IFAH-EUROPE COMMENTS TO THE PUBLIC CONSULTATION PAPER
IMPLEMENTATION OF THE NEW REGULATION ON MAXIMUM RESIDUE LIMITS

CONTRIBUTION FOR A FUTURE COMMISSION REGULATION ON FORMAT AND CONTENT OF APPLICATION AND REQUESTS SUBMITTED FOR AN OPINION ON MAXIMUM RESIDUE LIMIT FOR A PHARMACOLOGICALLY ACTIVE SUBSTANCE

06/07/2009

GENERAL COMMENTS
IFAH-Europe is pleased with the opportunity to contribute to a preliminary proposal for the format and content of applications for an MRL opinion. Industry has made a comparison of existing MRL requirements, MAA requirements as specified in the new Annex I, and the proposed new MRL requirements, as shown in the table in the annex of this document. It is important to us to have consistency between the MRL and MAA dossiers to avoid unnecessary reformatting of information for new applications for food-producing species. In general, the new MRL proposals meet this need (some exceptions are noted in the table) and are much clearer than the existing MRL requirements, which are, in some places, contradictory.As should be expected, the proposed content of the dossier is quite comparable to the previous Annex V of the Reg 2377/90. However IFAH-Europe would like to suggest additional amendments as described in the table below. <u>For consideration during the updating of Notice to Applicants, Volume 8,</u> IFAH-Europe would like to draw your attention to the following opportunities to improve Notice to Applicants Volume 8: - Annex V of 2377/90 is currently "hidden" in Part II. III (General Information) of Notice to Applicants Volume 8. The new Annex should be much more clearly labelled and easier to find. - Practically, for Article 9. Active substances, it would be helpful having a clear description of how a MS or the EU Commission or an interested party (like a practitioner) should proceed during applications. This should include the system for the EU commission or a MS to provide a detailed critical summary and the source of funding for this exercise (taking into account that from the applicant's experience, the constitution of a dossier is quite resource consuming).

Section	Proposed changes to the MRL dossier content	Outcome (if applicable) *<to be completed by DG ENTR>*
Page 5, last §	*"… included in a* ***medicinal product intended to be used pursuant to Article 11 of Directive 2001/82/EC*** *and no…"* The Article 11 of Directive 2001/82/EC concerns the records of a veterinarian. ***Proposal:*** Please correct as follows: *"… included in a* ***medicinal product intended to be used pursuant to Article 11 of Directive 2001/82/EC as amended*** *and no…"*	
A. Safety file 2nd bullet point ***B. Residue file*** 2nd bullet point	The requirement for *"- a statement confirming that all data known to the applicant at the time of submission…"* is contradictory to § 3 in the *Introduction* section (point 3) and Dir. 2009/9/EC that state *"All information* ***which is relevant*** *to the evaluation* of the safety of residues of the substance concerned shall be included in the application..." At the time industry commented on the Annex 1 of the Directive, the proposal to add *information relevant to the evaluation* was accepted by the Commission. This is scientifically sound since many studies are very preliminary and should not be considered as relevant for the final assessment of the substance. ***Proposal:*** Please amend the second bullet point on page 2/6 (under Safety file) and the second bullet on page 5/6 (Residue file) as follows: *"- a statement confirming that all data known to the applicant at the time of the submission, whether favourable or unfavourable, are included if relevant to the evaluation."*	
A. Safety file 5th bullet point ***B. Residue file*** 5th bullet point	*"- a discussion of the contribution that any study that pre-dates studies performed in line with GLP according to…"* Industry understands that pivotal studies must be GLP, and we appreciate the possibility to discuss the contribution that any non-GLP study makes to the overall risk assessment. The use of relevant and scientific literature (e.g. IARC analysis, scientific papers, etc.) is useful to support arguments and provide clarification. In addition, these data are important for substances falling into Article 9 (non registered substances). We assume that this is the correct interpretation of this bullet point. It could be made clearer with the following amendment: *"- a discussion of the contribution that any non-GLP study (i.e. a study that pre-dates studies performed in line with GLP according to Directive 2004/10/EC)…"*	

