



29 May 2026  
EMA/CVMP/SWP/591282/2021 Rev.1  
Committee for Veterinary Medicinal Products (CVMP)

## Guideline on determination of the need for an MRL evaluation for chemical-unlike biological substances

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
Revised version agreed by SWP-V	16 November 2023
Adopted by CVMP	17 January 2024
Date for coming into effect	1 August 2024
Revised guideline (revision 1) agreed by SWP-V	20 March 2026
Revised guideline (revision 1) adopted by CVMP	21 May 2026
Date for coming into effect	29 May 2026

<b>Keywords</b>	Chemical-unlike biologicals, MRL evaluation, safety data, residue data, veterinary medicinal products
-----------------	-------------------------------------------------------------------------------------------------------

This revision implements Commission Regulation (EU) 2025/1101 of 3 June 2025 amending Regulation (EU) 2018/782 concerning the assessment by the European Medicines Agency (EMA) of maximum residue limits for chemical-unlike biological substances. These substances are evaluated in order to determine whether a “no MRL required” classification is appropriate. The decision tree in the guideline is amended accordingly.

The scope of the guideline is also clarified by including the pharmacologically active chemical-unlike biological excipients.

**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](http://www.ema.europa.eu/how-to-find-us)

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact) **Telephone** +31 (0)88 781 6000

An agency of the European Union



# Guideline on determination of the need for an MRL evaluation for chemical-unlike biological substances

## Table of contents

<b>Executive summary .....</b>	<b>3</b>
<b>1. Introduction .....</b>	<b>3</b>
<b>2. Scope.....</b>	<b>4</b>
<b>3. Definitions .....</b>	<b>5</b>
<b>4. Legal basis .....</b>	<b>6</b>
<b>5. Criteria for the assessment of chemical-unlike biological substances concerning the determination of the need for an MRL evaluation.....</b>	<b>7</b>
5.1. General principle of the approach .....	7
5.2. Overview on stepwise assessment.....	8
5.3. Stepwise assessment of chemical-unlike biologicals .....	9
<b>6. References .....</b>	<b>14</b>

## 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 distinguishes, for the purpose of MRL methodology, two groups of biological other than immunological substances: 'chemical-like' and 'chemical-unlike' biologicals. 'Chemical-like' biological substances are subject to a standard maximum residue limit (MRL) procedure according to Regulation (EC) No 470/2009, 'chemical-unlike' biological substances are evaluated according to the aspects listed in point 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 structured and transparent assessment criteria on how to determine the need for an MRL evaluation according to Regulation (EC) No 470/2009 for 'chemical-unlike' biological substances. The substances are assessed individually in terms of their potential risk to the consumer safety and data requirements are specifically identified according to the nature and properties of the biological substance under consideration.

To this end, a stepwise (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 'chemical-unlike' biological may be included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as "No MRL required" if no full MRL evaluation is needed, (2) An MRL procedure is required where certain properties of the 'chemical-unlike' biological substance reveal that data necessary for the establishment of MRLs according to sections II and III of Annex I 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 (VMPs). According to the Article 4(7) of Regulation (EU) 2019/6, biological substances are substances 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 address the data needs and assessment requirements for biological substances.

This guideline is intended to provide guidance on determining whether an MRL evaluation is required for a 'chemical-unlike' biological substance, while ensuring consumer safety, enhancing the predictability of the assessment requirements and assisting the applicant in preparing the necessary information and data needed for such an evaluation. To support the assessment of whether a further MRL evaluation is required, this guideline provides a set of tailored criteria based on the data requirement aspects set out in point I.7 of Annex I to Commission Regulation (EU) 2018/782.

'Chemical-unlike' biological substances for which it is concluded that a full MRL evaluation is not required will subsequently be **Error! Bookmark not defined.** added to Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as "No MRL required". Biological substances for which an MRL evaluation is considered necessary, shall undergo an MRL procedure according to Regulation (EC) No 470/2009 to be listed in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

As immunological active substances are exempted from the need for MRL assessment pursuant to Article 1(2)(a) of Regulation (EC) No 470/2009, this guidance concerns 'biological substances other than immunologicals' only, namely – chemical-unlike biological substances. Chemical-like biological substances are excluded from the scope of this guidance.

