International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VICH/12/056
FINAL

PUBLIC CONSULTATION AT STEP 4 OF THE VICH PROCEDURE
OVERVIEW OF COMMENTS RECEIVED

VICH draft Guideline 54 - Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD)

VICH EWG: SAFETY

Name & Country of individual, organisation, or VICH delegation that commented

Comment n°	Name - Country
1	Chinese Taipai
2	Morocco
3	American Veterinary Medical Association (USA)
4	Silvia Pineiro (USA, Chair of the Former VICH eWG on mADI)
5	Tong Zhou (member of VICH eWG on Safety – USG)
6	Carrie Lowney (member of VICH eWG on Safety - USA, AHI)
7	John Reeve (observer in VICH eWG – NZ)

Discussion of comments

GENERAL COMMENTS – OVERVIEW		
Comment N°	**Comment received**	**Outcome of consideration**
1	A. Is an ARfD required for all veterinary drugs? B. What are the criteria? C. What specific adverse effects should be considered? D. Can the clinically suggested dose limit of a veterinary drug be made as its ARfD? E. What supporting data/documents should be collected/reviewed so as to waive and then derive an ARfD during registration?	A. and B. The current scope explicitly explains that the VICH guidance does not address when a national or regional authority might require an ARfD. Accordingly, it cannot provide detailed guidance on the necessary criteria. C. Page 5 of the current guidance describes examples of adverse effects that may be considered as the basis for an ARfD, and refers the reader to OECD GL 124 and EHC 240 for more detail. D. We do not currently address this issue of a dose limit as this falls outside of the scope of the current document. E. Studies that might be useful in the derivation of an ARfD are described in section 2.2.1 and 2.2.2 of the draft guidance.

3	We wish to express our support for FDA's efforts promoting international harmonization through VICH and see GFI #232 (VICH GL 54) as a step forward. We recognize that one of the goals of harmonization is to identify, and then reduce, differences in technical requirements for drug development among regulatory agencies in different countries. The AVMA understands that internationally harmonized guidances, such as GFI #232, contribute to innovation by supporting science-based regulatory policies and procedures supporting pre-approval product evaluations. They can also contribute to reducing product development costs; reduced numbers of animals used in product development, and reduced time to approval which helps increase availability of new products for use in veterinary medicine, over a shorter period of time	No changes were considered necessary based on these comments.
6	Based on review of the documents and correspondence from the microbiological task force, we see there is no suggestion, or explicit statement from the microbiological task force members email (either in meeting minutes, or response to questions, attached), that the mADI = the acute reference dose, or that it can be used as a substitute as stated in the current VICH GL54 draft 4. Here's what the microbial ADI task force members who wrote VICH GL36 recommended: *"The members also agreed that both the acute and chronic toxicity to the human gastrointestinal microflora are already addressed in the VICH Guideline 36, therefore the safety EWG may only refer to this guideline for this issue. "*	Considering these and other comments, changes were to the guideline. In Section 1.3*:* "Recognizing international efforts to address possible acute effects of residues of an antimicrobial veterinary drug on the human intestinal microbiota, the current guidance only provides a harmonized approach to a toxicological ARfD at this time." In Section 2.3 all language that addresses the microbiological was deleted, with the final sentence to read: "When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health."

SPECIFIC COMMENTS ON THE TEXT OF THE GUIDELINE

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
Section 1, Introduction	2	The elements which explain the general objective of this study or GL are missing.	The objectives for the current guideline are provided in section 1.1, Objective. Additional language was inserted in section 1.3, Scope of the current guideline, clarifying the use of the guidance for development of an ARfD in support of veterinary product registration.
Section 1.3, Scope, paragraph 1	2	Provide more information on the scope of the proposed guidance. Clarify whether it includes new substance/molecules.	When an ARfD is, or is not needed, is considered to be outside of the scope of the current guideline. As currently written, it is up to the regulatory authority to determine whether an ARfD would be applicable to new substances/molecules.
Section 1.2, Background, paragraph 2	2	Provide more description, with examples of molecules or bibliographic references.	More extensive examples are provided in OECD GL 124, as well as the 2005 publication by Solecki, et al. The full references are provided in the draft.
Section 1.2, Background, paragraph 3	2	It would be interesting to refer to an annex explaining the type of molecule that could be concerned by the ARfD approach.	The decision on whether an ARfD is needed or not is outside the current scope of this guidance. However, it is noted that discussion within OECD Guidance No. 124, and the 2005 publication by Solecki, et al. note certain classes compounds, particularly those with receptor based pharmacological effects, are more likely to be of concern.
Section 1.2, Background, paragraph 4	2	It is often referred to the OECD Guidance. It might be more appropriate to include the OECD requirements in this GL (by stating that the requirements originate from the OECD Guidance).	The eWG considered this approach, but determined that it would be more appropriate to point to the OECD document rather than repeat the information described there. However, additional language was included more explicitly referring the reader to OECD Guidance 124.
Section 2.2.1, Use of	2	It is often referred to the OECD Guidance. It might be more appropriate to include the OECD requirements in this GL (by stating that the requirements	See response to comment above

traditional repeat-dose toxicology studies, paragraph 2		originate from the OECD Guidance).	
Section 2.3, How to derive an ARfD, paragraph 3	2	The uncertainty factor is not defined in this GL: it does not provide information on the sources which enable to calculate them or to find data which enable to calculate this factor which can make the implementation difficult or unharmonized.	The uncertainty factor is defined in the existing glossary of the draft VICH guidance. Specific language has been added to the VICH guidance pointing to Step One of the Tiered Approach for the Derivation of an Appropriate ARfD within OECD Guidance No. 124. This section of the OECD guidance discusses selection of the uncertainty factor.

