EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

28 January 2022
EMA/CVMP/SWP/591282/2021
Committee for Veterinary Medicinal Products (CVMP)

Guideline on determination of the need for an MRL evaluation for biological substances

Draft

Draft agreed by Safety Working Party (SWP-V)	02 December 2021
Adopted by CVMP for release for consultation	19 January 2022
Start of public consultation	28 January 2022
End of consultation (deadline for comments)	29 April 2022

Comments should be provided using this template. The completed comments form should be sent to vet-guidelines@ema.europa.eu

Keywords	Biologicals, MRL evaluation, safety data, residue data, veterinary medicinal products

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 Un on

Guideline on determination of the need for an MRL evaluation for biological substances

Table of contents

Executive summary

Commission Regulation (EU) 2018/782 of 29 May 2018 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 introduces two groups of 'biologicals, other than immunologicals': while 'chemical-like' biologicals are subject to a standard MRL procedure according to Regulation (EC) No 470/2009, 'chemical-unlike' biologicals are evaluated according to the aspects listed in I.7 of Annex I to Commission Regulation (EU) 2018/782 on a case-by-case basis.

It is the intention of the guideline to provide a structured and transparent procedure on how to determine the need for an MRL evaluation according to Regulation (EC) No 470/2009 for 'chemical-unlike' biologicals. The substances are individually screened in regard to their possible consumer risks and data requirements are specifically identified according to the nature and properties of the biological under consideration.

To this end a step-wise (tiered) approach (decision tree) using a set of consecutive questions/criteria has been developed. The approach allows for a scientifically sound assessment while being sufficiently flexible to deal with a variety of different materials.

Two outcomes can result from the assessment procedure: (1) The biological can be added to the list of biologicals[1] if no MRL assessment is considered necessary, (2) An MRL procedure would be necessary if certain properties of the biological reveal that at least some data required for the establishment of MRLs according to Commission Regulation (EU) 2018/782 are needed to address consumer safety.

1. Introduction

Biological substances are a heterogeneous group of compounds used as active ingredients in veterinary medicinal products. According to Regulation (EU) 2019/6, they are substances that are produced by or extracted from a biological source and that need for their characterisation and the determination of their quality a combination of physico-chemical-biological testing, together with knowledge of the production process and its control.

Based on their specific nature, the standard assessment approaches currently used for MRL and consumer safety assessment do not always adequately match data needs and assessment requirements for biological substances.

It is the intention to provide guidance for determining whether there is the need for an MRL evaluation for a biological substance while ensuring consumer safety, to enable predictability of the assessment needs and to assist the applicant in preparing the information and data needed for such an evaluation. To allow for an assessment on the need for further MRL evaluation, this guideline provides a set of tailored criteria based on the data requirement aspects listed in I.7 of Annex I to Commission Regulation (EU) 2018/782.

Biological substances for which it is concluded that an MRL evaluation is not required will subsequently be published by the Agency in a list of such substances[1]. Biological substances for which an MRL evaluation is considered necessary need to undergo an MRL procedure according to Regulation (EC) No 470/2009 with the aim to be listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

[1] Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/572629/2019)

As immunological active substances are exempted from the need for MRL assessment according to Article 1 point 2 (a) of Regulation (EC) No 470/2009, this guidance concerns 'biological active substances other than immunologicals' only.

The guidance provided in this document is largely principles-based and general. However, if, during product development, an applicant wishes to have clarity on precise data requirements for the need of an MRL evaluation for a biological substance relating to a specific VMP, Scientific Advice is available upon request.

2. Scope

The objective of this guideline is to clarify the data requirements and rules for determination of the need for an MRL evaluation for biological non-immunological substances used in VMPs intended for use in food-producing species.

According to Commission Regulation (EU) 2018/782, there are two groups of 'biologicals, other than immunologicals' to be distinguished: those that can be characterised as 'chemical-like' and those characterised as 'chemical-unlike'. While the first group is subject to a normal (standard) MRL procedure according to Regulation (EC) No 470/2009, the evaluation of the latter group is to be conducted on a case-by-case basis.

