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

VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline: Stability Testing for Medicated Premixes VICH GL8 (R1).

VICH EWG: PREMIXES

Name & Country of individual, organisation, or VICH delegation that commented

Comment n°	Name - Country
1	Dr Innocent Ravingai, Botswana, Botswana Medicines Regulatory Authorithy (BOMRA)
2	MJ McNamee, USA, Animal Health Institute (AHI)
3	Heather Sedlacek, USA, Generic Animal Health Drug Alliance (GADA)

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
3	The Generic Animal Drug Alliance (GADA) appreciates the opportunity to provide comments on Draft Guidance for lndustry #91: Stability Testing for Medicated Premixes (Revision 1) VICH GL8(R). In general, the Generic Animal Drug Alliance notes that the draft guidance appears consistent with feedback that member companies have received trom the agency related to the stability assessment of medicated premixes. There are, however, a few points of the guidance which need to be better clarified or appear inconsistent with other regulations. In the Preamble the GFI states that, "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 registrations." In Section 4. the GFI states, "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." Based upon the wording in Section 4, the agency is recommending labeling changes if unacceptable degradation occurs. lt is not clear trom this section however how these labeling changes would be implemented fora generic product whose use directions must align with the pioneer product label. lf the pioneer and generic sponsor have not run the same feed studies, it is not clear how labeling changes would be implemented across medicated premixes when those changes may not be universally applicable. CVM should clarify if they intend to implement and allow different use directions between the pioneer and the generic specific to degradation. Section 3 states for demonstration of stability that, "The minimum time period covered by data at submission is 6 months on at least three primary batches". However, Section 4 states that, "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."	The comments are considered specific procedural questions for the CVM, which do not require changes to the Guideline.

	CVM should clarify what demonstration of stability is necessary for products having a labeled stability of less than 6 months but not intended for immediate consumption. For example, if a medicated premix is labeled as stabile for 3 months in the medicated feed, is stability data through 6 months still required. Section 4 states that, "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. lf 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. Bath 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." CVM requires assessment of stability in all types of feed (mash, meal, crumbles, crumb, etc.) and at highest and lowest inclusion levels at which the medicated premix may be incorporated into a medicated feed. This results in a multifactorial, complex, and expensive stability test for an unclear rationale which may limit the availability of producer preferred options for finished feed. CVM should consider the suitability of a representative risk-based stability assessment performed under the highest risk use case. For example, at the lowest inclusion rate and harshest processing based on drug characteristics (excluding pelleting, as it is its own case). The Generic Animal Drug Alliance looks forward to continued discussion and collaboration with the Agency regarding appropriate stability testing for medicated premixes to ensure the availability of safe and effective products for use in the animal health industry.	

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
171	1	Certain conditions are known to affect drug substances in a certain way. So, if a premix is to be used in various feed formulations, would it not be possible to consider testing stability of the premix during manufacture and/or storage of a feed formulation known to subject the drug substance under the worst conditions and then extrapolate to the other feed formulations considered to be of seemingly better conditions?. The question is based on the need to reduce the testing required and consideration to balance science and the need to develop cost-effectiveness products, especially for this type of product 'Premix' in question	When medicated feeds can be presented as mash and pellets, a stability study on both type of feeds is generally expected in the dossier (as the process conditions are specific). The EWG also would like to mention that this is a one-time study. The GL provides some flexibilities in different places for the design of the stability studies on the medicated feeds (number of batches, types of feed for target species related, bracketing, etc), and a specific approach can still be justified by the applicant. No change is needed to the Guideline
69-71	2	The third statement of section 2. Preamble (at the bottom of page 1 / 5) states, "The guidance only pertains to medicated premixes, and does not cover information for medicated feeds manufactured from medicated premixes." However, section 4. Demonstration of the Stability Potential of the Medicated Premix in Intended Types of Medicated Feed (page 3 / 5) contains extensive information about the stability tests specifically recommended for medicated feeds manufactured from medicated premixes and appears to contradict the statement in the preamble. This contradiction is confusing and difficult to interpret. Does this mean that the information in section 4 is included as a helpful FYI but not formally within scope of the draft guidance document? Background: When the VICH working group was working on draft 6 of this guidance (Sep. 2024), the wording in this guideline was carefully crafted to provide clarity for some of the VICH member regulatory authorities that asking for evidence that a medicated premix can be used to manufacture a stable medicated feed is completely independent from the	It was indeed an important discussion point in the EWG that the GL would not include the requirements for the registration of medicated feed. That is why the "2. Preamble" section includes the sentence "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 Guidance " The sentences concerned, were specifically aligned to make the point that: Although this guideline does not seek to cover information required for the actual

SECTION ….			
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		actual registration / formal approval of the medicated feed itself, which is typically registered via a separate system. It appears that is what the statement in section 2. Of the Preamble is attempting to communicate. It may be clearer to modify the aforementioned sentence of the preamble to state that: i. Some regulatory authorities may have additional, separate requirements that must be met in order to register a medicated feed ii. These additional requirements are not included in the current guideline iii. Sponsors should consult with the competent authorities accordingly.	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. To further clarify the situation, the word "information" is replaced by "requirements for the registration". That would change (in the preamble) the following sentence "The guideline only pertains to Medicated Premixes and does not cover information for medicated feeds manufactured from medicated premixes." Into "The guideline only pertains to Medicated Premixes and does not cover requirements for the registration of medicated feeds manufactured from medicated premixes."