26 January 2024
EMA/CVMP/244888/2022
Committee for Veterinary Medicinal Products

Overview of comments received on Guideline on determination of the need for an MRL evaluation for biological substances (EMA/CVMP/SWP/591282/2021)

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

Stakeholder no.	Name of organisation or individual
1	AnimalhealthEurope
2	Access VetMed

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	AnimalhealthEurope welcomes the opportunity to comment on this draft guideline. While this guideline (lines 98-102) aims to allow for determination of the need for an MRL evaluation for biological substances, technical guidance on the conduct of certain studies to meet the requirements of Annex I of Commission Regulation (EU) 2018/782 is not within the scope of this document. The need for such technical guidance may be identified based on the experience gained and lessons learnt from the implementation of this guideline and will be dealt with in follow-up guidance (technical guidance on the conduct of certain studies not in scope of the guideline, need for such guidance to be identified based on the experience gained/lessons learnt from implementation of the guideline). Therefore, it remains unclear how to deal with the resulting uncertainty for Applicants until technical guidance is established	We thank AnimalhealthEurope for their comments. It is noted that further technical guidance is highly appreciated. As assessment of consumer safety for biologicals is a new approach, some more experience is needed before technical guidance can be given. Applicants are invited to seek scientific advice before an application is made.
1	Lines 147 -149 state that "Mixtures consisting of several biologicals which contain (at least) one 'chemical-like' lead substance (defined by its chemical structure, its toxicological relevance and/or its relevance as residue(s) in food from animal origin) are assigned to the group of 'chemical-like biologicals'. In the absence of formal technical guidance, it is unclear how to define ADIs and MRLs as well as how to establish withdrawal periods for the single molecules within a mixture. For example, would a single primary constituent or metabolite be selected as the marker residue for MRL establishment, or would several components of such a mixture need to be considered? Would the toxicological relevance of a single "main" constituent need to be compared to that of the complex mixture/crude preparation?	In lines 147 - 149 mixtures naturally occurring together are addressed, e.g. plant extracts consisting of different biologicals of which one is a 'chemical-like' lead substance. What is not meant here are compilations of different biologicals. To make this clearer "naturally occurring" is added in line 147. As those naturally occurring mixtures which contain (at least) one 'chemical-like' lead substance are assigned to the group of 'chemical-like biologicals', in principle all substances are part of the MRL assessment. The applicant needs to show whether only the lead substance(s) is/are of relevance in terms of toxicity and residues or whether further components also need to be considered.

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		In case of ambiguities applicants are welcome to seek scientific advice to clarify things in advance of the application.
1	Section 5. Assessment of concerning the need for an MRL application (215-364): The step-wise/decision tree approach in the draft guideline provides a well-structured framework for orientation and is welcome. However, for some questions it remains unclear how to conduct evaluation due to experimental difficulties (e.g. bioactivity, comparison of bioavailability, extent of inactivation in the GI tract allowing to conclude on "relevant inactivation" etc). Moreover, it appears that the assessment of the need for an MRL evaluation already addresses some crucial questions that needs to be discussed in an MRL assessment. Hence, practical experience will show how much flexibility and simplification is introduced by this new guideline.	It is noted that the step-wise/decision tree approach is approved in principle. As only limited experience regarding consumer safety assessment for biologicals is available so far, further experience is necessary to fully assess the practicability of the system. Yes, the assessment of the need for an MRL evaluation already addresses some crucial questions that need to be discussed in an MRL assessment. As these are the key issues to be clarified to assess consumer safety, this is considered the only feasible approach.
2	Number the questions in the decision tree and refer to them by number where appropriate (eg. 'see next but one step - line 303, replaced with 'see question XX').	Accepted. The stakeholder is thanked for their suggestion. Numbers are now included in the decision tree and the respective sections in the text refer to these numbers. The reader needs to be aware that the numbering does not imply the order in which the questions are to be gone through. A footnote to address this was added.
2	Remove unclear wording such as 'relevant matter' in the decision tree in order to facilitate straightforward Y/N answers, the U (unknown) already adresses uncertainty/lack of information.	Not accepted. For biological processes in many cases no black/white decision can be taken and the relevant manner has to be taken into account for a decision. E.g. for the question on bioavailability (Question 7, see updated version of the GL) it may be the case that a certain biological shows very low bioavailability, which is assessed as not relevant and the question can be answered with 'N'. The next step would be Question 9 and probably the end of the procedure. In case of an 'U', a further step