This guideline aims to further clarify the terms 'chemical-like' and 'chemical-unlike' and presents a tailored approach allowing for a decision as to whether there is need for an MRL evaluation for a particular substance or not, and to identify the minimum data requirements for consumer safety assessment of 'chemical-unlike' biologicals. The approach takes into account the specific properties of biologicals as well as the fact that the types of studies and assessment approaches used for chemical compounds are not or are only partially applicable for certain biologicals. As this group comprises a variety of different materials the approach was designed to be flexible and to be used for a broad range of biologicals concerned.

A report, describing the scientific basis for the request on whether a full MRL evaluation is required or not, needs to be provided by the applicant. This report should be accompanied by the items listed in I.7 (a) to (e) of Annex I to Regulation (EU) 2018/782. The approach described in this guideline is intended to serve as a basis for the applicant to prepare the report and it should also allow for the European Medicines Agency to determine whether there is need for an MRL evaluation.

Depending on the outcome of this assessment procedure, biologicals can be included in the list of biologicals considered as not requiring an MRL evaluation[1] or should undergo a regular MRL procedure according to Commission Regulation (EU) No 470/2009 (resulting in a decision on whether and how they can be listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010). The list of biological substances not requiring an MRL evaluation as well as a summary of assessment of the substance is published on the EMA website.

While this guideline 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.

3. Definitions

Biological substance

'Biological substance' is defined as *a substance that is produced by or extracted from a biological source and that needs for its characterisation and the determination of its quality a combination of physico-chemical-biological testing, together with knowledge of the production process and its control* (Article 4(7) of Regulation (EU) 2019/6 of 11 December 2018).

The group of biological substances does not contain substances which are chemically synthesized.

Biological veterinary medicinal product

According to Article 4 (6) of Regulation (EU) 2019/6 of 11 December 2018 *'biological veterinary medicinal product' means a veterinary medicinal product where an active substance is a biological substance.*

Immunological veterinary medicinal products

According to Article 4 (5) of Regulation (EU) 2019/6 an *'immunological veterinary medicinal product' means a veterinary medicinal product intended to be administered to an animal in order to produce active or passive immunity or to diagnose its state of immunity.*

Biologicals other than immunologicals

'Biologicals other than immunologicals' are *biological substances* according to Article 4 (7) of Regulation (EU) 2019/6, which are not intended to produce active or passive immunity or to diagnose a state of immunity.

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).

As they may have unknown properties of concern, they are treated like 'biologicals other than immunologicals' to allow for a consumer safety assessment.

Chemical-like biologicals

According to Commission Regulation (EU) 2018/782 *'chemical-like biologicals' could be produced by chemical synthesis[2] and so present similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances.*

They do not belong to the group of biologic macromolecules (consisting of carbohydrates, amino acids and nucleic acids), lipids or biological organisms (e.g. cells, bacteriophages) but include substances derived from natural sources (herbal, bacterial, animal origin). Although derived from natural origin, no biological testing is needed for their characterization and/or for control during manufacture as they can be fully described by their physical-chemical properties. They likely have a structural formula and chemical name, a precise (discrete) molecular weight (MW), and a CAS number or other unique

[2] This is meant to be a substance produced by or extracted from a biological source but whose chemical synthesis is technically feasible.

identifiers. They typically have MWs lower than 10^3. Since they can also be expected to leave residues in the same way as chemical substances and so present similar concerns as chemical substances, they may be subject to residue controls.

The group of 'chemical-like biologicals' also includes substances which are chemically or otherwise modified in a second step. The modification needs to be considered in the assessment.

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'.

A number of active substances which were in use for long time in VMPs, like e.g. certain antimicrobial substances, can be assigned to this group.

