ANNEX II

Methodological principles for the risk management recommendations referred to in Article 7 of Regulation (EC) No 470/2009

I.ELABORATION OF MRLs

I.1. **Derivation of numerical MRLs**

I.1.1. Where it is considered appropriate in accordance with this Regulation to establish numerical MRL values, MRLs shall routinely be recommended for the edible tissues listed below:

(a) for mammals other than swine: muscle, fat, liver and kidney;

(b) for swine and poultry: muscle, fat and skin in natural proportions, liver and kidney;

(c) for fin-fish: muscle and skin in natural proportions;

(d) if the substance is proposed for use in a milk producing, egg producing or honey producing species, MRLs shall be recommended for milk, eggs and/or honey, respectively, wherever possible. As for tissues, recommendations for MRLs in milk, eggs and honey shall be based on data demonstrating the residue depletion profile in these commodities. Where no such data are available, it may be considered necessary to reserve an unused portion of the ADI for the future establishment of MRLs in these commodities (Section II.5).

I.1.2. When determining the MRLs, consideration shall be given to the following issues:

(a) the ADI (or alternative limit if appropriate) — MRLs shall be recommended at levels that ensure that consumer exposure to residues of concern remains below the ADI;

(b) the proposed marker residue;

(c) the ratio of the marker residue to total residues;

(d) the distribution of residues across edible tissues — the individual MRLs proposed for the different edible tissues shall reflect the distribution of residues across these tissues. In those cases where residues in a tissue rapidly fall below the limit of quantification (the smallest measured content of an analyte above which a determination of the analyte can be made with a specified degree of accuracy and precision) of the analytical method, it shall not be possible to establish MRLs that reflect the distribution of residues across tissues. Where this occurs, MRLs shall be set at twice the limit of quantification in order to provide an MRL for use in residue surveillance. Wherever possible, the tissue selected for residue monitoring purposes shall be one in which the MRL was set taking the distribution of residues across tissues into account;

(e) the overall exposure of the consumer to residues — this shall be demonstrated to be below the ADI based on the residue levels seen in the depletion studies, and using the standard food basket (see below).

I.1.3. In deriving MRLs it shall be assumed that the consumer will eat a standard food basket of animal-derived products every day. Consumer safety shall be ensured by keeping the total amount of residues in the standard food basket below the ADI.

The standard food basket shall be made up of the quantities of the food commodities shown in the table below:

Mammals		**Poultry**		**Fish**		**Bees**	
Muscle	0,300 kg	Muscle	0,300 kg	Muscle and skin in natural proportions	0,300 kg	Honey	0,020 kg
Fat	0,050 kg[a]	Fat and skin in natural proportions	0,090 kg				
Liver	0,100 kg	Liver	0,100 kg				
Kidney	0,050 kg	Kidney	0,010 kg				
Milk	1,500 kg	Eggs	0,100 kg				

a Fat and skin in natural proportions for pigs

I.1.4. Using the residue depletion data, the total residue burden in the standard food basket shall be calculated based on the observed residue levels at each time point on the residue depletion curve, so that the time point at which the total residue burden falls below the ADI is established. If the full ADI is available then these residue levels, rounded up as appropriate (usually to the nearest 50 µg/kg for tissues), shall be considered as potential MRLs. Consideration shall also be given to the factors listed under Section II points 1 to 7 and, if appropriate (e.g. if less than the full ADI is available), a subsequent time point on the residue depletion curve shall be used as the point from which to derive the MRLs.

I.1.5. Once MRL levels have been derived, the Theoretical Maximum Daily Intake ('TMDI') of residues shall be calculated using the standard food basket and assuming that residues are present in all food commodities at the level of the proposed MRLs. The TMDI is calculated by adding exposure to residues from all tissues obtained using the following calculation:

Amount per edible tissue or product = (proposed MRL for the tissue or product x (times) daily consumption of the tissue or product)/(divided by) Ratio of the marker to total residue in the tissue or product.