The guidance provided in this document is largely principles-based and general in nature. However, if, during product development, an applicant wishes to seek clarification on the specific data requirements necessary to assess the need for an MRL evaluation for a biological substance relating to a specific VMP, Scientific Advice may be sought 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 chemical-unlike biological other than immunological substances used in VMPs intended for use in food-producing species. This includes both those used as active substances and those used as excipients with pharmacological/biological activity.

According to Commission Regulation (EU) 2018/782, there are two groups of 'biologicals, other than immunologicals' to be distinguished: those that can be described as 'chemical-like' and those described 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 is to be conducted on a case-by-case basis.

This guideline aims to further clarify the terms 'chemical-like' and 'chemical-unlike' and in case of 'chemical-unlike' biological substances presents a tailored approach to support a decision on whether an MRL evaluation is required for a particular substance and to identify the minimum data requirements for the consumer safety assessment of 'chemical-unlike' biological substances. The approach takes into account the specific properties of 'chemical-unlike' biological substances 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 biological substances. As this group comprises a wide range of different materials, the approach is designed to be sufficiently flexible and applicable across the range of biological substances concerned.

A report describing the scientific basis for the request on determination of whether a full MRL evaluation is required needs to be provided by the applicant. This report should be accompanied by the information listed in point 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 to support the EMA in determining whether an MRL evaluation is required.

Depending on the outcome of this assessment procedure, 'chemical-unlike' biologicals can be directly included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as "No MRL required" or shall undergo a standard MRL procedure according to Regulation (EC) No 470/2009 (resulting in a decision on whether and under what conditions they can be included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010). A summary of assessment of the substance is published on the EMA website.

While this guideline aims to support the determination of whether an MRL evaluation is required for 'chemical-unlike' 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.

## 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 include substances which are chemically synthesized even if they are chemically identical to those produced by or extracted from a biological source.

### 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.

If there is any uncertainty as to whether a particular substance belongs in this group, the applicant should seek clarification from the EMA in advance.

### Chemical-like biologicals

Pursuant to section I.6.(a) of Annex I to Commission Regulation (EU) 2018/782 '[...] *the biological substance is chemical-like insofar as it could be produced by chemical synthesis<sup>1</sup> and so present[s] similar concerns to chemical substances and can be expected to leave residues in the same way as chemical substances [...]*'.

Although derived from natural source, they can be fully described by their physico-chemical properties. They likely have a structural formula and chemical name, a precise (discrete) molecular weight, and a CAS number or other unique identifiers. They typically have molecular weights lower than 10<sup>3</sup> Daltons. Since they can also be expected to leave residues in the same way as chemical substances and therefore present similar concerns as chemical substances, they may be subject to residue controls. They do not typically belong to the group of biological macromolecules (consisting of carbohydrates, amino acids and nucleic acids), lipids or biological organisms (e.g. cells, bacteriophages), but rather include substances derived from natural sources (e.g., herbal, bacterial, animal origin).

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

---

<sup>1</sup> This is meant to be a substance produced by or extracted from a biological source but whose chemical synthesis is technically feasible.

Naturally occurring 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 a residue(s) in food of animal origin) are assigned to the group of 'chemical-like biologicals' for the purposes of this guideline.

### **Chemical-unlike biologicals**

Pursuant to point I.6.(b) of Annex I to Commission Regulation (EU) 2018/782 '*chemical-unlike biological substances* are *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*'.

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 as well as on the source of origin and other factors). They cannot (or not readily) be produced by chemical synthesis and do not normally form residues.

Substances covered by the term 'chemical-unlike biologicals' typically belong to the group of biological macromolecules with molecular weights higher than  $10^3$  Daltons, 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 physico-chemical properties and, therefore, require additional biological testing for their characterisation and/or for control during manufacture.