Chemical-unlike biologicals

According to Commission Regulation (EU) 2018/782 *'chemical-unlike biologicals'* are *more complex than chemically synthetized pharmacologically active substances and they may contain multiple types of substances like cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products.*

This group contains biologicals which are typically characterised by their macromolecular nature and properties and a more variable, not precisely defined chemical structure(s) and a complex composition (depending on extraction/purification procedures well as on the source of origin and other factors). They cannot (or not readily) be produced by chemical synthesis and do normally not form residues.

Substances covered by the term 'chemical-unlike biologicals' typically belong to the group of biologic macromolecules with MW > than 10^3, consisting of carbohydrates, amino acids, lipids and nucleic acids, including highly complex combinations composed of these units (e.g. cells, bacteriophages, enzymes and some glycoproteins).

They cannot be fully described by their physical-chemical properties and, therefore, additional biological testing is needed for their characterisation and/or for control during manufacture.

The group of 'chemical-unlike biologicals' does also include biologic macromolecules which are modified in a second step. The modification needs to be considered in the assessment.

4. Legal basis

Regulation (EC) No. 470/2009 lays down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin. Article 1(1)(a) of Regulation (EC) No. 470/2009 defines its scope as follows:

"For the purposes of ensuring food safety, this Regulation lays down rules and procedures in order to establish:

a) the maximum concentration of a residue of a pharmacologically active substance which may be permitted in food of animal origin (maximum residue limit);"

Article 1(2)(a) of the above-referred Regulation states that:

"This Regulation shall not apply:

a) to 'active principles of biological origin intended to produce active or passive immunity or to diagnose a state of immunity, used in immunological veterinary medicinal products'."

Furthermore, Regulation (EU) 2018/782 establishes methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) 470/2009.

Section I.6 of the annex I to the above-mentioned Regulation provides that "Biological substances other than those identified in Article 1(2)(a) of Regulation (EC) No 470/2009 of the European Parliament and of the Council shall be:

(a) subject to normal MRL where the biological substance is chemical-like insofar as it could be produced by chemical synthesis and so presents similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances (e.g. cytokines, hormones);

(b) evaluated on a case-by-case basis where the biological substance is chemical-unlike insofar as being more complex than chemically synthesised pharmacologically active substances and so may contain multiple chemical types whose residues may generally be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products."

In addition, section I.7 of the annex I to the same Regulation states that "For chemical-unlike biological substances, a report describing the scientific basis for the request on whether a full MRL evaluation is required or not shall be required together with the following information:

(a) the nature of the biological substance (e.g. cell, tissue, live or killed organism) and a comparison with similar biological substances to which consumers are known to be routinely exposed;

(b) a description of the mechanism of action underlying the substances therapeutic effect and, if available, information on its potency;

(c) the fate of the substance in the treated animal (i.e. is it bioavailable, are residues expected in food commodities);

(d) any activity that the substance may have in the human gut (are the residues inactive or do they produce local effects);

(e) the systemic availability of residues following ingestion of residues by consumers, along with a worst-case consumer exposure estimate. The information provided above shall be evaluated in accordance with the guidance published by the European Medicines Agency ('Agency') in order to determine whether there is the need for a MRL evaluation. Biological substances for which it is concluded that a MRL evaluation is not required shall be published by the Agency in a list of such substances."

This guideline concerns the determination of the need for an MRL evaluation in the context of the above-mentioned sections I.6 and I.7 of Regulation (EU) 2018/782.

5. Criteria for the assessment of biological substances concerning the need for an MRL evaluation

5.1. General principle of the approach

The approach for determination of the need for an MRL evaluation for 'chemical-unlike' biologicals consists of guiding questions and criteria allowing for applicants to classify their substances and to collect the data required to address consumer safety. The set of step-wise questions has to be applied to each biological to allow for a conclusion on the need for further MRL evaluation.

While keeping regulatory requirements to a minimum, the approach aims to be sufficiently flexible and tailored specifically to the information needed to reach a meaningful, scientifically justifiable conclusion in each case. The efforts/requirements to answer the questions can be adapted based on properties of

the particular substance. This step-wise approach allows for identification of uncertainties or missing information, which should then be delivered in addition by the applicant.

