European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON THE DRAFT REVISED GUIDELINE ON STABILITY TESTING: STABILITY TESTING OF EXISTING ACTIVE SUBSTANCES AND RELATED FINISHED PRODUCTS

Table 1: Organisations that commented on the draft Guideline as released for consultation

Add name followed by link to individual received comment (upon publication by Web Services)

	Name of Organisation or individual	Country
1	IFAH-Europe	Belgium
2	EGGVP	Belgium

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Table 2: Discussion of comments

GENERAL COMMENTS – OVERVIEW

Comment:	Outcome:
IFAH-Europe: The CHMP/CVMP Quality WP has reviewed the Note for Guidance on 'Stability Testing of Existing Active Substances and Related Finished Products' (EMEA/CVMP/846/99) in light of the recent update of the VICH Guideline on 'Stability Testing of New Veterinary Active Substances and Medicinal Products' (VICH GL 3). In some aspects, e.g. amount of data to be submitted to cover active substance stability, an improvement has been made, partly addressing the IFAH-Europe comments to the corresponding Concept Paper submitted in March 2007. Other sections of the GL could on the other hand, benefit from additional refinements as explained below under 'Specific comments'. Page 2 of the draft GL 'Revision history' (last paragraph) reads: *'It is recommended that all marketing authorisation applications contain data from complete studies at the intermediate storage condition 30°C ± 2°C/65%RH ± 5%RH, if applicable, by 3 years after final adoption of the revised guideline*.' This way, we understand that this GL is not intended to be applied retrospectively to authorised products, which IFAH-Europe fully supports. However to ensure a smooth transition period for already ongoing applications, we further recommend a 5 years transition period from date of adoption of the revised GL since stability studies are usually designed for 5 years, and some use the intermediate storage condition throughout.	It is not intended to apply the GL retrospectively to authorised products. However, if new stability studies are started (e.g., in case of variations, where new stability data have to be generated) the principles of this guideline should be followed. A transition period of 3 years is still regarded to be sufficient. The changes in the revised guideline are not so fundamental that a transition period of 5 years seems to be necessary. The choice of test conditions refers to the Note for Guidance on Stability Testing of New Veterinary Drug Substances and Medicinal Products (VICH GL 3(R)) which was adopted by CVMP in February 2007 and came into effect in January 2008 (transition period less than 1 year). Also, these new conditions were published a long time ago and were already known from the GL on the Declaration of Storage Conditions (EMEA/CVMP/422/99/Rev.3 which came into effect in October 2003). Additionally, the revised guideline offers the possibility to change the condition of ongoing studies.

EGGVP: It makes sense to revise the guideline to bring it in line with the requirements of the Note for Guidance on Stability Testing of New Veterinary Drug Substances and Medicinal Products. It also makes sense change the relative humidity at storage under intermediate conditions, i.e. presently 30°C ± 2°C/60%RH ± 5%RH, to 30°C ± 2°C/65%RH ± 5%RH. The text of the guideline in question is almost identical to the text of the equivalent guideline for human medicines (CPMP/QWP/122/02, rev 1 corr) apart from references to other guidelines. In principle, we agree that the same stability requirements should apply to veterinarian medicines. We have noted that the minimum time covered by stability data at submission is 6 months. This is shorter than the period in the equivalent human medicines Note for Guidance but we agree to include the difference.	Noted.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no. + paragraph no.	Comment and Rationale	Outcome
Throughout the document	**IFAH-Europe:** Throughout the document, the terminology is not completely aligned with VICH GL 3. For instance, the term “Active Substance” (GL 3: “Drug Substance”) is used, as well as “Finished Product” (GL 3: “Medicinal Product”). IFAH-Europe recommends using the VICH GL 3 terminology i.e. 'Drug Substance' and 'Medicinal Product' throughout the document; that includes changing the title of the GL to: Stability Testing of Existing Veterinary **Drug Substances** and related **Medicinal Products**.'	The terms in the draft guideline are used on purpose. In the European Legislation the terms “active substance” and “finished product” are used. No amendments are therefore considered necessary.