The group of 'chemical-unlike biologicals' also include biological macromolecules that are modified in a subsequent step. Such modification needs to be considered in the assessment.

## **4. Legal basis**

Regulation (EC) No 470/2009 lays down Union 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-mentioned 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, Commission Regulation (EU) 2018/782 establishes methodological principles for the risk assessment and risk management recommendations referred to in Regulation (EC) No. 470/2009.

Point 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 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, point I.7 of the Annex I to the Commission Regulation (EU) 2018/782 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 a ‘no MRL required’ classification according to the classification provided for under Article 14(2), point (c), of Regulation (EC) No. 470/2009 is appropriate.”

This guideline concerns the determination of the need for a full MRL evaluation in the context of the above-mentioned points I.6(b) and I.7 of Annex I to Commission Regulation (EU) 2018/782.

## **5. Criteria for the assessment of chemical-unlike biological substances concerning the determination of the need for an MRL evaluation**

### ***5.1. General principle of the approach***

The approach for determining the need for an MRL evaluation for ‘chemical-unlike’ biological substances consists of guiding questions and criteria in relation to point I.7 of Annex I to Commission Regulation (EU) 2018/782, allowing applicants to classify their substances and to collect the data required to address consumer safety. The set of stepwise questions is to be applied to each chemical-unlike biological substance in order to allow for a conclusion on the need for further MRL evaluation. The approach is applicable to chemical-unlike biological substances used as active substances as well as to those used as excipients with pharmacological or biological activity.

While keeping regulatory requirements to a minimum, the approach aims to be sufficiently flexible and tailored to the specific information required to reach a scientifically justifiable conclusion in each case. The extent of data and justification required to address the questions may be adapted based on the

properties of the substance under consideration. This stepwise approach allows for the identification of uncertainties or data gaps, which should be addressed by the applicant, where necessary.

Responses to the set of questions and criteria enable the identification of potential hazards associated with 'chemical-unlike' biological substances with new or unknown properties, that may be of concern for consumer safety. This procedure is conducted by the EMA and may result in two possible outcomes (see [Figure 1](#), green boxes):

- It can be decided that no further MRL evaluation is required based on the properties of the particular chemical-unlike biological substance ("substance presenting a low risk to consumers"). This would result in a 'no MRL required' classification Table 1 of the Annex to Commission Regulation (EU) No 37/2010.
- Where the assessment reveals that an MRL procedure according to Regulation (EC) No. 470/2009 is necessary, the data requirements for MRL evaluation shall be applied to the substance concerned. The MRL procedure may result in the inclusion of the biological substance in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