Answers to the set of questions/criteria allow for hazard identification of biologicals with new/unknown properties, which might be of concern in terms of consumer safety. This procedure is conducted by the European Medicines Agency and may result in two possible outcomes (see Figure 1, green boxes):

- It can be decided that no further MRL assessment is necessary based on the properties of the particular biological substance ("substance with low consumer risk"). This would result in an inclusion of the substance in the list of biologicals[1].
- If the assessment reveals that an MRL procedure according to Commission Regulation (EU) No 470/2009 is necessary, MRL assessment requirements need to be applied to the substance concerned. The MRL procedure can result in inclusion of the biological substance in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

5.2. Step-wise assessment (Overview)

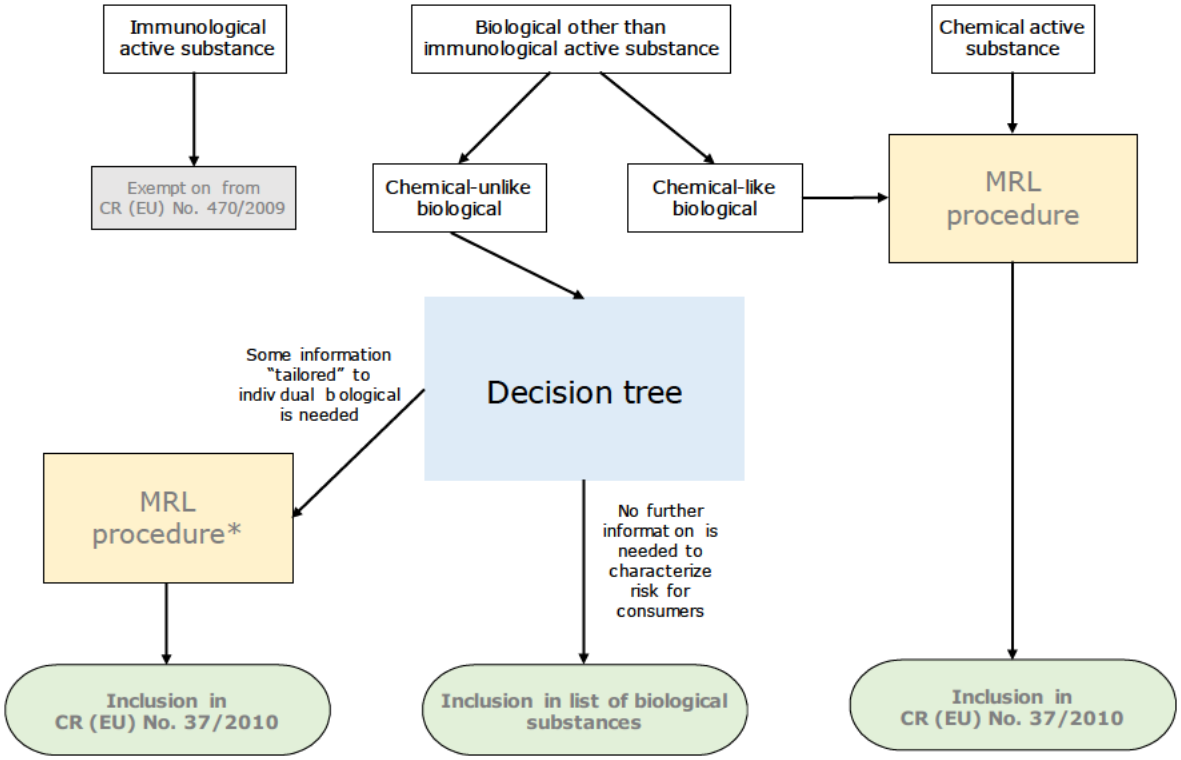
A step-wise (tiered) approach has to be applied to each biological to allow for a case-by-case assessment. The approach requires different levels and complexity of information depending on the biological concerned. An overview of the approach is provided in Figure 1.

The active substances to be dealt with here are 'biologicals other than immunologicals ' or considered as such. Other kinds of active substances (immunologicals and non-biological pharmacologically active substances, also called chemical active substances) are not within the scope of this guideline.

