25 March 2022
EMA/CVMP/SWP/11010/2022
Committee for Veterinary Medicinal Products (CVMP)

Overview of comments received on the Guideline on injection site residues (EMA/CVMP/SWP/185470/2004)

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

Stakeholder no.	Name of organisation or individual
1	Access VetMed (former EGGVP)
2	AnimalhealthEurope
3	FVE

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	Access VetMed welcomes the publication of this guideline and the opportunity to comment. The updated principles and requirements for the assessment of potential risks from veterinary medicines' residues At the injection site are generally supported, with a few comments stated under "detailed comments" section. With regards to the format, it is noticed that the text includes several cross references that complicate readability (for example "see paragraph 15", "see paragraph …".). This makes not easy finding the corresponding paragraph, as these are not marked and counting them does not lead to the correct reference. It is suggested that the references linked more precisely i.e. to the name of the section.	The stakeholder is thanked for their comments. Accepted. It was referred to paragraphs in the working document. Unfortunately, these paragraphs were no longer applicable in the guideline sent for consultation. There will be a check on appropriate link of the references. The stakeholder is thanked for their alertness.
2	AnimalhealthEurope welcomes the opportunity to comment on this draft revised guideline and only has minor comments below.	The stakeholder is thanked for their comments.
3	FVE welcomes the update of the guideline from 2005. Residues directly at injection sites can be comparatively high due to pharmacokinetic and -dynamic properties and tend to deplete erratically leading to large individual spatiotemporal variation to reach the MRL. Generic products shall demonstrate bioequivalence, equivalent depletion of residues from the injection site in order to adopt the withdrawal period established for the reference product or not. However, the experimental design and sampling could be improved.	The stakeholder is thanked for their comments. As this revision is only to update the definition of withdrawal periods according to Regulation (EU) 2019/6, no new scientific content will be included. Moreover, in the guideline it is reflected on the study design and sampling, i.e. `…. the formulated veterinary product should be administered in full compliance with the intended label instructions. Residues should be examined following application of the maximum possible dose and, where the intended use requires multiple treatments, the product should be used accordingly and for the maximum number of treatments. Animals should be representative of the age/weight group of the target animal population for which the product is intended and normal conditions of animal husbandry should be used throughout the

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		study.' Furthermore, it is referred to VICH GL 48 for guidance on study design. This is expected to provide sufficient guidance on the experimental design and sampling.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
78-82	1	**Comment:** the use of brackets in this paragraph is not clear. It states: "which replaced the former Note for Guidance: Approach towards Harmonisation of Withdrawal Periods (EMEA/CVMP/036/95) [4] and the VICH GL 48 [5] and 49 [6] and VICH GL57 for aquatic species [9]". It seems that VICH GL48, GL49 and GL57 have been replaced when it is not the case and they are still applicable. Additionally, we believe VICH GL46 should be mentioned here too. For clarification. **Proposed change:** Listing the applicable documents with bullet points to avoid misunderstandings. Adding VICH GL 46.	Partly accepted. This comment refers to the sentence: 'The assessment of injection site residues should follow the general principles set out in Regulation (EU) 2018/782 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC No 470/2009 [8], which replaced the former Volume 8 [2], the CVMP Guideline on determination of withdrawal periods for edible tissue (EMA/CVMP/SWP/735325/2012 [3], which replaced the former Note for Guidance: Approach towards Harmonisation of Withdrawal Periods (EMEA/CVMP/036/95) [4] and the VICH GL 48 [5] and 49 [6] and VICH GL57 for aquatic species [9].' It is agreed that this sentence is rather confusing. The following sentences are proposed: The assessment of injection site residues should follow the general principles set out in - Regulation (EU) 2018/782 Establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 [8], which replaced the former volume 8 [2]. - The CVMP Guideline on determination of withdrawal periods for edible tissue (EMA/CVMP/SWP/735325/2012) [3], which replaced the former Note for Guidance: Approach towards Harmonisation of Withdrawal Periods (EMEA/CVMP/036/95) [4]

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			- and the VICH guidelines: VICH GL 48 on marker residue depletion studies to establish product withdrawal periods [5], VICH GL 49 on validation of analytical methods used in residue depletion studies [6] and VICH GL57 for aquatic species [9]. See final version. VICH GL 46 provides guidance on metabolism studies (most often radiolabelled studies), to be used for the establishment of MRLs. The current guideline is dealing with withdrawal periods. It is therefore not specifically referred to VICH GL46. However, the reference to VICH GL46 is now added in section 8.1 General principles, where it was already stated that 'This information is generally obtained in radiometric residue depletion studies (i.e., total residues). ' See final version.
162	1	**Comment:** Again, metabolism studies (VICH GL46) seem to be missing in this paragraph. These are also important to determine the total and marker residue and know what residues and metabolites look for in the depletion studies.	See above comment. Information on marker residues/residue of concern is obtained from Regulation (EU) 37/2010 and/or the MRL summary reports on the active substance.
88 to 90	2	**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. This comments 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 are laid down in Commission Regulation (EU) No 37/2010 [7] or below the ISRRV if applicable.' Followed by 'If no MRLs or ISRRV are available other reference values may be used, such as the ADI or alternative exposure limit (see section 12 of this guideline). See also the Guideline on determination of