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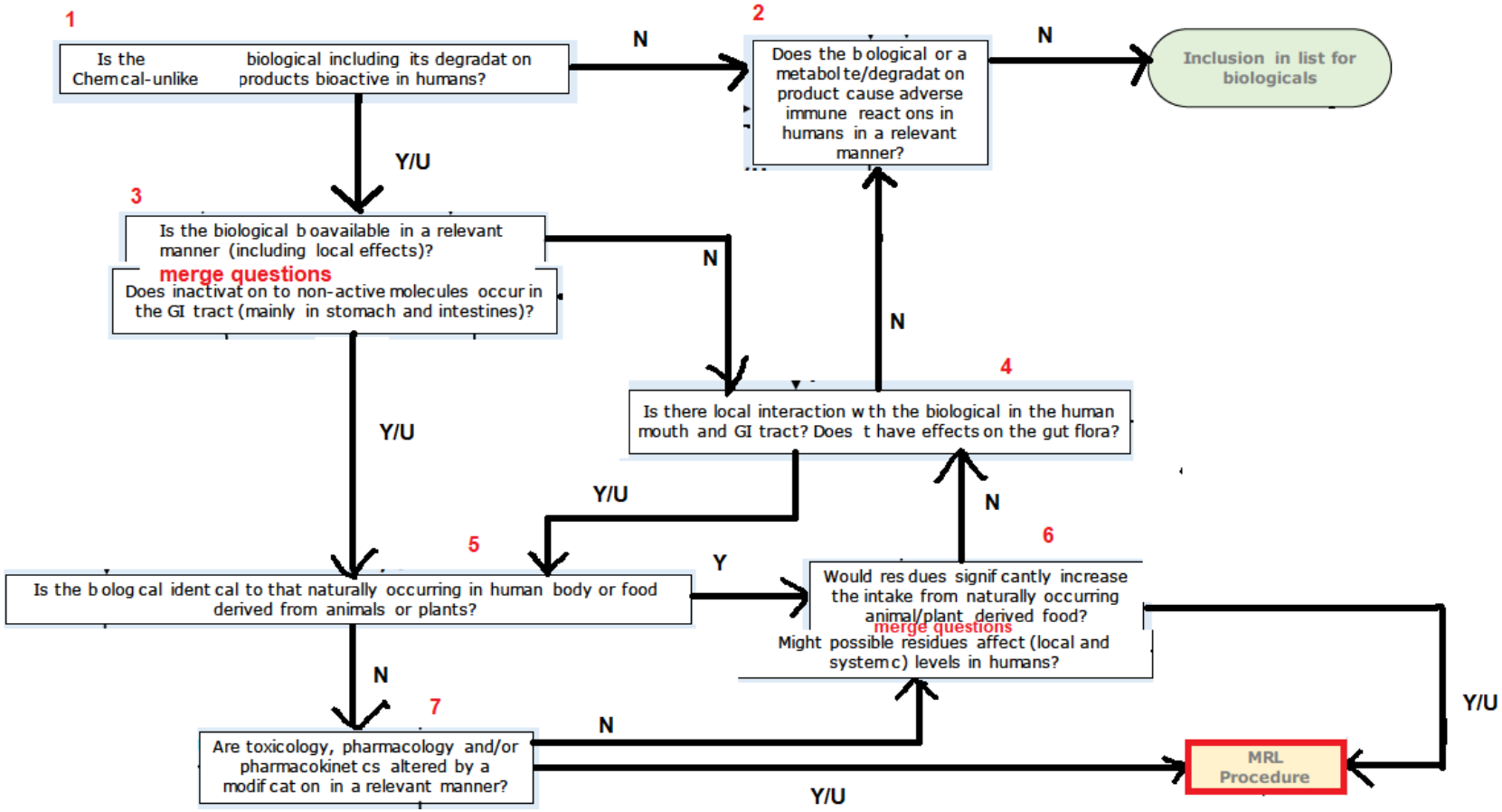
		(Question 8) would follow. 'U' (i.e. missing knowledge) is something different than bioavailability being lower than 100% or somewhere above 0%.
2	Except for the first question in the decision tree, where the question could refer specifically to the chemical-unlike biological non-immunological substance and its effects in humans, does 'the biological' in subsequent questions in the decision tree not refer to the residue(s) of the biological and not to the biological itself? The whole decision tree refers not to the biological itself (in the animal body) but to its residue(s) in the human body. The term 'residue' would also encompass not only the active substance itself but also its degradation products, metabolites etc. According to the definition in Reg. 470/2009: << 'residues of pharmacologically active substances' means all pharmacologically active substances, expressed in mg/kg or µg/kg on a fresh weight basis, whether active substances, excipients or degradation products, and their metabolites which remain in food obtained from animals >>	Not accepted. It depends on the question whether the biological itself or its residues are addressed. E.g. the questions on pharmacology, toxicology and pharmacokinetics refer to the biological itself. As a certain biological can only reveal bioactivity in humans in case residues remain in food derived from treated animals, a sentence on this aspect was added in the answer to the question on bioactivity (Question 1).
2	See next page (proposed alterations to decision tree according to proposals in the next table - specific comments on text).	Not accepted. By merging the questions more information has to be made available by the applicant compared to the 9 questions as currently stated. The current set of questions is designed to reduce the amount of information that needs to be provided as much as possible. E.g. if the questions addressing local interaction and the adverse immune reactions can be answered with 'N', no further information is needed and the substance can be included in the list for biologicals.