Within the group of 'biologicals other than immunologicals' there are two groups of biologicals to be considered (for details on definitions please refer to section 3):

(1) 'Chemical-like biologicals' are subject to a standard MRL procedure (yellow box) according to Commission Regulation (EU) 2018/782.

(2) 'Chemical-unlike biologicals' shall be assessed on a case-by-case basis according to Commission Regulation (EU) 2018/782. Details for their assessment are outlined in the decision tree (blue box, for details see Figure 2 below).



*Requirements to be adapted to the respective biological, possibility to omit some studies in an MRL application if this is justified

Figure 1: Stepwise approach for determination of the need for an MRL evaluation (Overview)

5.3. Step-wise assessment of chemical-unlike biologicals (Details)

For substances considered as 'chemical-unlike biologicals' information from a predetermined set of questions is needed to decide whether these may be added to the list of biological substances or whether they need to undergo a MRL procedure due to consumer safety concerns. Each of the questions can be answered with 'Yes', 'No' or 'Unknown', which then leads to the next question, respectively and eventually to a decision on further action (yellow/green boxes). The inclusion of the 'Unknown' category allows for data gaps, nevertheless the approach ensures that relevant information is provided for a conclusion on consumer safety.

The set of questions provided below covers the items listed in I.7 (a) to (e) of Annex I to Regulation (EU) 2018/782, except item (b) 'a description of the mechanism of action underlying the substances therapeutic effect and, if available, information on its potency'. Therefore, a brief description of the mechanism of action should be added to the report.