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			withdrawal periods for edible tissue (EMA/CVMP/SWP/735325/2012)[3].' 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.
267	2	**Comment:** Please delete "-" in "7-days" to be consistent with following "11 "days	Accepted. The stakeholder is thanked for correction of this typo. See final version.
Line 66	3	**Comment:** Would food-production animals, including farmed fish be in scope? **Proposed change** (if any): -	The scope states 'This guideline addresses the assessment of potential consumer risk from veterinary drug residues remaining at intramuscular and subcutaneous injection sites and the elaboration of appropriate pre-slaughter withdrawal periods.' Therefore, the principles in this guideline refer to all injection sites, no matter the species. Nevertheless, e.g. sampling the injection sites, including the surrounding tissues, of farmed fish may in practice be somewhat different from other food producing species.
Line 107	3	**Comment:** Who estimates how and when this inconsistency ? **Proposed change** (if any): -	This comments refers to the sentences: 'Experience shows that the MRL based approach, in most cases, leads to adequate and safe withdrawal periods at the injection site. When this approach is applied, it should however be ascertained that the marker residue in muscle is valid for predicting the residues of concern at injection sites as well, for example, a marker residue may not be considered appropriate if it is not a component of the residue at the injection site (e.g. a metabolite in muscle not present

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			at injection sites)[1]. In other words, in certain circumstances, the MRL based withdrawal period does not necessarily ensure that residue intake in the standard food basket including the injection site is below the ADI. If there is any indication that the MRL based approach might be inconsistent with the ADI, an ADI based estimate needs to be performed to confirm the appropriateness of the calculated withdrawal period (for ADI based assessments see below).' The applicant is responsible for a safe product and should assure that the proposed withdrawal periods results in no risk after consumption of the meat.
Line 258	3	**Comment:** .. , the tested product mixed with a coloured dye and a coloured dye only, … **Proposed change** (if any): -	Accepted, to revise the sentence. The sentence currently reads: 'Conduct one of the above study designs using a coloured dye to provide a visual assessment of the migration potential of injection site residues.' The sentence has been changed into 'Conduct one of the above study designs using the candidate product mixed with a coloured dye to provide a visual assessment of the migration potential of injection site residues.' See final version.
Line 266	3	**Comment:** Only if demonstrable that there is no migration to the other injection site of the neck which micht be the case for smaller animals. Data as suggested in this example have to be processed as paired sample in the statistical analysis. **Proposed change** (if any): -	Not accepted. As this revision is only to update the definition of withdrawal periods according to Regulation (EU) 2019/6, no new scientific content will be included. This comment refers to the sentence: 'For a product that utilizes only a single injection, treatment can be given on the

[1] According to Regulation (EC) No 470/2009 and associated guidelines, selection of the MRL and marker residue in muscle is to be based solely on the residue pattern observed in non-injection site muscle. Hence, this marker and its ratio marker/total residues are not automatically predictive for the injection site residues. If the muscle marker residue is not present/"under-represented" at the injection site, the withdrawal period according to the MRL approach alone may be too short to ensure that residues of concern at the injection site and in a food basket including the injection site have reached levels below the ADI.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			right side of the neck on day 0 and then on the left side of the neck on day 4. Euthanasia on day 7 following the final treatment would provide depletion data at 7-days (left injection site) and 11 days (right injection site) withdrawal.' The prevention of overlapping injection sites is a common essential for studies with injection preparations, and not specifically for this study design.
Line 273	3	**Comment:** Sample integrity is here of utmost priority and the raw materials must not be diluted or changed in composition. are required. If it is necessary to breakdown all fibres and in large quantities, a two-step approach with professional precision meat homogenisers is often needed. **Proposed change** (if any): -	Not accepted. This comment refers to the sentence: 'Following removal, the entire samples for the core and surrounding injection sites, as collected, should each be homogenised thoroughly prior to sub-sampling for residue determinations, in order to avoid analysis of potentially non-homogeneous material.' This sentence is considered clear in that it mentions that tissues should be homogenised thoroughly.
Line 282	3	**Comment:** …, animal welfare assessment protocol, … **Proposed change** (if any): -	This comments refers to the sentence: 'In addition to general data reporting according to Regulation (EU) 2018/782 [8], residue studies at the injection site should be accompanied by a complete and detailed description of the study design/experimental conditions in relation to selection of the anatomical site(s) of drug injection, the injection technique and equipment used, depth of injection (intramuscular), measures taken to allow precise location and identification of the injection site at slaughter, relevant technical details on sample collection procedures and sample preparation techniques.' Reference to Directive 2010/63/EU on protection of animals used for scientific purposes and to the 3Rs principles has been added in the Scope section. See final version.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 72, 73, 145, 251, 263, 264, 266, 285	3	**Comment:** Please delete the extra spaces. **Proposed change** (if any): -	Accepted. The stakeholder is thanked for correction of these typo's. See final version.
Line 78, 80, 161, 280,	3	**Comment:** Please close the brackets. **Proposed change** (if any): -	Accepted. The stakeholder is thanked for correction of these typo's. See final version.