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# Stability Testing for Medicated Premixes (Revision 1)

## VICH GL8(R)

### Guidance for Industry

### Draft Guidance

*This guidance document is being distributed for comment purposes only.*

*This version of the guidance replaces the version made available March 2000. This revision contains updated recommendations for stability testing of a medicated premix as well as considerations for demonstrating the stability of the medicated premix in the intended medicated feed.*

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with docket number FDA-2021-D-0613.

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Additional copies of this guidance document may be requested from the Policy and Regulations Staff, Center for Veterinary Medicine, Food and Drug Administration, 5001 Campus Drive, College Park, MD 20740, and may be viewed on the Internet at <https://www.fda.gov/animal-veterinary>, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>, or <http://www.regulations.gov>.

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Veterinary Medicine (CVM)  
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International Cooperation on Harmonisation of Technical Requirements  
for Registration of Veterinary Medicinal Products

**VICH GL8 (STABILITY PREMIXES)**  
**September 2024**  
**Revision at Step 9**  
**For adoption at Step 2**

# **STABILITY TESTING FOR MEDICATED PREMIXES (Revision 1)**

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Revision at Step 9  
Recommended for Adoption at Step 2 of the  
VICH Process by the Expert Working Group in September 2024

This Guideline has been developed and revised by the appropriate VICH Expert Working Group and will be 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.

*Contains Nonbinding Recommendations*  
*Draft — Not for Implementation*

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## **Stability Testing for Medicated Premixes (Revision 1)**

### **Draft Guidance for Industry**

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#### **1. General**

The VICH<sup>1</sup> guidance covering the Stability Testing of New Veterinary Drug Substances and Medicinal Products (Revision),<sup>2</sup> hereafter referred to as the Parent Guidance, references additional guidance for medicated premixes. This document is an annex to the Parent Guidance and addresses the recommendations for stability testing of new medicated Premixes. The Parent Guidance 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. Other stability studies which are important to consider for medicated premixes, such segregation and homogeneity studies and analytical method validation are (to be) covered in a separate guidance.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

#### **2. Preamble**

The guidance primarily addresses the generation of acceptable stability information for submission in registration applications for medicated premixes. Medicated premixes are intended for oral administration following incorporation into animal feed. The guidance only pertains to medicated premixes, and does not cover information for medicated feeds manufactured from medicated premixes. Stability studies carried out with a medicated premix should be in line with the Parent Guidance. However, the application of the Parent Guidance may be limited in some instances. This guidance therefore describes those areas where there may be differences in the stability data package for medicated premixes.

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<sup>1</sup> International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

<sup>2</sup> GFI #73 (VICH GL3(R)), "[Stability Testing of New Veterinary Drug Substances and Medicinal Products \(Revision\)](#)," (November 2007).

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Whereas the Parent Guidance and this guidance refer to the stability of new veterinary drug substances and medicinal products, the competent authorities can decide to allow a broader use of this guidance 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:

<b>Study</b>	<b>Climatic Zones</b>	<b>Storage Conditions</b>
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 Guidance for medicinal products.

The minimum time period covered by data at submission is 6 months on at least three primary batches (see the Parent Guidance).

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 should be 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 GFI #259 (VICH GL58)<sup>3</sup>). Selection of the conditions for stability

<sup>3</sup> GFI #259 (VICH GL58), "[Stability Testing of New Veterinary Drug Substances and Medicinal Products in Climatic Zones III and IV](#)," (April 2020).

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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 the Parent Guidance. No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV (see GFI #259 (VICH GL 58)).

Evidence should demonstrate the stability of the medicated premix before incorporation into feed. The stability of the medicated premix after the opening of the primary packaging should 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 the Parent Guidance, the use of matrixing and bracketing can be applied, if justified. For this purpose, the guidance provided in GFI #198 (VICH GL45)<sup>4</sup> 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 GFI #219 (VICH GL51)<sup>5</sup> 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 should 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, should 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.

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<sup>4</sup> GFI #198 (VICH GL45), [“Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal Products,”](#) (July 2015).

<sup>5</sup> GFI #219 (VICH GL51), [“Statistical Evaluation of Stability Data,”](#) (May 2014).

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When a particular process or series of procedures causes unacceptable degradation of the drug substance, this must be specifically contraindicated 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. \*Demonstration of the Stability of Medicated Premix\*](#) of this guideline, data taken at appropriate intervals for the intended use should be submitted for the medicated feeds. Records should 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) should 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 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.

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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 guidances referenced in this guidance.