I.2. **The 'No MRL required' classification**

I.2.1. A 'No MRL required' classification may be recommended in those cases where it is clear that the establishment of numerical MRLs is not necessary for the protection of the consumer. The consumer exposure to residues shall always remain at safe levels (below the ADI or alternative limit) in order for a 'No MRL required' classification to be recommended.

I.2.2. Substances may be regarded as candidates for a 'No MRL required' status, if they fulfil one or more of the criteria stated below. It shall be noted, however, that fulfilment of one or more of these criteria shall not be regarded as automatically implying that a 'No MRL required' status shall be recommended. The following specificities of each individual substance shall be fully evaluated before reaching a conclusion:

(a) substances of endogenous origin, particularly if exposure to residues has only a minor impact on the overall exposure to the substance;

(b) substances which are essential nutrients or normal constituents of the diet in man and animals;

(c) substances for which no pharmacological activity considered to be biologically relevant has been identified;

(d) substances that have been demonstrated to be of low toxicity following exposure by the oral route;

(e) substances that are not absorbed or are poorly absorbed from the gastro-intestinal tract or from the sites of local application (e.g. skin or eyes);

(f) substances that are rapidly and extensively detoxified or excreted;

(g) substances that have been demonstrated not to result in detectable residues in food derived from treated animals.

I.2.3. In some cases a 'No MRL required' recommendation may incorporate a restriction on the way the substance is to be used (for example, a restriction 'for cutaneous use only' may be recommended in cases where it is clear that no residues of concern will result following cutaneous use, but the possibility of harmful residues cannot be ruled out following administration of the substance by a different route).

II. AVAILABILITY OF ALTERNATIVE MEDICINES AND OTHER LEGITIMATE FACTORS

II.1. **Availability of alternative medicines**

The need for the substance in order to avoid unnecessary suffering for target animals or to ensure the safety of those treating them may be relevant factors to consider in those cases where practical treatment alternatives are lacking. These considerations may justify acceptance of a reduced data package in line with the recommendations provided in the Agency's '*Guideline on safety and residue data requirements for pharmaceutical veterinary medicinal products intended for minor use or minor species (MUMS)/limited market*'[(1)]. These factors may also be considered in relation to the need to set MRLs at levels that will allow development of a product with a practicable withdrawal period, as defined in Directive 2001/82/EC of the European Parliament and of the Council[(2)].

II.2. **Technological aspects of food and feed productions**

II.2.1. Where relevant, consideration shall be given to the possibility that microbiologically active residues impact on microorganisms used for industrial food processing, in particular as regards the manufacture of dairy products.

II.2.2. Information on testing that shall be considered in order to address this issue is detailed in Annex I Section III.6.

II.2.3. The recommended MRLs shall be set at levels that ensure that food processing is not adversely affected (e.g. dairy starter cultures).

II.3. **Feasibility of controls**

II.3.1. For some substances, for which setting numerical MRLs is not practicable (e.g. substances that may be naturally present in animal produce), the feasibility of undertaking residue control shall be considered on a case-by-case basis. This shall be determined based on the consideration of the potential risk posed to the consumer.

II.3.2. In cases where the time taken for residues to deplete to the recommended MRL may be longer in one (or more) tissue type than in others, it shall be recommended that, if the entire carcass is available, the tissues selected for monitoring of residues shall be those in which depletion of residues to the level of the MRL is slowest, as compliance

with the MRL in this tissue will indicate compliance with the MRLs in other tissues also. This is particularly likely in those cases where residues are seen to be low in one or more tissues at all-time points and consequently the recommended MRL values for this (or these) tissue(s) are based on the limit of quantification of the analytical method.

II.4. **Conditions of use and application of the substances in veterinary medicinal products, good practice in the use of veterinary medicinal products and biocidal products, the likelihood of misuse or illegal use and other relevant factors**

II.4.1. For substances proposed for use in species that produce milk or eggs, consideration shall be given to the possibility of recommending MRLs in these commodities. Where MRLs cannot be recommended in milk or eggs for safety reasons, it shall be stated that use of the substance shall be restricted to animals not producing milk or eggs for human consumption.