Section	Proposed changes to the MRL dossier content	Outcome (if applicable) *<to be completed by DG ENTR>*
A. Safety file last bullet point	Regarding the content of the individual study reports, the request to include the *"relevance of the results for the evaluation of potential risks presented by residues to humans"* makes no sense. The studies, in particular the toxicity studies, are not performed with the only goal to address the safety of residue. At the time of report writing, and particularly at CROs, such an evaluation can not be made. In many cases, studies are performed at early stage of development (e.g. for human drug development), and even the formulation may change. Hence, what was relevant at that time may not be anymore at the time of dossier submission. It should be up to the expert to summarise the data and discuss the findings in this context. ***Proposal:*** If discussion by the expert (or the applicant) is required in addition to the critical summary, this should be in a separate document.	
A.1 10th bullet point	It is not clear if it is each batch used in the safety evaluation, or the specifications of the active ingredient that should be assessed for the *"Qualitative and quantitative composition of impurities"*. ***Proposal:*** Please clarify.	
Detailed and Critical Summaries and sections A.2 – A.5 and B.1	With the introduction of Chapter 3 in the MRL Annex, *Detailed and Critical Summaries* seem superfluous. Furthermore they are not explicitly required in the new MRL regulation. The sections ***A.2 – A.5 and B.1*** represent the basic toxicology and residue data packages, respectively, for the dossier. These studies are discussed in detail here and the key data are reproduced in summary form (tables and graphs). While critical reviews of these studies are important components of the dossier, these assessments can be included within this section of the dossier (***A.2 – A.5 and B.1)***. The generation of separate Expert Reports under A.0 and B.0, where the identical studies are discussed and summarized, often using the exact same tabular and graphical presentations, is repetitive and unnecessary. ***Proposal:*** It is suggested to delete the A.0 and B.0 sections include the Expert comments for each study as part of A.2-A.5 and B.2, as appropriate. If *Detailed and Critical Summaries* are to remain, we would suggest maintaining the old name *"Expert Report"* to avoid confusion, and the tabular formats in NtA Vol. 6B should be reviewed and simplified.	

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B.2	It is not clear what the "monitoring and exposure data" are meant to be about. For a new substance, such data would not exist, and for an older substance, it would be very difficult for companies to get these data from the surveillance labs.	
B. Residue file last bullet point	*"- a detailed description and a through discussion of the results of the study and their relevance for the establishment of maximum residue limits"* Please also refer to our comments to "*A. Safety file, last bullet point*". The statement above makes no sense. The studies, particularly PK studies, are not performed with the only goal to address the residue. In many cases, studies are performed at an early stage of development and also for efficacy purpose. In addition, it is practically impossible to discuss the relevance of each study on determining the MRL, as this is defined based on the overall fate of the substance, the ADI, the analytical method, etc. ***Proposal:*** If discussion by the expert (or applicant) is required in addition to the critical summary, this should be in a separate document.	
Chapter 3	This new chapter makes sense as an overall conclusion based on safety and residue aspect. ***Proposal:*** For a practical aspect, we would suggest merging Chapter 1 and Chapter 3 in one chapter "*Summary*" that would contain *Part 1- Administrative data*, *Part 2 – Summary of the evaluation*, and *Part 3 - Risk management considerations*. In this section, reference is made to Article 7-Risk Management recommendations- of Regulation xxx/2009. The revised MRL Regulation Art 7 includes (a) the "*assessment of the availability of alternative substances for the treatment of the relevant species or the necessity of the substance evaluated in order to avoid unnecessary suffering for animals <u>or to ensure the safety of those treating them</u>*." However, the scope of the MRL Regulation is to protect the health of the consumer and not the user, whose safety should be protected through the so-called User Safety section of the marketing authorisation application. ***Proposal:*** Please omit the reference to Article 7, and also consider this on the next revision of the MRL regulation.	

Annex

Reg 2377/90 Annex V and NtA Vol 8 (old)	Dir 2001/82 Annex I, as amended by Dir 2009/9 (new)	Reg xxxx/2009 Annex, based on EMEA/CVMP/126767/2009 (new)	IFAH-Europe proposal
A.0 Expert Report	Detailed and critical summaries of safety tests (Art 15, Art 12(3)j)	A.0 Detailed and critical summary	With the introduction of Chapter 3 in the MRL Annex, Detailed and Critical Summaries seem superfluous. Also, they are not specified for MRLs in the new Regulation. See introductory comment for more detail. If they remain, the tabular formats in NtA Vol 6B need reviewing/simplifying
3.3 Tolerance in the target species	3.3 Tolerance in the target species		Omission of this section makes the MRL numbering different to the MAA numbering from this point on. IFAH-Europe suggests keeping it as *"Tolerance in Target Species, <u>if applicable</u>"*
B.0. Expert Report	Detailed and critical summaries of residue tests (Art 15, Art 12(3)j)	B.0. Detailed and critical summary	With the introduction of Chapter 3 in the MRL Annex, Detailed and Critical Summaries seem superfluous. Also, they are not specified for MRLs in the new reg. See introductory comment for more detail. If they remain, the tabular formats in NtA Vol 6B need reviewing/simplifying.
B.1. Precise identification of the substance concerned by the application.	1. ??? (introductory text only in Chapter I, but "identification of the product" in Chapter II)		In MAA, please combine B.1 with A.1. It is unnecessary repetition and makes the numbering of Part B different from the MRL.
4.2.4 LOD	LOD	LOD	This requirement should be deleted as it is not relevant. The LOQ is the critical component.