## **5.2. Overview on stepwise assessment**

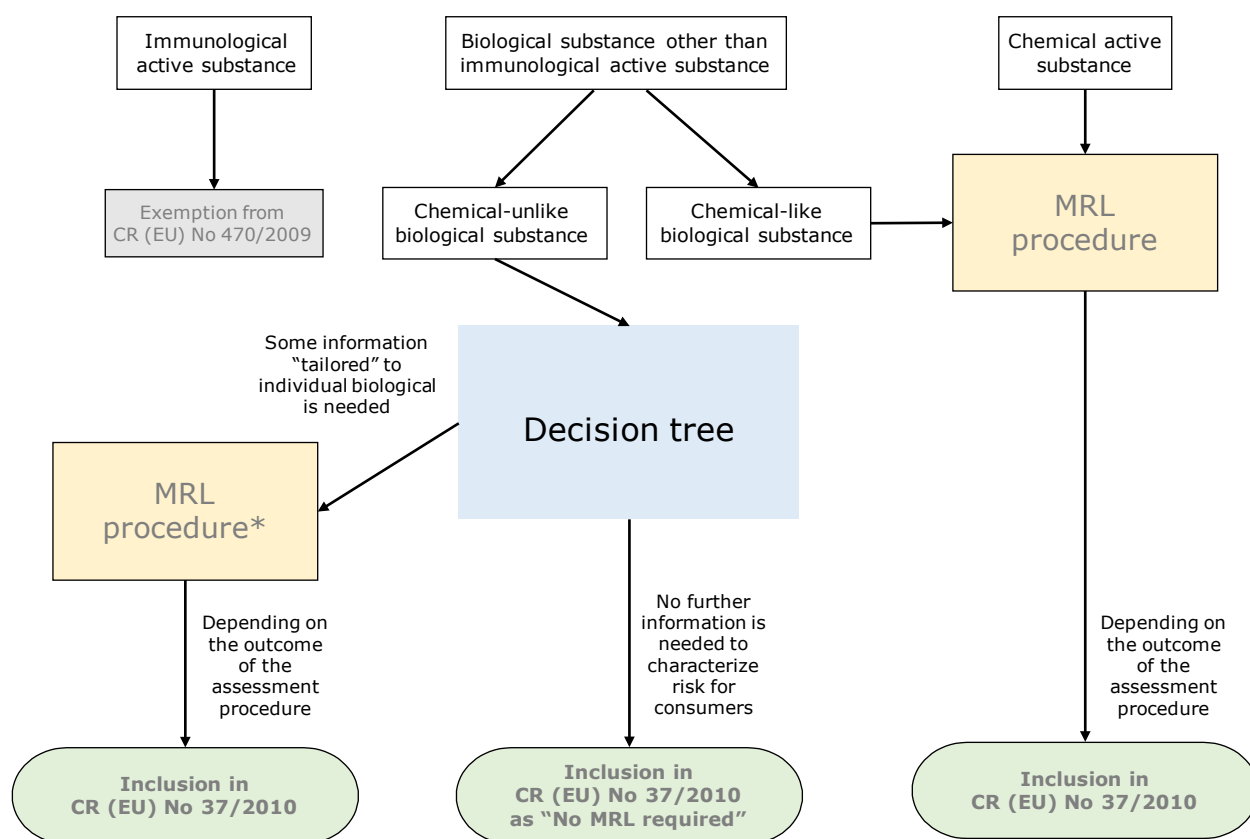
A stepwise (tiered) approach is to be applied to each biological substance to enable a case-by-case assessment. The approach requires varying levels and complexity of information depending on the substance concerned. An overview of the approach is provided in [Figure 1](#).

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

Within the group of 'biologicals other than immunologicals' two groups are distinguished (for definitions, refer to section 3):

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

(2) 'Chemical-unlike biologicals' are assessed on a case-by-case basis according to Commission Regulation (EU) 2018/782. Details of 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. Stepwise assessment of chemical-unlike biologicals

For substances considered as 'chemical-unlike biologicals', information from the answers to a predetermined set of questions is required (please see figure 2) to decide whether these may be included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 with a 'No MRL required' classification, or whether they need to undergo a full MRL procedure due to consumer safety concerns<sup>2</sup>. Each of the questions can be answered with 'Yes', 'No' or 'Unknown', which then leads to the next step and ultimately to a decision on the appropriate course of action (yellow/green boxes). The inclusion of the 'Unknown' category allows for data gaps, nevertheless the approach ensures that sufficient relevant information is provided to support a conclusion on consumer safety.

A scientific report addressing the set of questions should be submitted. The set of questions provided below covers the items listed in point I.7 (a) to (e) of Annex I to Regulation (EU) 2018/782, with the possible exception of point (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 and, where available- its potency should be added to the report.

<sup>2</sup> The decision tree itself covers only 'chemical-unlike biological substances', as can be seen in figures 1 and 2. In order to keep the text in the decision tree as well as in the explanations short and clear, these are referred to in the following only as 'biological substances'.