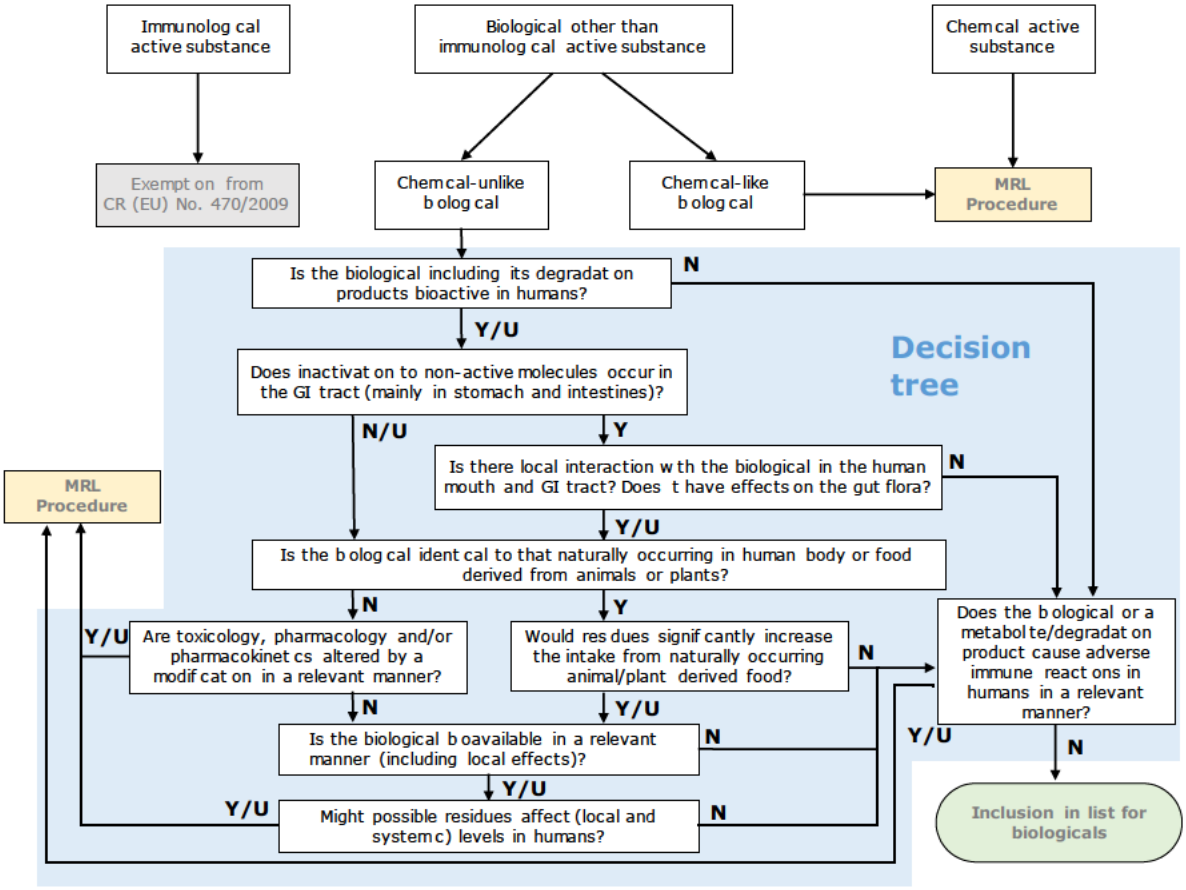


Figure 2: Stepwise approach for determination of the need for an MRL evaluation for biological substances (Details)
Y: 'Yes', U: 'Unknown', N: 'No'

Questions raised in the decision tree and implications of possible answers concerning relevance for consumer safety are described below:

Is the biological including its degradation products bioactive in humans?

Information on this aspect might be needed to decide whether the biological itself or its degradation products may have an impact on physiological processes in the human body. 'Bioactive' means that the biological can produce an effect (toxicologically, microbiologically or pharmacologically) in humans.

If the biological including its degradation products is not bioactive in humans, e.g. based on missing receptors for the particular substance and no cross-interaction, no (adverse) effects can be expected and no further data (except information on adverse immune reactions, see below) is needed. If there are effects of the biological on physiological processes in the human body or if this is unknown, further information based on the subsequent questions is needed.

Does relevant inactivation to non-active molecules occur in the GI tract (mainly in stomach and intestines)?

If the biological is bioactive in humans, but is inactivated in the gastrointestinal tract, systemic effects are unlikely to occur. In case of non-complete inactivation, one may consider that possible remaining concentrations of still potentially active fractions of the biological need to be lower than the relevant reference value (e.g. naturally occurring concentrations, recommended daily consumption).

If the question is answered with 'Yes', possible local interaction needs to be assessed in the following question. If the biological is not inactivated or if this remains 'Unknown', further information is needed.

Is there local interaction with the biological in the human mouth and/or GI tract? Does it have effects on the gut flora?

Since inactivation only occurs during the passage of the gastrointestinal tract, possible local reactions in the respective proximal parts must be taken into account. If there are data available showing that there are no local effects of the biological or its degradation products with mucous membranes of mouth cavity, oesophagus, stomach and/or intestines and that there are no effects on the gut flora, it can be concluded that the biological does not have the potential to cause (harmful) effects in the human body. Its potential to cause adverse immune reactions needs to be checked (see below) before a final conclusion can be drawn.

If the available data show (or it remains unknown whether) that there is local interaction, possible effects on the human body need to be further investigated based on the next steps.

Is the biological identical to that naturally occurring in human body or food derived from animals or plants?

Biologicals used as active ingredients in VMPs might already naturally occur in the human body or might be part of the normal human diet via food derived from animals or plants. If a biological is foreign to the human body and/or not part of the normal human diet, its properties need to be further assessed concerning their hazard potential whereas for those biologicals naturally occurring in the human body and/or in food a quantitative risk assessment (see next but one step) would be appropriate.

Are toxicology, pharmacology and/or pharmacokinetics altered by the modification in a relevant manner?

Modifications (e.g. pegylation, sequence modifications) might lead to e.g. an increase in bioactivity or to longer persistence in the human body both leading to increased or longer lasting effects. Properties of the biological concerning these aspects need to be evaluated to allow for comparison to the unmodified biological and to allow for an assessment of relevance of the modification in terms of consumer safety.

