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

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Final

DISCUSSION DOCUMENT IN THE FORM OF A DRAFT CONCEPT PAPER ON THE DEVELOPMENT OF FURTHER GUIDANCE AROUND MEDICATED PREMIXES

INTRODUCTION AND PROBLEM STATEMENT

At the tenth VICH Outreach Forum, the subject of guidance on medicated premixes and their application in feed was put forward. As a result, the current GL8 was reviewed by the topic leader (Japan) and a draft discussion paper was prepared by AnimalhealthEurope on whether further guidance on medicated premixes could be appropriate.

In a follow up of that discussion at SC 37, AnimalhealthEurope was asked to prepare a clarified discussion document. To achieve this the rapporteur decided that the best approach to clarify the intention in the DD was to present a draft concept paper.

The starting point for future work is already embedded in VICH GL8 and is mentioned in a clarifying message from a VOF country. The GL8 itself identifies indeed some gaps to be filled by stating that "*Other stability studies which might be important to consider, like stability in relation to conditioning and pelleting, segregation and homogeneity studies are not within the scope of this guideline.*"

The request as formulated by VOF is broader than just the premix stability study, but also asks for broadening the focus of VICH GLs to include other requirements/data that are critical when assessing dossiers for medicated premixes. So, apart from the fact that technical requirements for medicated premixes are incomplete, the VOF as well called for technical requirements for medicated premixes that refer to a premix's suitability for use in the preparation of medicated feed.

The Steering Committee asked to review the current VICH guidance and where additional guidance on medicated premixes could be given. At the same time, it is clear that the guidelines would only pertain to medicated premixes and would not be about registration of medicated feed as such.

DEFINITIONS

- Medicated premix (also called Type A medicated article): 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 drug to animals when mixed with feed (see VICH GL8). Medicated premixes for liquid feed would be in scope.
- Feed additive: additives used in feeds for non-veterinary uses (specified by each country/region). Such additives are not considered to be veterinary medicinal products and will be out of scope.

- Medicated feed: Feed containing medicated premixes. Such medicated feed is not to be considered a veterinary medicinal product and will be out of scope.
- Medicated drinking water and topdressing formulations /oral formulation (like oral powders) are out of scope.

WHAT IS THE CURRENT SITUATION?

THE CURRENT SITUATION IN VICH GUIDANCE

GL3 Stability VMP

"Further guidance on new dosage forms, medicated premixes, and on biotechnological/biological products can be found in VICH guidelines GL4, GL8, and GL17, respectively. Stability testing following first use of the product (e.g., first broaching of a vial) is not covered within this guideline."

GL4 (annex to 3) for new vet dosage forms

This GL relates to "what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products."

…"Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time may be acceptable in certain justified cases."

GL17 Stability testing of new biotechnological/biological veterinary medicinal products

Does not contain info on premixes.

GL58

- Covers stability test parameters in climatic zones III and IV.
- Not yet referenced in GL8

GL8

- Covers stability test parameters in climatic zones I and II.
- Pertains only to the premix
- Requires necessary stability indicating test parameters without further specification
- Requires testing in final packaging material, smaller pack sizes can be justified

In the introduction of the (short) GL8, we read: "This document is an annex to the parent guideline and addresses the recommendations for stability testing of veterinary medicinal Medicated Premix drug products. The parent guideline (VICH GL3) 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 drug products being evaluated. Other stability studies which might be important to consider, like stability in relation to conditioning and pelleting, segregation and homogeneity studies, are not within the scope of this guideline."

THE CURRENT SITUATION FOR SOME MEMBERS AND OBSERVERS

In general, we see a different level of requirements depending on the region and the local regulations (e.g. feed-additive vs medicated premix).

Japan:

- Only type A medicated articles (veterinary premixes) are regulated as VMPs. They need to follow VICH GL8

Canada:

- stability of the premix
- samples for analysis
- homogeneity and segregation of the medicated feed mix
- feed assay validation, including attention for interference via concurrently used other medicines/products
- stability of the medicated feed, in mash and pellets for 3 months

EU:

- NTA vol 6, p 53, 2G - Other Information: For medicated premixes (products intended for incorporation into medicated feedingstuffs), information shall be provided on:
  - inclusion rates,
  - instructions for incorporation,
  - homogeneity in-feed,
  - compatibility/suitable feedingstuffs,
  - stability infeed, and the proposed in-feed shelf life,
  - a specification for the medicated feedingstuffs, manufactured using these premixes in accordance with the recommended instructions for use shall also be provided