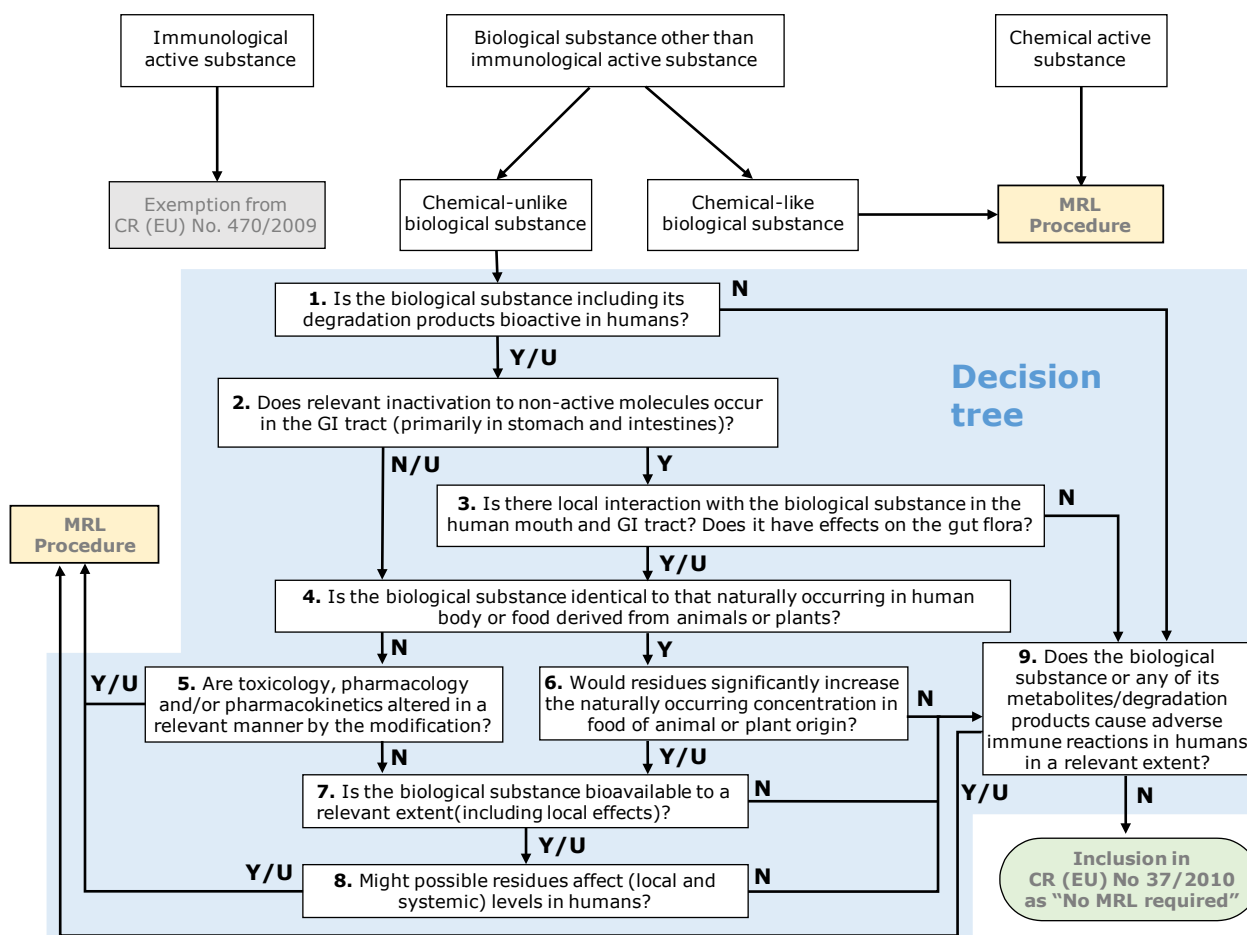


Figure 2: Stepwise approach for determination of the need for an MRL evaluation for chemical-unlike biological substances (Details)<sup>3</sup>  
 Y: 'Yes', U: 'Unknown', N: 'No'

Questions raised in the decision tree and implications of possible answers concerning relevance for consumer safety are described below<sup>3</sup>:

### 1. Is the (chemical-unlike) biological substance, including its degradation products, bioactive in humans?

Information on this aspect may be required to determine whether the chemical-unlike biological substance itself, or its degradation products, may have an impact on physiological processes in human. 'Bioactive' means that the biological substance can produce an effect (toxicological, microbiological or pharmacological) in humans.