1
Is the Chemical-unlike biological including its degradation products bioactive in humans?
N
2
Does the biological or a metabolite/degradation product cause adverse immune reactions in humans in a relevant manner?
N
Inclusion in list for biologicals
Y/U
3
Is the biological bioavailable in a relevant manner (including local effects)?
merge questions
Does inactivation to non-active molecules occur in the GI tract (mainly in stomach and intestines)?
N
N
Y/U
4
Is there local interaction with the biological in the human mouth and GI tract? Does it have effects on the gut flora?
Y/U
N
5
6
Y
Is the biological identical to that naturally occurring in human body or food derived from animals or plants?
Would residues significantly increase the intake from naturally occurring animal/plant derived food?
merge questions
Might possible residues affect (local and systemic) levels in humans?
N
7
N
Y/U
Are toxicology, pharmacology and/or pharmacokinetics altered by a modification in a relevant manner?
MRL Procedure
Y/U

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
74-76	1	**Comment:** the wording "characterisation" has a specific meaning and may not fit the scope of the sentence – A rewording is suggested. **Proposed change:** According to Commission Regulation (EU) 2018/782, there are two groups of 'biologicals, other than immunologicals' to be distinguished: those that can be ~~characterised~~ **described** as 'chemical-like' and those ~~characterised~~ **described** as 'chemical-unlike'.	Accepted. The wording was modified accordingly.
122-131	1	**Comment**: this paragraph as currently worded raises concerns as it may be incorrectly interpreted and mis-used during discussions (outside the context of this present guideline) on the classification of some products as IVMPs or biologicals non-IVMPS. We suggest providing clarity on this topic. Additionally, there are authorised immunomodulators which should definitively be seen as IVMPs and outside of the scope for MRLs (for example, an immunomodulator consisting of inactivated parapoxvirus and used to stimulate non-specific immune responses). The fact that the product's indication is to raise unspecific immune responses should not in itself be sufficient to lead to MRL considerations – Essentially, every immunological product – like vaccines - may raise non-specific immune responses – in addition to the specific immune responses). And immunological active substances are out of scope for MRLs.	Agreed. This part of the definition of 'Biologicals other than immunologicals' was removed. The CVMP will take the decision whether a substance is a biological or an immunological, which then determines whether this GL applies or does not apply. In line with your request it was agreed that antibodies acting against endogenous proteins are classified as 'biologicals other than immunologicals', and are within the scope of MRL regulation and of this GL. However, the antigens stimulating the immune system to produce antibodies intended to act against endogenous proteins are classified as immunologicals, and are out of scope of the MRL regulation and of this GL. In case of uncertainty as to whether a particular substance belongs in this group or not, it is recommended that the applicant should contact EMA to clarify the classification in advance.

