13 September 2018
EMA/CVMP/SWP/81095/2017
Committee for Medicinal Products for Veterinary Use (CVMP)

Overview of comments received on 'Guideline on approach towards harmonisation of withdrawal periods (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	Federation of Veterinarians of Europe
2	European Group for Generic Veterinary Products (EGGVP)
3	IFAH-Europe

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1. General comments – overview

Stakeholder number	General comment (if any)	Outcome (if applicable)
1.	FVE has many times re-iterated the need for harmonisation of SPC's and elimination of any discrepancies between authorised withdrawal periods for the same product. As such, we very much welcome and applaud the effort of EMA/CVMP to harmonise withdrawal periods in the European Union and provide a standardised approach for their determination.	No comment necessary.
2.	EGGVP welcomes the publication of this guideline and appreciates the opportunity to comment. The only comment from EGGVP is a request for clarification to comparisons of different approaches for dealing with values below the LOQ issue: in some parts the text refers to LOQ, in some parts to LOD and in some parts to both. For clarification purposes it would be appreciated to be consistent to which limit the approaches apply to. At EGGVP we are under the impression that they apply to LOQ and that levels under LOD are to be replaced with zero.	Partially agreed. All values below the LOQ are replaced with ½ LOQ, including those below LOD.
3.	IFAH-Europe welcomes the opportunity to comment on this draft guideline. We congratulate the CVMP on a thorough assessment of the management of data < LOQ. We are pleased to see that the current policy will continue as the new approaches evaluated, whilst useful, did not result in a clear improvement for human food safety.	No comment necessary.

2. Specific comments on text

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12-129	3.	**Comment:** If the intent is to retain these lines in the final guideline, please move this update to an Annex because it is confusing with the rest of guideline**.**	Agreed. These sections have been moved to a separate Annex, as proposed.
178 and 186	3.	**Comment:** Please add a definition of “New chemical entities” and “Old chemical entities” or replace by “ Recent studies” and “Old studies”	Agreed. It is not relevant whether the chemical is ‘new’ or ‘old’, but the available studies and the existing regulatory framework at the time that they were conducted (e.g., pre-Vol 8-type studies, Vol 8-type studies or VICH GL 48/49 studies). Additionally, the reference to Volume 8 has been deletedfrom this section, as Volume 8 does not deal with studies for setting withdrawal periods (although, before implementation of VICH GLs and in the absence of specific CVMP guidelines, Vol 8 was used as a template for withdrawal time studies) and VICH GL48/49 now provide the relevant guidance. The guideline has been updated to reflect this.
259 – 262	3.	**Comment:** An analytical method must meet the criteria specified within GL 49, which for example could be an accuracy (recovery) of 70-110%. This does not mean that every run will have a 70% recovery or a 90%	Comment noted; however, the CVMP considered that there may be occasions where correction for recovery may be

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		recovery but that when validated all runs will be within this specification and may change within this specification run to run. The accuracy requirements (70 – 110%) in GL 49 are more accurately the sum of all factors that result in the overall accuracy of the method (e.g. recovery + instrument precision / variability + human precision / variability, etc…). Therefore, one can't substitute a single accuracy value to correct for recovery concerns. If a method meets this standard, there is no justification or reason why the observed data should be corrected for recovery before determining a withdrawal period. Our recommendation is that these lines be deleted from the guidance. Alternatively, if the Committee insists that recovery correction must be included, then the only way it can be valid is if recovery correction was also used to set the MRL. Consider: **Scenario 1** • TRR data are collected from the pivotal study. • A validated method exists for the marker residue which meets the 70-110% criteria. • The validated method is used on the TRR tissues to assay the marker and determine the marker/total ratios. • The analytical run has average VC samples showing 78% recovery. • For Sample A, a TRR value is 1000 µg/kg. The marker residue value is 500 µg/kg (uncorrected). So the uncorrected M/T ratio is	required. Correction of data for recovery is a prerequisite for a meaningful comparison of residue depletion data from different studies. Additionally, even within a study, recovery might differ significantly when analyses are performed on different days. In such cases, correction for recovery could be necessary to achieve comparability of the data within the study. Correction for recovery may not be necessary in all cases, perhaps where matrix-matched calibration has been conducted in each of the analytical runs; however, incurred or spiked residues in the same matrix may behave differently, and the same matrices from different animals may also behave differently; matrix-matched calibration does not always balance out such differences. Because of these nuances in analytical methodology, it was decided that careful consideration was required to determine whether the correction was necessary on a case-by-case basis, and this is reflected in the updated GL. This applies to both the analytical methods

