European Medicines Agency
Veterinary Medicines and Inspections

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON QUALITY ASPECTS OF SINGLE-DOSE VETERINARY SPOT-ON 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

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW		
First of all, IFAH-Europe would like to thank the CVMP Quality Working Party for its letter dated June 2007 in response to the IFAH-Europe comments to the Concept Paper; we especially acknowledge the QWP confirmation that the scope of the GL will be limited to new products only and exclude excipients. With regard to the implementation deadline, we strongly recommend a 3-years transition from the date of release of the final GL. Other points of the draft GL that need further discussion are presented below. **Outcome:** *The usual implementation time is 6 months after publication of a final EU guideline. Exceptionally a 1 year implementation period is considered acceptable in this instance.*		
SPECIFIC COMMENTS ON TEXT		
4.2 Part IIB Method of manufacture		
Line no.[1] + paragraph no.	**Comment and Rationale**	**Outcome**
Page 4/5, Last paragraph	The draft GL reads: "*Fill volume limits should be defined based on process validation data. Consideration should be given to the requirement for the finished dosage form to meet the requirements of European Pharmacopoeia general text 2.9.40, Uniformity of dosage units.*" Process validation data would usually not need submitting as most of the processes used are standard processes in accordance with Annex II to the Note for Guidance on Process Validation (EMEA/CVMP/395/03). Amend the sentence to read: *Fill volume limits should be ~~defined~~* ***confirmed*** *based on process validation data.*	QWP accepted that this section of the original draft was badly worded. The point here is that data are required to show the volume retained in the tube. We propose to change this section to say **"Fill volume limits should be defined based on development studies".**

[1] Where applicable

4.3 Part IIF Control of the finished product		
Line no. + para no.	**Comment and Rationale**	**Outcome**
Page 4/5, First paragraph	IFAH-Europe has further considered this section, which we feel underestimates the variations that will occur just by different users squeezing the pipettes. Such variations make it impossible to determine assay limits in a range of 95 – 105 % of the declared content and IFAH-Europe proposes the following instead: 1. Apply Ph. Eur. 2.9.40 limits to a potency per dosage test; 2. Apply the 95-105% limits to a test on the assay on a concentration basis. We propose <u>replacing the first paragraph of section 4.3</u> with the following 2 tests (with the 2nd § to become test 3): *1.) <u>Control of the correct application of dosage form:</u> potency per dosage should be expressed in terms of the quantity by mass of the active substance in a container of average delivered mass or volume. Limits of 85-115 % of the declared content in units of [mass/dosage form e.g. mg/dosage form] should be applied to this parameter. This should preferably be determined by expressing a specified number of dosage units in a manner likely to be used by the person treating the animal, bulking the resultant contents, determining the assay on a concentration basis and calculating the quantity by mass of the active substance in a container of average delivered mass or volume.* *2.) <u>Control of the correct content of drug substance:</u> assay on a concentration basis of 95-105% of the declared content in units of [mass/volume (e.g. mg/ml)], as obtained under test 1).* *3.) <u>Control of uniformity of delivered dose:</u> a test for uniformity of delivered dose should be applied in accordance with the European Pharmacopoeia general text 2.9.40, Uniformity of dosage units. This should be determined by expressing the required number of dosage units in a manner likely to be used by the person treating the animal.*	Not all accepted. Obviously it is important to express potency in terms of the quantity by mass of the active substance in a container of average delivered mass or volume. However for this average container the limits should be 95-105% in accordance with normal standards. Already covered in Section 4.2 of the Guideline. Agreed, although wording amended.
Page 4/5, Second paragraph	The test for uniformity of dosage test should be kept (to become test 3).	(See above.)

Last paragraph	Microbiological testing: As IFAH-Europe already stressed in its response to the Concept Paper, spot-on products are used for the control of external parasites, i.e. the formulation is applied to a healthy skin and microbiological testing should not be required. Delete the sentence: ~~*Microbiological aspects should be considered…, bearing in mind that spot-on products are sometimes applied to damaged skin*~~ and replace with a reference to**:** ***monograph 5.1.4, category 2 for dermatological preparations*****.** Moreover, non-aqueous compounds, which do not support microbiological growth, are usually used in spot-on products.	Not all agreed. These products are <u>not</u> always applied to healthy skin. It was however agreed to mention the Ph.Eur. monograph 5.1.4 in the guideline (and indeed this was done) but not to include mention of category 2 (as the new Ph.Eur. harmonised monograph no longer has a category 2). Usually, but not always, therefore the requirement should stand.

4.4 Part IIG Stability

Line no. + para no.	**Comment and Rationale**	**Outcome**
Only paragraph	The first sentence reads: "*Stability testing should include determination of the mass of individual containers*." For the sake of clarity, amend to read: "*Stability testing should include determination of the* ***extracted*** *mass of individual containers*".	Partially accepted. The extracted mass is not the important issue here. It is necessary to know the actual weight loss of filled containers. Otherwise this can mask degradation. Therefore the first sentence has been clarified by the addition of "…***in order that the actual weight loss of filled containers can be established.***"
Only paragraph	For consistency with the proposed 2 new tests under section 4.3, IFAH-Europe further proposes to amend this section to read: "***In addition to tests 1 and 2 under section '4.3 Part IIF Control of the finished product',*** *stability testing should include determination of the* ***extracted*** *mass* ***of formulation*** *of individual containers.* ~~*Assay results should be expressed in terms of mass of active substance per container of average extractable mass and on a concentration basis.*~~ *The possibility of water uptake or solvent loss through the containers should be considered."*	Not accepted (but text clarified – see above). Weight loss of tubes can mask degradation. It is important to know both the mass of active substance per container of average extractable mass and the concentration of active substance.