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		Proposed change: In the context of this guideline for the purpose of consumer safety assessment, biologicals having an immunological mechanism not targeting pathogens but dealing with internal processes (e.g. antibodies against endogenous proteins) are included in this definition. There are certain biologicals which can neither be clearly assigned to the group of 'immunologicals' nor to the group of 'biologicals other than immunologicals'. This could e.g. ~~be immunomodulators (triggering unspecific immune response) or~~ substances with a mode of action similar to that of immunologicals (stimulation of the immune system to produce antibodies intended to act against endogenous proteins). **While the latter products would be classified as immunological veterinary medicinal products under the Regulation 2019/6, a**~~A~~s they may have unknown properties of concern, they are treated like 'biologicals other than immunologicals' **for the purpose of this present guideline** to allow for a consumer safety assessment.	
136-137 and 160-162	1	**Comment**: Collectively, when reading the sentences on these lines around "chemical-like" and chemical-unlike" classifications, we are left with the impression that, in the group of proteins, only enzymes and "some glycoproteins" could be considered as "chemical-unlike". This may be overly restrictive – Is this really intended?	Not accepted. The definitions as currently stated offer certain flexibility. To further address this 'typically' is also included in line 136. Complex proteins belong the group of 'chemical-unlike' biologicals, whereas for simple proteins, which may e.g. act as protein hormones, a consumer safety assessment is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: please consider an alternative wording.	
142 and 161	1	**Comment**: unit (Dalton?) seems to be lacking **Proposed change**: please mention the unit.	Accepted. Unit was added to the text.
168-212	1	**Comment:** Information appear to be partially redundant to prior content **Proposed change:** Please revise and avoid duplication of information.	Not accepted. The guideline needs to follow the usual standard structure for GLs and sections need to be complete and should be able to stand on their own. Hence, some redundancy may strike you when reading the entire document but this needs to remain.
194 ff	1	**Comment:** Deviating font type used **Proposed change:** Use same font type as for the rest of the document	Accepted. Font types will be adapted.
248-249	1	**Comment:** Please improve the format of the decision tree (some information is hard to read).	Accepted. Errors have crept in here when converting to a PDF file. The document will be updated accordingly.
255-364	1	**Comment:** By definition, it is technically impossible to prove the absence of something – Therefore, we suggest that the wording used for the different questions under section 5.3 is adjusted accordingly – For example, "No" could become "unlikely" or "highly unlikely". The decision tree could also be adjusted to reflect new wording. **Proposed change:** Please adjust the wording.	Not accepted. It is acknowledged that it is not possible to prove the absence of something. However, this is already included in the wording of the questions. Whenever there may be no absolute 'Y' or 'N' answer possible, this is addressed by the term 'in a relevant manner'.
342-364	1	**Comment:** As mentioned above, it is impossible to prove the negative – The paragraph as it stands really opens the door for a lot of studies to be conducted to address the point. We would appreciate additional guidance being given on this specific point – For example, we would expect that the use of in silico tools for assessing immune-related risks together with general theoretical considerations would be	Partially accepted. Concerning 'prove the negative', please see the answer above. Regarding additional technical guidance, it is agreed that there is a need for this guidance which will be developed in further steps based on the experience gained. Previous procedures for inclusion of biologicals in the dedicated list have shown that the proposed approach is feasible. Whenever there may be uncertainties on how to proceed with the application for a

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		appropriate and (possibly sufficient) in many instances. **Proposed change:** Please consider provide some additional guidance in this regard with the objective to improve predictability of assessment outcomes.	certain biological, applicants are welcome to seek scientific advice.
11	2	**Comment**: Replace 'the biological' to clarify scope of guideline **Proposed change**: 'the chemical-unlike biological non-immunological substance' or variant	Accepted. The title of the GL was modified accordingly. It now states "Guideline on determination of the need for an MRL evaluation for chemical-unlike biological substances".
269	2	**Comment**: Replace 'biological substances' to clarify **Proposed change**: 'chemical-unlike biological non-immunological substances' or variant	Partially accepted. At the top of figures 1 and 2 a clarification of terms takes place, making clear that the questions raised in the decision tree do only cover 'chemical-unlike biologicals'. A footnote was added.
286 and 322	2	**Comment**: Bioavailability [Is the biological bioavailable in a relevant matter (including local effects)?] should be evaluated after bioactivity – if the biological and its degradation products are active in the human body but are not bioavailable, they should be evaluated for local effects, effects on the gastrointestinal flora and immunological effects. The question on inactivation in the GI tract is one of bioavailability. **Proposed change**: merge the bioavailability question with or move it before 'does inactivation on to non-active molecules occur in the GI tract?'	Not accepted. It is relatively complex to prove the bioavailability of a substance. Hence, this question is only raised at a later point in the decision tree. As already mentioned above, merging of questions increases the amount of information to be delivered. However, if an applicant already has data on bioavailability of a substance, he has the possibility to submit a different set of data as the inclusion of the 'Unknown' category allows for data gaps.
303	2	**Comment**: 'see next but one step. Replace 'step' because of the multiple steps possible from that box in the tree. **Proposed change**: 'see next but one question' (in the current order) or 'see question number XX'	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
317-319 vs. 336-340	2	**Comment**: Questions 'Would residues significantly increase the intake from naturally occurring animal/plant derived food' could be merged with 'Might possible residues affect (local and systemic) levels in humans?' Lines 317-319 If available data indicate that the biological naturally occurs in the human body and/or food, it needs to be quantitatively assessed whether ingestion of residues in animal derived food would significantly increase the concentrations naturally occurring. vs very similar Lines 336-340 For biologicals which are bioavailable in a relevant manner, possible effects of residues on endogenous levels in humans need to be assessed. If levels in humans are significantly affected (i.e. via residues of naturally occurring substances increasing levels in humans or via residues of foreign substances), data on nature and quantity of possible effects are needed and biologicals like this need to undergo a MRL procedure. **Proposed change**: Merge questions.	Not accepted. Merging of questions increases the amount of information to be delivered. It is relatively easy to show whether residues significantly increase the concentration naturally occurring in animal/plant derived food. If this can be answered with "N", only question 9 needs to be addressed before a decision can be taken.