SECTION ….			
Line No.	**Comment N°**	**Comment received and rationale; proposed change**	**Outcome of consideration**
Section 1.3, Scope of the current guideline, paragraph 3 Section 2.3, How to derive an ARfD, second to last paragraph	4	In order to avoid any misunderstanding and inconsistencies, and to best represent the final conclusions of the mADI EWG, it is recommended to remove the following two sentences from the VICH GL 54 Step 4: • "Therefore, in the case of acute effects on the human intestinal microflora, this microbiological ADI can serve as a value to address the acute microbiological endpoint." • "Because the process for the derivation of a microbiological ADI for acute or chronic effects is the same, the microbiological ADI can serve as a value to address acute microbiological effects."	Considering these and other comments, changes were made to the guideline. In Section 1.3*:* "Recognizing international efforts to address possible acute effects of residues of an antimicrobial veterinary drug on the human intestinal microbiota, the current guidance only provides a harmonized approach to a toxicological ARfD at this time." In Section 2.3 all language that addresses the microbiological was deleted, with the final sentence to read: "When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health."
Section 1.3 Scope of the current guideline, paragraph 3	5	A. Replace the term "microflora" with the new term "microbiota. B. ARfD is not lower than ADI (because if an ARfD is lower than the ADI, then the ADI would normally be established at the same numerical value as the ARfD, see EHC 240), so ADI can serve as a conservative value to address the acute effect. Would it be the same situation for the microbiological endpoint? If so, then this statement [*Therefore, in the case of concerns for acute effects on the human intestinal microflora, this microbiological ADI can serve as a value to address the acute microbiological endpoint*.] is not incorrect. If it is changed to "this microbiological ADI can serve as a conservative value to address the acute microbiological endpoint", would it address the concerns raised?	A. The phrase "human intestinal microbiota" accepted into the document. B. These comments are no longer relevant based on the changes made to section 1.3 regarding a microbiological ADI.

Section 2.2.1, Use of traditional repeat-dose toxicology studies, paragraph 2, second sentence	5	Insert "pharmacological effects" to the sentence "Endpoints could include, but are not limited to, haematoxicity, immunotoxicity, neurotoxicity, hepatotoxicity, nephrotoxicity, developmental effects, reproductive effects, pharmacological effects, and direct…"	This change was made.
Section 2.3, How to derive an ARfD, second to last paragraph	5	Please see related comments for this paragraph provided in section 1.3	Considering these and other comments, changes were to the guideline. In Section 2.3 all language that addresses the microbiological was deleted, with the final sentence to read: "When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health."
Section 3, Glossary	5	A. For the definition of the ARfD, delete "no more than' so that it reads "An estimate of the amount of residues expressed on a body weight basis that can be ingested in a period of 24 h or less without adverse effects or harm to the health of the human consumer." B. For the definition of BMD, the dates for the embedded citations may need to be updated.	A. The proposed change to the definition of ARfD was made. B. The dates have been updated (2015 for EPA BMDS, and 2014 for RIVM PROAST.
Section 5, Annex 1.	5	Minor formatting edits provided for the flow chart.	The proposed edits to the flow chart were accepted.
Lines 105-113. Section 1.3, Scope of the current guideline,	6	Delete the sentence, "Therefore, in the case of acute effects on the human intestinal microflora, this microbiological ADI can serve as a value to address the acute microbiological endpoint."	Considering these and other comments, changes were made to the guideline. In Section 1.3*:* "Recognizing international efforts to address possible acute effects of residues of an antimicrobial veterinary drug on the human intestinal microbiota, the current

paragraph 3			guidance only provides a harmonized approach to a toxicological ARfD at this time."
Lines 247-251. Section 2.3, How to derive an ARfD, second to last paragraph	6	Delete the sentence, "Because the process for the derivation of a microbiological ADI for acute or chronic effects is the same, the microbiological ADI can serve as a value to address acute microbiological effects."	Considering these and other comments, changes were to the guideline. In Section 2.3 all language that addresses the microbiological was deleted, with the final sentence to read: "When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health."
Section 1.3, Scope of the current guideline, paragraph 3 Section 2.3, How to derive an ARfD, second to last paragraph	7	I have been thinking about the issue raised by Dr Lowney, and on looking at the VICH Guideline 36, and the recently available summary of the 81st JECFA, it seems clear to me that the relevant microbiological endpoint from GL 36 for potentially determining an acute reference dose is the disruption of the colonisation barrier. Thus the wording in GL 54 that is being suggested for removal may be able to be tweaked so that it simply states that "The microbiological endpoint informing an acute reference dose is the disruption of the colonisation barrier that is discussed in GL 36" - and avoid mentioning the microbiological ADI which takes into account both this and antimicrobial resistance endpoints.	Considering these and other comments, changes were made in response to these comments. In Section 1.3*:* "Recognizing international efforts to address possible acute effects of residues of an antimicrobial veterinary drug on the human intestinal microbiota, the current guidance only provides a harmonized approach to a toxicological ARfD at this time." In Section 2.3 all language that addresses the microbiological was deleted, with the final sentence to read: "When an ARfD could be determined based on toxicological and/or pharmacological endpoints, the ARfD should be based on the endpoint that is most relevant for protecting public health."