15 July 2021
EMA/CVMP/QWP/485008/2019
Committee of Medicinal Products for veterinary use (CVMP)

Overview of comments received on the guideline on Manufacture of the Veterinary Finished Dosage Form (EMA/CVMP/QWP/798401/2015)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	European Group for Generic Veterinary Products (EGGVP)
3	French Association for Veterinary Medicines (SIMV)

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1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1	Having a specific GL for veterinary is very much welcome. In the executive section, it is highlighted that the traditional approach is still acceptable which is appreciated. However, when reading the complete document and apart from the clear annex, **only** wording from ICH GLs Q8-9-10 is used which could be confusing.	The comment is noted The text of the guideline was proposed in a way to reflect the CHMP guideline EMA/CHMP/QWP/245074/2015 (Guideline on manufacture of the finished dosage form) as the general concepts and approach to the manufacture should not be very different in both domains, however the wording as it is should be fully understandable even without knowledge of ICH GLs Q8-9-10.
2	General comment on 'Definitions' Section (line 254). References 3 and 5 are only to be considered voluntary for veterinary medicinal products (see lines 7-10). Those definitions would therefore seem less relevant.	Comment noted Even though the enhanced concepts in the manufacturing process of the final dosage forms are voluntary, when voluntarily chosen by the veterinary company, the ICH Q8-Q10 guidelines are considered scientifically relevant for such a veterinary application. Furthermore, the terms are used in the guideline and thus they should be kept in the 'Definitions' section.
3	Having a specific GL for veterinary is very much welcome.	The comment is noted

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
51-56	2	Comment: The whole Section 4.1. should eb deleted to avoid duplicate with Part IA, Annex 5.8, Flow chart indicating all Sites involved in the manufacture of the finished product or active substance (including sites involved in sampling, testing and release of products manufactured in third countries). Proposed change: Delete the text.	Accepted. According to the new Commission Regulation (EU) 2019/6 and its annex II, the information on the manufacturer should be included in Part 1 only. The section of the guideline on manufacturers is thus removed. As the headings of the guideline no longer follow the structure of CTD format, the introduction part of 'section 4 – manufacture' was slightly amended.
53	2	Comment: Outsourcing activities are already described in GMP. Moreover, contractors are under the responsibility of manufacturers. Proposed change: Please delete "including contractors".	Partly accepted. Each site where some operation concerning the finished product manufacture takes place has to be clearly stated within the application dossier. However, the section was removed from the guideline (see above).
53	3	Comment: Name, address and responsibility of contractors is a GMP matter. Part 2B of quality dossier is not the place to include such details. Proposed change: Please delete "including contractors".	See above

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54	1	Comment: Including ongoing stability managed after post approval in section 2.B is a risk to quickly have an obsolete section because this is not a section of the part 2.B. This is not described in the annex 1, section B: description of the manufacturing method. This information is given in the Part I – administrative. In post approval, when the testing site is modified for on-going stability, the update of the part 2.B is not requested. Proposed change: Please delete "including on-going stability testing if different from the manufacturing site."	Accepted. The whole section was removed from the guideline (see above).
64	2	Comment: Broad definition 'bulk' used. Proposed change: Please add unambiguous and prevailing definition for 'bulk' under heading definitions.	Accepted. Bulk product was already defined in the guideline in line with GMP guideline definition in section 4.3, but it was moved to the 'Definition' section.