If the chemical-unlike biological substance, including its degradation products, is not bioactive in humans, e.g. due to the absence of relevant receptors for the particular substance and lack of cross-interaction, no (adverse) effects can be expected and no further data (other than information on adverse immune reactions, see below) are required. Bioactivity can also be excluded for chemical-unlike biological substances which do not lead to residues in treated animals, e.g. where they are administered orally and it is demonstrated that no absorption from the gastrointestinal (GI) tract occurs. If there are effects of the chemical-unlike biological substance on physiological processes in the human or if this is unknown, further information based on the subsequent questions is required.

<sup>3</sup> Please note that the numbering of the questions only serves the better assignment of the boxes in the decision tree to the text. The questions do not have to be run through according to the numbering.

See also points I.7(b) and (e) of Annex I to Commission Regulation (EU) 2018/782.

## **2. Does relevant inactivation to non-active molecules occur in the GI tract (primarily in the stomach and intestines)?**

If the chemical-unlike biological substance is bioactive in humans, but is inactivated in the GI tract, systemic effects are unlikely to occur. In case of incomplete inactivation, it should be considered whether the remaining concentrations of still potentially active fractions of the chemical-unlike biological substance are lower than the relevant reference value (e.g. naturally occurring concentrations or recommended daily intake levels).

If the question is answered with 'Yes', potential local interaction needs to be assessed in the subsequent question. If the chemical-unlike biological substance is not inactivated, or if this remains 'Unknown', further information is required.

See also point I.7 (e) of Annex I to Commission Regulation (EU) 2018/782.

## **3. Is there local interaction with the (chemical-unlike) biological substance in the human mouth and/or GI tract? Does it have effects on the gut flora?**

Since inactivation only occurs during passage of the GI tract, potential local reactions in the proximal regions must be taken into account. If data are available demonstrating the absence of local effects of the chemical-unlike biological substance or its degradation products on the mucous membranes of oral cavity, oesophagus, stomach and/or intestines and that the absence of effects on the intestinal microbiota, it can be concluded that the chemical-unlike biological substance does not have the potential to cause (harmful) effects in humans. Its potential to cause adverse immune reactions should be assessed (see below) before a final conclusion can be drawn.

If the available data show, or it remains unknown whether, there is local interaction, possible effects on humans should be further assessed in accordance with the subsequent steps.

See also point I.7(d) of Annex I to Commission Regulation (EU) 2018/782.

## **4. Is the (chemical-unlike) biological identical to that naturally occurring in human body or food derived from animals or plants?**

Chemical-unlike biological substances used in VMPs may already occur naturally in the human body or may form part of the normal human diet via food derived from animals or plants. If a chemical-unlike biological substance is foreign to the human body and/or not part of the normal human diet, its properties should to be further assessed with regard to their hazard potential, whereas for those chemical-unlike biological substances naturally occurring in the human body and/or in food, a quantitative risk assessment (see question 6) may be appropriate.

See also point I.7(a) of Annex I to Commission Regulation (EU) 2018/782.

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

Modifications (e.g. pegylation, sequence modifications) may lead, for example, to an increase in bioactivity or to prolonged persistence in the animal or human body, both of which may result in increased or longer-lasting effects. The properties of the chemical-unlike biological substance concerning these aspects should be evaluated to enable comparison with the unmodified chemical-unlike biological substance and to assess the relevance of the modification for consumer safety.

Where toxicology, pharmacology and/or pharmacokinetics are altered by the modification, further data are required and the chemical-unlike biological substance shall undergo an MRL procedure. Otherwise,

the next step in this approach is an assessment of the bioavailability of the chemical-unlike biological substance (see below).

See also points I.7(a) (b) and (c) of Annex I to Commission Regulation (EU) 2018/782.