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		0.5. • An ADI of 3000 µg/day exists and for illustration assume 30% is assigned to liver across the entire market basket (or 900 µg). • The liver consumption value is 0.1 kg, so the total liver consumption could be up to 9000 µg/kg of total residues. • The MRL consistent with this consumption for liver would be 9000 x 0.5 = 4500 µg/kg. **Scenario 2** • TRR data are collected from the pivotal study. • A validated method exists for the marker residue which meets the 70-110% criteria. • The validated method is used on the TRR tissues to assay the marker and determine the marker/total ratios. • The analytical run has average VC samples showing 78% recovery. • For Sample A, a TRR value is 1000 µg/kg. The marker residue value is 500 µg/kg (uncorrected). • Applying recovery correction would give a value of 500/0.78 = 641 µg/kg. So the corrected M/T ratio is 0.64. • An ADI of 3000 µg/day exists and for illustration assume 30% is assigned to liver across the entire market basket (or 900 µg).	for MRL applications and the analytical methods for marketing authorisation applications.

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		• The liver consumption value is 0.1 kg, so the total liver consumption could be up to 9000 µg/kg of total residues. • The MRL consistent with this consumption for liver would be 9000 x 0.64 = 5760 µg/kg. So if recovery correction is used to adjust the marker residue data, then the MRL must have been established using this same procedure, otherwise, a WDP is being calculated with recovery corrected marker residue data (higher) relative to an MRL that was not (or may not have been) established using the same procedure. Such a calculation would result in a longer WDP created artificially by improper manipulation of the data set. It is more straightforward to simply continue to insist on a method that meets the GL 49 guidance and then use that method to establish both the MRL and the WDP using uncorrected data. **Proposed change:** These lines should be deleted as the philosophy is incorrect.	
349	3.	**Comment:** Typing error in Cochran test **Proposed change:** Replace “Chochrane test” with “Cochran test”	Agreed.
370-371	3.	**Comment:** In plasma, the half-life is a well described secondary parameter and based on the slope of the linear regression line if the decline is monoexponential. If it is a biexponential process, interpretation has to take into account the 2 phases and the 2 slopes. This notion could not be extrapolated to tissue in order to avoid a misunderstanding between the plasmatic half-life and this “new parameter”. Elimination	It is agreed that tissue depletion half-life is not the same parameter as the plasma half-life. It is proposed to use the more precise term ’terminal tissue depletion half-life’.

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		process in tissue could not be summarised with this parameter to define a safety span without a clear explanation. **Proposed change:** please delete or clarify this parameter.	The lines in question are describing an alternative option to obtain a scientifically justifiable safety span. This option is only viable if the terminal tissue depletion half-life (i.e., if the tissue distribution is completed) is known, or if a sound estimation can be made on the basis of existing tissue depletion data. In this case, the tissue depletion half-life estimate is a conservative and valid scientific tool.
372 – 382	3.	**Comment:** The illustrations of how to select a correct safety factor using the alternative procedure is welcome. It has been our experience that in most all cases, authorities default to the 30% extension when the risk to human health is low or negligible. The WDP extension should be proportional to the risk of the adverse event.	Agreed. However, the extent of the safety factor should not be based on the risk of the adverse event (the risk assessment has already been done before the MRL was set) but should account for variability of and overall confidence in the residue data.
383 – 384	3.	**Comment:** The suggestion that the longer safety factor extension be required when residues are below MRL prior to 10 days seems inconsistent with the entire alternative proposal. The logic for a safety factor should be independent with respect to this arbitrary value. A short time period until residues fall below an MRL indicates more rapid depletion kinetics. Therefore, the additional safety span should be expected to have a similar proportional effect to residues that fall below the MRL after 10 days. This recommendation seems quite arbitrary and is not well-substantiated by known examples.	Not agreed. However, an amendment has been made to make it clear that if a short withdrawal period of less than 10 days is calculated, the underlying data typically show a large(r) variation, especially at early data points. Hence, to account for this, a longer safety span should be considered. This can be decided on a case-by-case basis, depending on the variability of the data submitted, and with a good justification by the applicant. It is

