products containing existing drug substances (for example for variations or for generic products registration).

3. Demonstration of the stability of medicated premix

Medicated Premixes are recommended to be tested under the following storage conditions:

Study	Climatic Zones	Storage Conditions
Long term	I and II	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH
Long term	III (Hot and Dry)	30°C ± 2°C / 35% RH ± 5%
Long term	IVA (Hot and Humid)	30°C ± 2°C / 65% RH ± 5%
Long term	IVB (Hot and very Humid)	30°C ± 2°C / 75% RH ± 5%
Intermediate	I and II	30°C ± 2°C / 65% RH ± 5% RH
Intermediate	III, IVA and IVB	Not Recommended
Accelerated	I and II	40°C ± 2°C / 75% RH ± 5% RH
Accelerated	III (Hot and Dry)	40°C ± 2°C / Not more than 25% RH
Accelerated	IVA (Hot and Humid)	40°C ± 2°C / 75% RH ± 5% RH
Accelerated	IVB (Hot and very Humid)	40°C ± 2°C / 75% RH ± 5% RH

The same schedule of test intervals should be used as described in the Parent Guideline for medicinal products.

The minimum time period covered by data at submission is 6 months on at least three primary batches (see VICH GL3(R)).

When the product is intended for use in Zones I and II, it is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition to be tested.

If the product is intended to be marketed in several climatic zones, it is up to the applicant to decide whether long term studies are performed at the highest temperature and humidity conditions, as applicable (see VICH GL58). Selection of the conditions for stability testing is based on a risk analysis by the applicant considering the intended market. Other storage conditions are allowable if justified.

Where "significant change" occurs due to accelerated testing for zones I and II, additional testing at an intermediate condition e.g., 30°C ±2°C / 65% RH±5% should be conducted. "Significant change" is defined in VICH GL3(R)). No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV (see VICH GL 58).

Evidence is needed to demonstrate the stability of the Medicated Premix before incorporation into feed. The stability of the medicated premix after the opening of the primary packaging must also be demonstrated for the claimed period that the medicated premix can be used after the first opening. The recommended use pattern and closure systems should be taken into consideration.

The shelf-life specification of a Medicated Premix should include necessary stability indicating test parameters.

As mentioned in parent Guideline VICH GL 3 (R), the use of matrixing and bracketing can be applied, if justified. For this purpose, the guidance provided in VICH GL45 should be followed. For the statistical evaluation of stability data of a medicated premix, including the evaluation for the shelf life, the guidance provided in VICH GL 51 should be followed.

Stability testing should be conducted on the medicated premix packaged in the container closure system proposed for marketing (including primary packaging, any functional secondary packaging and container label). In some cases, a smaller container closure system simulating the actual container closure system for marketing may be acceptable. In these instances, a justification for using a smaller and/or similar container closure system should be provided.

4. Demonstration of the stability potential of the medicated premix in intended types of medicated feed

Evidence is needed to demonstrate the stability of the drug substance after incorporation of the medicated premix in a typical feed to which it is likely to be added. If a medicated premix can be used for the manufacture of intermediates, from which medicated feed is manufactured at a later time point, this should also be reflected in the stability studies. Both the stability of the drug substance during manufacturing and processing of the medicated feed (e.g. before and after pelletizing) as well as the stability on storage of the medicated feed must be considered. During manufacturing of medicated feed, the stability of the drug substance could be affected by conditioning and pelletizing. During such procedures, the drug substance can be subjected to high pressure and high temperatures (up to 110°C for 10 minutes to inactivate bacteria). The effects of such processing conditions on the stability of the drug substance should be evaluated. When a particular process or series of procedures causes unacceptable degradation of the drug substance, this must be specifically contra-indicated in the product information, such as label and package leaflet.
It is always recommended to consult with the competent authorities when planning the studies needed when such consultation is possible.

Ideally, to demonstrate the storage stability of the medicated feed, produced with the medicated premix, three batches of each medicated feed likely to be used should be evaluated. Different approaches to evaluate the stability of the medicated feeds may be justified. Competent authorities should be consulted on justification for demonstration of the stability using fewer batches of medicated feed.

Using the storage conditions described in section 3 of this guideline, data taken at appropriate intervals for the intended use should be submitted for the medicated feeds. Records must be kept of the batch numbers, batch sizes and manufacturing date for the Medicated Premix and the medicated feed produced.

The composition, type and quality of feed used (for instance mash or meal, pellets, crumbles or crumbs) must also be stated. As feed for different species and for different categories or age of animals may be substantially different in composition, the potential stability of the drug substance when preparing these different types of feed, should be examined.
When different feeds are sufficiently similar, authorities could allow extrapolation between feeds when the justification provided by the applicant is acceptable.
If a medicated feed produced with the medicated premix, can be supplied both as pellets and as a mash, studies should include both types of feed.
If the label of the medicated premix indicates a range of incorporation rates, studies should be run at the lower and at the higher levels of the range.
When the intended medicated feed manufactured with the medicated premix is only intended to be consumed immediately, it might be acceptable for some competent authorities to waive the need for stability studies in the final feed. In such cases, a clear mentioning of such limitation on the label of the medicated premix should be made as expected by the competent authority.

Time, temperature, humidity, light, and other conditions under which the medicated feed was stored should be stated. The nature and type of the container in which stability samples were stored should be stated and must be representative of the packaging/material in which the medicated feed normally might be stored.

The analytical procedures for the medicated feed manufactured with the medicated premix should be identified and appropriately validated.

The results should be tabulated and presented graphically where appropriate.
A summary should be provided to present the conclusions drawn from the stability trials.
Storage conditions and shelf-life for the medicated feed produced with the Medicated Premix as well as any specific instructions for incorporation of the Medicated Premix in medicated feed should be included in the Medicated Premix product labelling.

5. Glossary

New veterinary drug substance: The designated therapeutic moiety that has not been previously registered in a region or member state for use in a veterinary medicinal product (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved substance.

Medicated Premix (or Type A Medicated Article) - A Medicated Premix is a veterinary medicinal product consisting of a mixture of one or more drug substances, generally with a carrier, that is prepared to facilitate oral administration of the medicinal product to animals when mixed with feed.

Medicated feed: a mixture of animal food and a medicated premix, produced under controlled conditions.

Primary packaging: any packing material that comes into direct contact with the medicated premix or medicated feed.

Secondary Packaging: any outer packaging or overpacking material that lies outside of the primary packaging.

For additional definitions, please refer to regional guidance or regulations and to the other VICH guidelines referenced in this guideline.