USA:

- Type A medicated articles (veterinary premixes) are regulated as VMPs. They need to follow VICH GL8
- Other requirements include:
  - stability of the Type A Medicated Article
  - homogeneity and segregation of the Type A Medicated Article and representative Type B and C Medicated Feeds manufactured from it
  - feed assay validation, including attention for interference via concurrently used other medicines/products, and including a feed method trial demonstrating comparable results for feed assays between three naïve laboratories
  - Stability of the Type B Medicated Feed for a period of 6 months is recommended
  - Stability of the Type C Medicated Feed is recommended for a minimum of 8 weeks, and the feed must carry an expiration date on the label if 8 weeks stability at the routine condition cannot be demonstrated. This requirement applies in mash and pellets

IMPACT FOR PUBLIC HEALTH, ANIMAL HEALTH AND ANIMAL WELFARE

In feed medication is an important route of administration in (food) animal medicine. Improved quality of medicated premixes and demonstration of their ability to be used in medicated feed will have a positive impact public health, animal health and animal welfare.

POTENTIAL SCOPE OF MEDICATED PREMIX GUIDELINES

VICH GL8 is not very specific on stability of medicated premixes. There are two different elements in the potential work for an Expert Working Group on medicated premixes

In first instance, the Expert Working Group should review and update GL8 to include requirements around:

a. **Zone III, Zone IV A and Zone IVB** (30°C/60% or 65% RH) (ref to GL58)
b. **In feed stability** for the intended **medicated feed must also be covered** (using different feed types)
c. **Stability** of the premix **after opening of the primary packaging**
d. **Bracketing, matrixing** (referring to GL 45) **or statistical evaluation (reference to GL 51) including extrapolation** of results of stability studies on medicated premixes

In a second and separate effort, the same EWG could develop a further assessment on the necessity and possibility to develop further guidelines on other related topics with potentially a major impact on the quality of medicated premixes and their suitability to manufacture medicated feed, such as:

1. **Analytical method validation** in the premix and in different types of feed
2. **Homogeneity and segregation** studies for premix and medicated feed
3. **Pelleting/extrusion stability** where stability parameters are very different (high temperature and/or high pressure)
4. Stability of **premixes with different compounds** (e.g. vitamins or different medicinal substances or additives with different stability profiles)
5. **…**

In no case the new or revised guidelines are intended to regulate medicated feed.

RECOMMENDATION TO THE STEERING COMMITTEE

As seen in several regions and countries, more guidelines have been or will be developed for medicated premixes, outside of the VICH-agreed test parameters for medicated premixes in GL8. The current GL8 only covers part of the test parameters for stability studies with medicated premixes.
This concept paper proposes to create an EWG that should focus on the technical requirements for medicated premixes.
The EWG should have two major tasks.

A first task will be to **review and update VICH GL8** to include:

a. **Zone III, Zone IV A and Zone IVB** (30°C/60% or 65% RH) (ref to GL58)
b. **In feed stability** for the intended **medicated feed must also be covered** (using different feed types)
c. **Stability** of the premix **after opening of the primary packaging**
d. **Bracketing and matrixing** (referring to GL 45) **or statistical evaluation (reference to GL 51) including extrapolation** of results of stability studies on medicated premixes

As a second task, the EWG should **develop a concept paper on the necessity and feasibility** of guidelines covering other technical requirements for premixes (such as amongst others):

a. **Analytical method validation** in the premix and in different types of feed
b. **Homogeneity and segregation** studies for premix and medicated feed
c. **Pelleting/extrusion stability** where stability parameters are very different (high temperature and/or high pressure)
d. Stability of **premixes with different compounds** (e.g. vitamins or different medicinal substances or additives with different stability profiles)

TIMETABLE AND MILESTONES :

The first task should be relatively easy and should be leading to a revision of GL8 at step 4 at the "next" Steering Committee in November 2021 or by written procedure.

For the second task, the EWG should finish the initial assessment and recommendations for additional topics and guideline development by end July 2021 which is three months before the November 2021 Steering Committee.

IMPACT ASSESSMENT AND ANTICIPATED BENEFIT

Industry:

a. Clarity and global consistency of requirements for medicated premixes, including VOF regions
b. Reduction in number of studies needed for global marketing
c. Increased regulatory predictability

Regulators:

a. Increase in clarity of requirement (less uncertainty expressed by Industry)
b. Decrease in submission of failed studies or dossiers
c. Increase in consistency of studies and dossiers