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70-71	1	Comment: It is frequent that the commercial batch size for solid oral dosage forms cannot be "at least 100,000 units" due to the large number of presentation/dosages. The example provided in this section is questionable. Proposed change: Please delete the sentence "For example, a commercial batch size for solid oral dosage forms should be at least 100,000 units unless justification is provided (ref. 7)".	Accepted
81-84	1	Comment: It seems that this section is not linked to the paragraph on "continuous manufacture" paragraph. Proposed change: If this is the case and paragraph 78-80 is independent, we would suggest placing the paragraph on "continuous manufacture" at the end of the section 4.2 in order to avoid any confusion.	Not accepted Each paragraph stands on its own, similarly as the paragraph on sub-batches above this one (72-77).
81-82	2	Comment: Names, quantities and reference to the quality standards of all ingredients used in the course of the manufacture are already indicated in part IIA and IIC. Is it strictly relevant adding this in Part IIB as well? Proposed change: Please replace to: "The names and quantities of all ingredients used in the course of the manufacture should be stated".	Partly accepted. The text has been amended to clarify that in case of VNeeS format reference to quality standards of all ingredients is included in Part 2.A and not Part 2.B.

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82	3	Comment: ingredients are already listed in parts 2a and 2c of the Quality file. Proposed change: Please clarify the need for specifying the excipients again in part 2b.	Comment is noted Part 2.B includes a list of ingredients (names and quantities) used for the intended batch size. Part 2.A includes a list of ingredients (names, quantities and reference standard) per unit dose or per unit of mass or volume. Part 2.C does not include an actual list of ingredients. The text in the guideline has been amended (see above).
83-84	1	Comment: It is almost impossible to quantify gases removed from the product, even as a range. Proposed change: We would suggest modifying line 84 by adding "(apart from gases)" at the end of the sentence after "as ranges".	Not accepted. The term "ranges" should be sufficiently flexible and may cover also gases.
83-84	2	Comment: Manufacturers used to verify the removal of these ingredients. As a consequence, it is not useful to indicate a range in the formula. If ranges are given, validation of these ranges could then be requested. Proposed change: Please delete "but their quantities may be expressed as ranges".	Not accepted. Quantitative information on the ingredients which are removed during the process is part of the process control strategy. Their quantity should thus be stated as appropriate, i.e. as a range or fixed value. In regard to the needs for process validation data, there is a separate guideline dealing with this issue, which is not detailed in this guideline (see section 4.5., resp. ref. 7).

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88-89	2	Comment: In our opinion, upper and lower acceptances are a GMP matter. This should be indicated in the internal Batch record but not in the MA dossier. Proposed change: Please delete "Upper and lower acceptance limits for the actual quantity of each ingredient may be stated in the batch formula; however, the proposed acceptance limits should be justified."	Not accepted. The text says that these limits may be stated i.e. only where relevant for specific excipient and where justified. These are specific cases not covered by general GMP standards. The intention is not to require limits related to GMP and which are in the batch records.
88-89	3	Comment: Upper and lower acceptances are matter for GMP and should be indicated in batch record (not in a MA dossier). Proposed change: Please delete the sentence "Upper and lower acceptance limits for the actual quantity of each ingredient may be stated in the batch formula; however, the proposed acceptance limits should be justified."	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
99-103	1	Comment: This section in referring to 2.A.4, which is not the place to detail the process operating conditions or ranges in the traditional approach. The vocabulary used is around Design Space and typically used in ICH which is confusing. Proposed change: To bring clarity, we would propose to move the lines 99-103 to the beginning of the paragraph starting with line 116. Please add at the beginning of this new paragraph the following heading: "In case of design space and/or particular controls strategy, the description should be adequately given in part 2.A.4 (CTD 3.2.P.2)".	Not accepted. Justification of the manufacturing process should be provided in the development section of the dossier even in case of traditional approach. The intention is to highlight that the process description in 2.B is closely related to the information on the process development. This is general principle not related only to the enhanced ICH Q8-Q10 approaches.
104	2	Comment: Unclear definition 'Full' used. Proposed change: Replace 'Full scale' to 'Production (or Commercial) scale'. Add also definition under heading definitions.	Not accepted. The term "Full-scale" is used in the currently effective process validation guideline (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1 Corr.1) as well and the sentence is referencing this guideline for more information.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
112-113	3	Comment: It is frequent that authorities request hold time for any product, whatever the nature of the process or the product. Proposed change: To bring clarity, we would propose to add a list of processes for which hold time determination is not required?	Not accepted Such a list would not be sufficiently comprehensive as it depends on the nature of the process and the product (as stated in the guideline). The text presents a general principle.
126	2	Comment: 'Reference 3' would appear to be considered as voluntary for veterinary medicinal products (See lines 7-10). Proposed change: Delete '(ref. 3)'.	Accepted.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
192	2	Comment: In our opinion, it is not reasonable to divide manufacturing details for intermediates from Part 2.B. Instead, it would be suggested taking over the structure of the EU CTD or keep this section within Part 2.B.2. Proposed change: The heading should be named same as applies in the GL for human medicinal products: "4.4 Control of Critical Steps and Intermediates". Addition of an appropriate sentence is also suggested under the new heading: "All critical steps and intermediates identified during the manufacture of the finished product should be listed in this section including any in-process controls, applied tests and acceptance criteria".	Not accepted. The structure of EU CTD is accepted however part 2.D as "Control tests carried out on isolated intermediates during the manufacturing process" is included as a separate section in the Annex II to the Commission Regulation (EU) 2019/6 so any dossier that follows the structure presented in the Annex should reflect it.
195-197	2	Comment: It is our understanding this matter is strictly related to GMP Compliance, so probably not appropriate being included in a Regulatory guideline. Such matters should most likely be covered in internal GMP SOPs from each company. If these lines cannot be eliminated of the guideline I think I would ask for an example of the type of information to be provided. Proposed change: Eliminate the text, or alternatively, list examples of the type of information that should be provided.	Not accepted. The text is related to complex control strategies (models for process controls, continuous manufacturing), where additional information needs to be provided in the dossier to enable understanding of how deviation(s) will be investigated and addressed. In traditional approach this would be considered to be covered by GMP.