Only if toxicology, pharmacology and/or pharmacokinetics are altered by the modification, further data is needed and the biological needs to undergo an MRL procedure. Otherwise the next step in this approach is an assessment concerning bioavailability of the biological (see below).

Would residues significantly increase the concentration naturally occurring in animal/plant derived food?

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. Data from studies may be used or otherwise a worst case assessment may be sufficient. I.e. certain information on the amount of residues that may be ingested and on the amount of the biological naturally occurring is needed to allow for comparison.

Is the biological bioavailable in a relevant manner (including local effects)?

Only the bioavailable proportion from an ingested amount of a biological may cause systemic effects in the human body. To assess whether a relevant proportion would become bioavailable, the percentage of bioavailability should be estimated (theoretically, e.g. based on literature) or determined. The possible (total) exposure to possible residues in food (e.g. potential intake via normal diet of a consumer plus residue of biological) should be also considered. This can be a worst-case estimate. Even if bioavailability in humans is low, residues might nevertheless be of importance if huge amounts of the substance might be ingested with food derived from treated animals (e.g. local residues).

In any case potential local effects have to be assessed.

If the question is answered with 'Yes' or 'Unknown', possible effects would need to be assessed (see next box). If there are data available showing that the biological is not bioavailable in a relevant manner, the potential of the substance to cause adverse immune reactions needs to be checked before a final conclusion on the need for an MRL procedure can be drawn.

Might possible residues affect (local and systemic) levels in humans?

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. If endogenous levels in humans are not significantly affected, residues from a certain biological would not lead to harmful effects.

Does the biological or a metabolite/degradation product cause adverse immune reactions in humans in a relevant manner?

The potential of a biological or its metabolites/degradation products to cause adverse immune reactions (e.g. sensitisation, immunodepression, immunostimulation including auto-immunity) in humans needs to be checked for each biological independent from the outcomes of other questions/criteria. As the mechanisms of causing adverse immune reactions are different from other kinds of interaction with the human body and as those reactions might be particularly harmful, adverse immune reactions from ingestion of residues from a biological need to be highly unlikely.

Hence, only if available data show that the biological or a metabolite/degradation product are highly unlikely to cause adverse immune reactions in humans or that the risk of adverse immune reaction is not relevantly different compared to ingredients naturally occurring in the particular foodstuff, can the substance be included in the list for biologicals. Otherwise an MRL procedure is needed for further evaluation of consumer safety.

After passing through the decision tree, a choice has been reached whether an MRL evaluation is needed or whether the biological can be included in the list for biologicals[1]. If the biological under consideration is a mixture of certain biological substances, all relevant residues should be assessed.

Scientific data allowing for an assessment of the questions raised in the decision tree are to be provided by the applicant. Published documentation may not be detailed enough to undertake an independent assessment. Inclusion of bibliographic data will, therefore, need a thorough evaluation as to the reliability and relevance of this information.

If answers to all questions raised in the decision tree reveal that no MRL evaluation is needed, most likely none of the standard toxicological studies normally required for an MRL evaluation have to be provided.

6. References

The following legislation and CVMP document are relevant to this guideline:

1. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC https://ec.europa.eu/food/animals/health/veterinary-medicines-and-medicated-feed/imp-regs-2019_en

2. Regulation (EC) No 470/2009 of the European Parliament and of the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) 726/2004 of the European Parliament and of the Council http://ec.europa.eu/health/files/eudralex/vol-5/reg_2009-470/reg_470_2009_en.pdf

3. Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02010R0037-20210506&from=EN

4. Commission Regulation (EU) 2018/782 of 22 May 2018 establishing the methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No 470/2009 https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32018R0782&from=EN

5. Biological substances considered as not requiring an MRL evaluation as per Regulation (EU) 2018/782, with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/572629/2019) https://www.ema.europa.eu/en/documents/report/biological-substances-considered-not-requiring-mrl-evaluation-regulation-eu-no-2018/782-regard-residues-veterinary-medicinal-products-foodstuffs-animal-origin_en.pdf