25 March 2022
EMA/CVMP/SWP/10857/2022
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on the Guideline on determination of withdrawal periods for edible tissues (EMA/CVMP/SWP/735325/2012)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this draft revised guideline and only has minor comments below.	The stakeholder is thanked for their comments.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
79	1	**Comment:** (found on the EMA website) **Proposed change:** we suggest including the name or any further identification for ease of retrieving the software	Accepted. The stakeholder is thanked for their suggestion. This comment refers to the sentence: 'On these occasions, applicants should use the statistical software provided by the CVMP (found on the EMA website) in order to determine a suitable WP for their product(s).' The sentence has been changed into: 'On these occasions, applicants should use the statistical software provided by the CVMP (to be found on the EMA website as 'Updated application software: withdrawal time calculation for tissues') in order to determine a suitable WP for their product(s).' Moreover, a footnote with hyperlink has been included. See final version.
89	1	**Comment: "**Union"…. or "European Union"	Accepted. The stakeholder is thanked for their alertness. See final version.
95	1	**Comment:** "This guideline …": It is not clear whether "This" refers to the guideline mentioned in the preceding sentence or the present guideline. **Proposed change:** Please specify, e.g. "In the present guideline …"	Accepted. The stakeholder is thanked for their suggestion. See final version.
101	1	**Comment:** "… FDA guidelines"	Accepted. The stakeholder is thanked for their alertness. See final version.
101-104	1	**Comment:** It remains unclear whether the 99% tolerance limits / 95% confidence approach is only present in the current guideline to compare with the FDA approach or whether the	Accepted. This comment refers to the sentence: 'It is recommended in this paper to determine withdrawal periods at the time when the upper one-sided 95% tolerance limit for the residue is below the MRL (or other

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		sponsor is requested to calculate this additional approach. **Proposed change:** Please specify the intention of the guideline	reference value[1]) with 95% confidence. However, for comparison of approaches (cf. FDA), 99% tolerance limits with 95% confidence are also calculated. ' The last sentence has been extended into: 'However, for comparison of approaches (cf. FDA), 99% tolerance limits with 95% confidence are also calculated in this guideline. ' See final version.
286 to 288	1	**Comment:** For clarification **Proposed change:** "As a default the establishment of the withdrawal period is at the time point where foodstuffs do not contain harmful residue levels for public health based on ~~the concentrations of residues in all tissues for all animals are at or below the respective~~ MRLs as laid down in Commission Regulation (EU) No 37/2010"	Not accepted. The stakeholder refers to the sentence: 'As a default the establishment of the withdrawal period is at the time point where the concentrations of residues in all tissues for all animals are at or below the respective MRLs as laid down in Commission Regulation (EU) No 37/2010.' Followed by sentence 'If no (numerical) MRLs are available other reference values may be used.' The default approach is still that WPs should be established based on the MRLs. However, other approaches are possible as further discussed in the guideline. In order to clarify, the word 'approach' is added to the original sentences. See final version.
294	1	**Comment:** For clarification **Proposed change:** "(...) ADI of other reference value [2]. (...)" Please amend the Footnote on reference value [2]: "The ADI should be preferably used. However, depending on the particular substance this could be another health based guidance value set by competent authorities or scientifically justified, like the "normal intake via food" in case of substances being part of the human diet"	Accepted. The stakeholder is thanked for their suggestion. See final version.

[1] In the absence of a numerical MRL, another reference value may be used as the relevant limit for residue concentrations. This is applicable whenever "MRL" is mentioned further below.

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296 - 297	1	**Comment:** For clarification **Proposed change:** "Since no MRLs are set for such compounds, the withdrawal period has to be estimated on the basis of the ADI or other reference value."	Accepted. The stakeholder is thanked for their suggestion. See final version.
301-305	1	**Comment:** For clarification **Proposed change:** "For compounds which may cause injection site residues with potential harmful effects for public health (e.g. pharmacological) ~~effects~~ it may be necessary to establish a precautionary withdrawal period even when an ADI has not been set (e.g. in the case of hormones the naturally occurring levels in edible tissues should be used as the starting point of the determination of a withdrawal period). In addition, other reference values may be used, such as daily intake values for vitamins or other food-additives, set by EFSA as an example but not limited to; if scientifically justified."	Accepted. The stakeholder is thanked for their suggestion. See final version.
310	1	**Comment:** For clarification **Proposed change:** "(...) in formulation are so minor such that they will not impact on residue depletion (including injection site residues), then the withdrawal period of the latter can be used for the former."	Not accepted. The stakeholder refers to the sentence: 'When the formulation (active and inactive ingredients), the dose schedule, the route(s) of administration and the target species of a specific generic product, are identical to a currently approved product (i.e., the reference product), or it has been adequately justified that any differences in formulation are so minor such that they will not impact on residue depletion, then the withdrawal period of the latter can be used for the former. ' The suggestion made by the stakeholder is not adopted, as later in the respective section it is specifically focussed on injection site residues, i.e. 'However, in the case of products administered subcutaneously or intramuscularly, small differences in composition may have significant

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			effects on injection site depletion which may not be detected in the standard blood level bioequivalence studies….etc'.
320	1	**Comment:** For clarification **Proposed change:** "(...) for such formulations, in addition to the demonstration of bioequivalence**,** equivalent depletion (...)"	Accepted. The stakeholder is thanked for their alertness. See final version.
330 - 331	1	**Comment:** For clarification **Proposed change:** "(...) data from the site of administration would also be required. Samples of relevant tissues from the administration site (e.g. muscle, subcutaneous fat where skin is not part of the foodbasket, or skin/fat in natural proportions ~~from the application site~~)	Partly accepted. The stakeholder is thanked for their suggestion. The sentences have been rewritten into: (..) data from the site of administration would also be required. Samples of relevant tissues from the administration site (e.g. muscle, subcutaneous fat or skin/fat) should be analysed. See final version.