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204	2	Comment: In our opinion, it is not reasonable to divide manufacturing details for intermediates from Part 2.B. It is suggested to keep this section within Part 2.B.2 or take over the structure of the EU CTD. Proposed change: The heading should be put together with the previous one and named same as applies in the GL for human medicinal products: "4.4. Control of critical steps and intermediates". The subheading at this place should be same as applies in the GL for human medicinal products: "Storage of intermediate and bulk products".	Not accepted. The structure of EU CTD is accepted however part 2.D as "Control tests carried out on isolated intermediates during the manufacturing process" is included as a separate section in the Annex II to the Commission Regulation (EU) 2019/6 so any dossier that follows the structure presented in the Annex should reflect it.
205	2	Comment: In our opinion, it is not reasonable to divide manufacturing details from Part 2b. Proposed change: Suggested to keep this section within Part 2b2 or take over the structure of the EU CTD. In line with previous comments, the sentence in Line 208 could also read: "All critical steps and intermediates identified during the manufacture of the finished product should be listed in this section, including any in-process controls, applied test methods and acceptance criteria".	Not accepted. The structure of EU CTD is accepted however part 2.D as "Control tests carried out on isolated intermediates during the manufacturing process" is included as a separate section in the Annex II to the Commission Regulation (EU) 2019/6 so any dossier that follows the structure presented in the Annex should reflect it.

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208-211	2	Comment: See previous related comments. Proposed change: Put the definition under 'heading' definitions. Take into account current definitions in other references/sources (e.g. QA Quality – Stability).	Accepted. Both definitions were moved to Definitions section.
217-218	2	Comment: The use of the wording "..normally need not be presented routinely" is too vague for both Competent Authorities and MAHs in relation to these time consuming studies. Proposed change: A clearer and more unambiguous guideline for these type of intermediate products should be developed, or 'products' shall be restricted to refer to sterile and biological products only. Otherwise, intermediate product should be excluded from the application for a MA since it is already covered as part of cGMP.	Not accepted. It is not possible to provide a definite list of intermediates where such data is needed. It is neither possible to restrict the requirement only to biologicals or sterile intermediates which are examples for such cases.
230	2	Comment: See below. Proposed change: Replace "…any prolonged storage/processing times" to "…any prolonged storage/processing times of the bulk product".	Not accepted. This line does not concern only the bulk, but the whole processing stages and also intermediates.