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		Proposed change: Please delete this bullet point.	not expected to be a default position, but to be part of the decision-making process.
536-542	3.	**Comment:** While we agree that the residues must deplete statistically to below the respective tissue MRLs and that the ADI must not be exceeded when IJS residues are taken into account, statistical evaluation and depletion of injection site residues to below the ISRRV is an inappropriate application of policy and this requirement should be deleted. According to CVMP draft Reflection paper on injection site residues: considerations for risk assessment and residue surveillance, the ISRRV is not an MRL and as such, it is not included in Regulation (EU) No. 37/2010 and should not be used for routine residue surveillance. The purpose of this value is to provide guidance to surveillance personnel in the event that a "high" muscle value is obtained during a targeted analysis. Therefore there is no added safety value to calculate a WDP based on the ISRRV**.** On 99.9% of the occasions when muscle is analysed, residues will be well below the MRL provided the WDP is followed. On the rare occasion, where a surveillance result exceeds the MRL by a wide margin (due to collection and sampling of an IJS), the ISRRV serves as a reference point. An observation of a high residue value during surveillance would indicate that an IJS had probably been sampled, which may trigger additional laboratory investigation but would not, in itself, prohibit the carcass from entering the food chain. **Proposed change:** Delete all references for the need for statistical calculation of withdrawal periods based on depletion of IJS residues to below the ISRRV.	Not agreed for the following reasons: EMA/CVMP/520190/2007-Rev.1 (p. 5): *'The withdrawal period for the VMP is then derived in a manner that ensures that residues at the injection site will be below the ISSRV and that residues in non-injection site muscle, liver, kidney and fat will be below the MRLs for these tissues.* *This approach provides residue monitoring authorities with a single MRL for muscle while also allowing withdrawal periods to be derived that ensure consumer safety but which are not longer than necessary in order to do this.'* As clearly stated in the CVMP reflection paper on injection site residues, and alluded to in Regulation 782/2018, the ISRRV is not intended to be used for routine control purposes. However, it has to be taken into account for calculation of withdrawal periods to ensure that the sum of residues from the food basket (with injection site tissue accounting for muscle tissue) does not

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			exceed the ADI. This does also imply that the level of consumer protection, i.e. 95/95 % tolerance limit, is the same as for the other tissues. Therefore, the same approach has to be taken in relation to residues at the injection site when an ISSRV has been set, as for the other tissues with numerical MRLs set.
613-614	3.	**Comment:** The notion of a **strong causal** justification in the section "**6.4** Dealing with obvious outliers" seems an excessive wording, especially when the origin of the problem could occur during the *in vivo* phase e.g. injection site experiment, a very delicate study. The true origin of the problem is never well established in animals and the relation cause and effect may always be reconsidered. **Proposed change: "**defined as statistical outliers should only be accepted if there is a ~~**strong causal**~~ justification (e.g. dosing error, sick animals, obvious sampling/analytical error)."	Partially agreed. We suggest deleting 'sick animals' as an example of a causal justification, as the term might be misleading and it could be (mis-)understood that the withdrawal period is not applicable to 'sick animals', which are the actual target population for a VMP. Proposed change: '…defined as statistical outliers should only be accepted if there is a causal justification (e.g. dosing error, obvious sampling/analytical error, any of which should be properly documented).'
882-886 (Annex D)	3.	**Comment:** There is no objection to the requirement that different formulations (injectables) need full assessment of IJS residue depletion, but why must this result in "equivalent (or faster)" depletion rates. The study result could be the same, or shorter or longer with respect to withdrawal time. It is not clear why the guidance seems to indicate that	Not agreed. If the IJS depletion is not equal or faster, this is an indication of a slower absorption from the injection site; residue depletion at the injection site could possibly therefore be longer (in comparison to the

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		the withdrawal time cannot simply stand on its own results. **Proposed change:** delete “equivalent (or faster)” and modify “depletion of residues from the injection site should be appropriately demonstrated.”	reference product). Hence, the withdrawal periods established for the reference product could not be directly applied to the generic, and further residues data may be necessary (depending on other available data, which may support the absence of new depletion data). If plasma BE is demonstrated (Art 13(1)), then a change of WP compared to the reference product is not considered to be appropriate when equivalent (or faster) depletion from the injection site is demonstrated. In the case where depletion from the injection site is slower, the injection site may determine the withdrawal period. The applicant for the generic product will not know which tissue(s) determined the WP for the reference product.
887 to 889	3.	Comment: The determination of residues data from the application site is not possible with the current guidelines. For the topically applied products, no sample of the application site is performed currently in residue depletion studies. How do you want to obtain residues data from the application site? In which case residues data from the site of administration would be	Partially agreed. The lines 887-889 are conveying the same notion as the Bioequivalence GL (EMA/CVMP/016/00-rev.2) under point no. 4.4: ‘…bioequivalence or waivers cannot be used for extrapolation of withdrawal periods between products with a potential to leave local residues (for example

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		required? Proposed change: Please clarify	intramuscular and subcutaneous injectables, dermal and transdermal applications). In this case, information in the behaviour of residues at the site of administration needs to be assessed before the withdrawal period is extrapolated.' The commenter notes correctly that current GLs do not provide guidance on sampling of application sites, apart from injection site. The GL has therefore been clarified to indicate which tissues would be appropriate to sample from the site(s) of application.