#### **6. Would residues significantly increase the naturally occurring concentration in food of animal or plant origin?**

If available data indicate that the chemical-unlike biological substance naturally occurs in the human body and/or in food, a quantitative assessment should be performed to determine whether ingestion of residues in food of animal origin would significantly increase the naturally occurring concentrations. Data from studies may be used or alternatively, a worst-case assessment may be sufficient. That is, information on the amount of residues that may be ingested and on the naturally occurring levels of the chemical-unlike biological substance is required to enable comparison.

See also points I.7(a) and (e) of Annex I to Commission Regulation (EU) 2018/782.

#### **7. Is the (chemical-unlike) biological substance bioavailable to a relevant extent (including local effects)?**

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

In any case potential local effects have to be assessed.

If the question is answered with 'Yes' or 'Unknown', possible effects should be assessed (see next box). If data are available demonstrating that the chemical-unlike biological substance is not bioavailable to a relevant extent, the potential of the substance to cause adverse immune reactions should be assessed before a final conclusion on the need for an MRL procedure can be drawn.

See also points I.7(c) and (e) of Annex I to Commission Regulation (EU) 2018/782.

#### **8. Might possible residues affect (local and systemic) levels in humans?**

For chemical-unlike biological substances that are bioavailable in a relevant extent, the potential effects of residues on existing levels in humans should be assessed. If levels in humans are significantly affected (e.g. through residues of naturally occurring substances increasing endogenous levels in humans, or through residues of foreign substances), data on nature and magnitude of the potential effects are required, and such chemical-unlike biological substances shall undergo an MRL procedure. If endogenous levels in humans are not significantly affected, residues of the chemical-unlike biological substance are not expected to result in harmful effects.

See also point I.7(e) of Annex I to Commission Regulation (EU) 2018/782.

#### **9. Does the (chemical-unlike) biological substance, or any of its metabolites/degradation products cause adverse immune reactions in humans in a relevant extent?**

The potential of a chemical-unlike biological substance or its metabolites/degradation products to cause adverse immune reactions (e.g. sensitisation, immunodepression, immunostimulation including auto-immunity) in humans should be assessed for each substance independently of the outcomes of

other questions/criteria. As the mechanisms underlying adverse immune reactions differ from other types of interaction with the human body and as such reactions may be particularly harmful, adverse immune reactions from ingestion of residues of a chemical-unlike biological substance should be highly unlikely.

Hence, only if available data show that the chemical-unlike biological substance or its metabolites or degradation products are highly unlikely to cause adverse immune reactions in humans, or that the risk of such reactions is not significantly different from that associated with substances naturally occurring in the relevant foodstuff, can the substance be included as "No MRL required" in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. Otherwise, an MRL procedure is required for further evaluation of consumer safety.

See also point I.7(a) of Annex I to Commission Regulation (EU) 2018/782.

#### **Outcome of the decision tree:**

Upon completion of the decision tree, a determination is made as to whether the chemical-unlike biological substance may be directly included as "No MRL required" in Table 1 of the Annex to Commission Regulation (EU) No 37/2010. If the chemical-unlike biological substance under consideration is a mixture of multiple chemical-unlike biological substances, all relevant residues should be assessed.

Scientific data to support the assessment of the questions set out in the decision tree shall be provided by the applicant. Published documentation may not be sufficiently detailed to allow for an independent assessment. The inclusion of bibliographic data therefore requires a thorough evaluation of its reliability and relevance. The submission of information that goes beyond the decision tree, such as toxicological studies, may be useful in individual cases, is welcomed, and will be taken into account in the assessment on the need for an MRL procedure.

If, on the basis of the scientific report provided by the applicant addressing the items set out in point I.7. of Annex I to Commission Regulation (EU) 2018/782 and the corresponding questions of the decision tree in this guideline, it is concluded that no further MRL evaluation is required, the substance will be included as "No MRL required" in Table 1 of the Annex to Commission Regulation (EU) No 37/2010.

## 6. References

The following legislation is 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://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006>
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 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009R0470>
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/PDF/?uri=CELEX:02010R0037-20230611>
4. 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 <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02018R0782-20250624>