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232	2	Comment: 'General rule' is missing details for other prevailing dosage forms (oral liquids, spot on/pour on solutions, and so on). Proposed change: Replace "…prolonged storage means more than 30 days for solid oral dosage forms and more than 24 hours…." to ""…prolonged storage means more than 30 days for solid/liquid oral, topical dosage forms, and more than 24 hours….".	Not accepted. It is not possible to list in the guideline all kinds of dosage forms/routes of administration. Even the proposal by the company does not cover all situations. Case-by-case consideration has to be made for cases out of the given examples for sterile and solid oral forms.
232	3	Comment: if prolonged storage means more than 30 days for solid oral dosage forms, does that mean that validation is not needed for shorter storage? Proposed change: We would suggest modifying line 232 which is confusing.	Not accepted. For the indicated examples, it is generally not required to provide stability data to support the holding time in the marketing authorisation dossier when storage period is shorter (e.g. less than 30 days for oral solid dosage forms), but this can still be required during assessment. Note: Stability data for shorter periods might be still required within GMP inspections but that is out of the scope of this guideline and thus not addressed here.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
232-233	2	Comment: Does this mean no validation shall be required when the whole processing time is below 30 days for solid oral form and 24 hours for sterile products ? Proposed change (if any): EMA to clarify and/or list this in the guideline.	See above
233-234	2	Comment: Inclusion of a Risk based approach in the event of various strengths being used should be proposed (worse case tested as part of the stability study). Proposed change: Where relevant, stability data to support the holding time should be provided (on at least two pilot scale batches). In the event of having different strengths, stability data (on at least two pilot scale batches) should be conducted for the most critical strength or, in line with the bracketing approach, on at least one pilot scale batch for each one of the higher and lower strengths.	Partly accepted. Bracketing approach may be applied and the text was thus amended. Other approaches should be sufficiently justified on a case by case basis but it is not deemed necessary to specifically mention this in the guideline.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
234	1	Comment: It is correct that the holding time is usually supported by data on at least two batches but this does not take into account the nature of the product. If a product is very stable and the requested holding time short, one batch may be sufficient to confirm the holding time. Proposed change: There are different practices in Industry but it may be advisable to make the number of batches dependent on prior stability knowledge of the product e.g. if a product is very stable and hold time short, one batch may be sufficient to confirm hold time due to a very large safety margin.	Not accepted. Two pilot batches are the minimum requirement for the marketing authorisation file to allow conclusion on the intermediate or bulk stability.
239	2	Comment: Possible typo ?. See below. Proposed change: Replace '(ref. 13)' to '(ref. 12)'.	Accepted.
241	2	Comment: See below. Proposed change: Replace "bulk product (intermediate)" to "intermediate and/or bulk product".	Accepted.

Line no.	Stakeholder no.	Comment and rationale ; proposed changes	Outcome
247	2	Comment: See below. Proposed change: Replace "bulk product (intermediate)" to "intermediate and/or bulk product", unless intermediate product is excluded since already covered by cGMP.	Accepted.
247, 249	2	Comment: See below. Proposed change: Replace the word "bulk" to "intermediate and/or bulk product", unless intermediate product is excluded since already covered by cGMP.	Accepted.
261-263 and 264-266	3	Comment: Critical Proces Parameter (CPP) and Critical Quality Attribute (CQA) are linked to the ref 3 that is ICH Q8, as well as design space (267-272). It should be underlined that in case ICH Q8 is applied, then CPP, CQA and design space are part of the discussion in the dossier. Currently, there some confusing situation where Authorities ask for data on CPP, CQA and/or design space even if the company did not apply, mention ICH Q8.	Not accepted. It is already clearly highlighted that the traditional approach is acceptable and when enhanced concept is voluntarily chosen, the ICH Q8 should be followed.