2.1.1 and 2.1.2 a) Page 4/17 also 2.1.5, paragraph 2 Page 5/17	**IFAH-Europe:** Reference should not only be limited to EU Pharmacopoeias. In cases where an active substance monograph is only contained in the US or Japanese Pharmacopoeias, this should be regarded as an appropriate monograph for controlling the active substance and its degradation products. IFAH-Europe recommends amending 2.1.1 as follows: *"For active substances described in an official pharmacopoeial monograph (European Pharmacopoeia or the Pharmacopoeia of a European Union Member State* ***or the Pharmacopoeia of a 3rd country****)…"* and amending 2.1.2 and 2.1.5 as follows: *"When an active substance is described in an official pharmacopoeial monograph (European Pharmacopoeia, the Pharmacopoeia of a European Union Member State* ***or the Pharmacopoeia of a 3rd country****)…*	The European legislation only permits reference to the European Pharmacopoeia or to the Pharmacopoeia of an EU Member State. Additionally, it should be noted that not only are there the USP and JP, but also some other Pharmacopoeias of 3rd countries. No amendments are therefore considered necessary.
2.1.2 b) Stress testing Page 4/17 and 5/17	**IFAH-Europe:** The GL reads: *"Stress testing is likely to be carried out on a single batch of the active substance"* The nature of the batch for such stress testing should be defined. Stress testing on laboratory or similar batch obtained during development of an Active Ingredient should be sufficient. IFAH-Europe recommends including *"at least laboratory batch"* as follows: *"Stress testing is likely to be carried out on a single batch of the active substance or* ***at least a laboratory batch****".*	As there is no specific requirement stated in the guideline, the use of laboratory batches is acceptable. No amendment is therefore considered necessary.
2.1.6 Testing frequency Page 6	**EGGVP:** Add a statement indicating that stability can be aborted as soon as one parameter is out of specifications.	The studies should be carried out until the end (6 months in case of accelerated studies and 12 months in case of studies at intermediate conditions) unless there is clearly a significant change. No amendment is therefore considered necessary.
2.1.7 & 2.2.7	**IFAH-Europe:** A temperature difference of 15°C between long term and accelerated storage should be defined as already is the case in the current GL. IFAH-Europe recommends the following sentence should be added at the end of each of the paragraphs: *…alternative storage conditions can be used if justified.* ***The 6 months accelerated testing should then be carried out at a temperature at least 15°C above this designated long term storage temperature (together with the appropriate relative humidity conditions for that temperature)****."*	In the revised guideline the testing conditions for different storage conditions are described more in detail than in the current guideline (e.g., see accelerated storage conditions for finished products for storage in a freezer). Therefore, the sentence proposed by IFAH seems to be not necessary any longer and may be misleading, as normally the standard test conditions should be followed.

2.2.3 Selection of batches Page 10/17	**EGGVP:** In case of a range of size of the same containers it does not seem reasonable to perform studies on all container sizes. "Stability studies should be performed on each individual strength and container size. If a range of containers are used, at least the smallest and biggest container should be included in the test."	Reduced testing design in case of a range of containers is defined as bracketing or matrixing. The whole sentence in the draft guideline reads: "Stability studies should be performed on each individual strength and container size of the finished product unless bracketing and matrixing is applied." Therefore this concern is already covered in the text of draft guideline. Specific requirements in case of stability testing of a range of containers will be described in detail in the VICH Guideline on bracketing and matrixing designs for veterinary drug substances and medicinal products (still under consultation). No amendments are therefore considered necessary.
2.2.4. Container Closure system	**IFAH-Europe:** The VICH GL 3 wording on using simulated containers is omitted. As veterinary medicines have a significant probability to be packed in large containers, this wording is important. IFAH-Europe recommends including the VICH GL 3 wording in section 2.2.4 as follows: *"Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing.* ***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 container closure system should be provided***.	The wording has been revised exactly as suggested here. (This option is also written in VICH GL 3(R).)
2.2.5 Selection of specifications Page 10/17	**EGGVP:** There is no discussion of potential degradation, impurities or related substances in the specification. In some cases, impurities / related substances are not defined in the active substance monograph but have to be controlled in the finished product.	Selection of specifications is described in detail in separate guidelines (VICH GL 39 / 40). No amendment is therefore considered necessary.

2.2.7, § 1 Page 12/17	**IFAH-Europe:** According to the draft GL, a minimum of 6 months stability data are required for a finished product. However, VICH GL 4 on "Stability Testing for New Veterinary Dosage Forms" allows the owner of the original application to submit reduced stability data for a new dosage form, in certain cases. Thus to ensure alignment with VICH, we recommend introducing a reference to VICH GL 4. IFAH-Europe recommends adding the following sentence at the end of the paragraph: *"…such as might occur during shipping.* ***For new dosage forms, reduced stability data may be submitted by the owner of the original application, in certain justified cases (VICH GL 4)***"	The proposal made by IFAH is different from VICH GL 4 which states: "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." The introduction of this draft revised guideline already leaves flexibility for specific cases ("Alternative approaches can be used when there are scientifically justifiable reasons." *See last sentence of section 1.1.*) No amendments are therefore considered necessary.
2.2.7.3 Page 13/17	**EGGVP:** It might be an idea to provide a reference to the definition of permeable and impermeable materials, because many suppliers indicate that the material used is impermeable.	There is a definition of "Impermeable Containers" and "Semi-permeable Containers" in the glossary of VICH GL 3(R). As this guideline is an extension of VICH GL 3(R) these definitions are applicable. No amendments are therefore considered necessary.
Annex II Extrapolation of data Page 16/17	**EGGVP:** In the current version is stated: that "normally extrapolation to twice the length of real time studies can be accepted." In the consultation version there is stated: "the extrapolated retest period or shelf-life may be up to twice, but should not more than 12 months beyond." Rationale: The guideline is applicable for existing active substances and related finished products for veterinary use. This means that the guideline is applicable for active substances and finished products that are already used for many years in veterinary and often in human practice as well. Because enough information and safety data are already available for such products extrapolation to twice the length of real time studies is justified. Furthermore, it must be noted that in the past we never concluded that the "…extrapolation to twice the length of real time studies …" resulted into a proposed shelf-life which was not acceptable according to the results obtained afterwards with the real time stability study.	According to the current CVMP guideline the retest period / shelf life may be extrapolated to twice the length of the real time studies with a maximum shelf life justified by extrapolation of 3 years. The draft CVMP guideline as well as the CHMP guideline also allows extrapolation to twice the length of real time studies. According to the draft CVMP guideline and the CHMP guideline the maximum extrapolation should not be more than 12 months. However, extrapolation beyond 3 years is possible. Only in case of real time studies of 18 months the present CVMP guideline allows a longer extrapolation. In all other situations the new approach results in an identical or even longer retest period / shelf life. See the attached table (below) comparing the results when maximum extrapolation of real time data is possible. It should be underlined, that according to the draft guideline limited extrapolation even in case of stability data at intermediate conditions is possible.

		The conditions for extrapolation taken from the CHMP guideline are in line with ICH conditions (ICH Q 1E on evaluation of stability data). Also, the decision tree taken from the CHMP guideline is identical with the one in ICH Q 1E. Different approaches for extrapolation may cause problems (e.g. for active substances within EDQM). No amendments are therefore considered necessary.
Annex II Extrapolation of data Page 16/17	**IFAH-Europe:** The possible length of extrapolation is narrowed compared to the current GL. According to the proposed new wording, 18-month data would result in a 30-month shelf life (vs. 36-month shelf life under the current GL). In addition, a rather complicated procedure is proposed in order to determine how to proceed - see flow chart (Annex II). This approach does not appear in VICH GL 3 and is a specific addition to the present document. As the Guideline covers existing drug substances (with a known stability behaviour) and their associated medicinal products, the current procedure and extrapolation ranges in EMEA/CVMP/846/99 should remain applicable. Introducing the new procedure will cause an additional burden on industry, where as it is not even mandated by VICH GL 3. IFAH-Europe recommends deleting the decision tree page on page 17 and amending the wording from the second sentence onwards in Annex II as follows: *'The extrapolated retest period or shelf-life may be up to twice the length of the real-time studies. However, the maximum shelf life justified by extrapolation should not exceed three years ~~but should not be more than 12 months beyond, the period covered by real time data, depending on the change over time, variability of data observed, proposed storage conditions and extent of statistical analyses performed. The decision tree depicts the various situations envisaged~~*.	According to the current CVMP guideline the retest period / shelf life may be extrapolated to twice the length of the real time studies with a maximum shelf life justified by extrapolation of 3 years. The draft CVMP guideline as well as the CHMP guideline also allows extrapolation to twice the length of real time studies. According to the draft CVMP guideline and the CHMP guideline the maximum extrapolation should not be more than 12 months. However, extrapolation beyond 3 years is possible. Only in case of real time studies of 18 months would the present CVMP guideline allow a longer extrapolation. In all other situations the new approach results in an identical, or even longer, retest period / shelf life. See the attached table (below) comparing the results when maximum extrapolation of real time data is possible. It should be underlined, that, according to the draft guideline, limited extrapolation, even in case of stability data at intermediate conditions, is possible. The conditions for extrapolation taken from the CHMP guideline are in line with ICH conditions (ICH Q 1E on evaluation of stability data). Also, the decision tree taken from the CHMP guideline is identical with the one in ICH Q 1E. Different approaches for extrapolation may cause problems (e.g., for active substances within EDQM). No amendments are therefore considered necessary.

Attachment: Comparison of extrapolation

Real time data	**max. extrapolation** current CVMP GL	**max. extrapolation** CHMP GL / draft CVMP GL
6 months	12 months	12 months
9 months	18 months	18 months
12 months	24 months	24 months
18 months	**36 months**	**30 months**
24 months	36 months	36 months
36 months	36 months	**48 months**
48 months	48 months	**60 months**