II.4.2. If appropriate, consideration shall be given to recommending a restriction on the use of the substance. For example, if the residue data provided relate only to cutaneous application of the substance and there are concerns that residue levels in food of animal origin would be considerably higher if the substance were applied by another route, then consideration shall be given to recommending that use of the substance be restricted to cutaneous use.

II.4.3. If establishment of MRLs may increase the likelihood of misuse or illegal use of the substance (for example in relation to use as a growth promoter) this shall be clearly stated. Similarly, if the establishment of MRLs may increase good practice and limit misuse or illegal use this may also be stated.

II.4.4. Other factors may be considered on a case-by-case basis where evidence exists to indicate that there is a specific relevant concern regarding the use of the pharmacologically active substance. As a general principle, MRL assessments do not consider the effects of food processing (particularly cooking) on residues. However, if data are available indicating that food processing can be expected to increase levels of residues of concern, consideration shall be given to the potential impact on consumer health.

II.5. **Need for an unused portion of the ADI**

II.5.1. Since it is not possible to predict, with certainty, the future use of a substance in other species and with a view to increasing availability of veterinary medicinal products, as a general principle, it shall be considered that, unless MRLs are proposed in all food commodities included in the standard food basket, an adequate portion of the ADI shall remain unused.

II.5.2. MRL applications usually focus on tissues, however, potential future uses in milk, eggs and honey shall be considered. In general, a part of the ADI shall be reserved for future uses and MRLs that use the full ADI shall only be accepted in exceptional cases.

II.5.3. When considering the need to maintain an unused portion of the ADI, a number of substance specific factors shall be considered, including:

(a) information relating to the likely usefulness of the substance in other species (e.g. indication in the original species, mechanism of action, known toxicity of the substance in different species);

(b) physico-chemical and pharmacokinetic data that may indicate the likely distribution of the substance to milk, eggs or honey;

(c) whether the intended use of the substance requires MRLs that use up almost the entire ADI and are there particular considerations (such as availability concerns) that would justify recommending MRLs that would limit the possibility for future development of the substance;

(d) consideration of existing uses of the substance in fields other than veterinary medicine, and the consumer exposure that may result from these uses (indicated under Section II.6).

II.6. **Exposure from other sources (combined exposure to dual-use substances)**

II.6.1. In order to ensure that all sources of consumer exposure to the substance are considered, all known uses of the substance shall be considered and the consumer exposure that results from these uses shall be estimated. MRLs shall be proposed at levels that ensure that the total amount of residues from all sources likely to be ingested do not exceed the ADI.

II.6.2. In the case of substances also used as plant protection products, a general guidance figure for the portion of the ADI that may be reserved for veterinary use shall be 45 % of the ADI.

II.6.3. Where the existing pesticide product authorisation allows and sufficient data are available on intake from plant protection use, it may be possible to allocate a larger part to veterinary use without exceeding the ADI. In order to identify the proportion of the ADI that is available, the MRL approved for the plant protection product shall be taken into account.

II.6.4. As the methodology used in establishing MRLs for edible tissues for plant protection products differs to that used for veterinary use, care shall be taken when combining the estimated exposure risk from the different methodologies.

II.6.5. For dual-use substances used as biocides in animal husbandry, the CVMP Guideline on risk characterisation and assessment of maximum residue limits (MRL) for biocides[(3)] shall be followed.

II.6.6. With regard to feed additives, consultation with the European Union Register of Feed Additives shall indicate if the substance has been authorised for use in animal feed. When evaluating such substances, EFSA shall be consulted.

II.7. **Injection site residues**

II.7.1. The muscle MRL shall be set at a level for monitoring of residues in non-injection site muscle, as consumers routinely ingest non-injection site muscle and rarely ingest injection site muscle.

II.7.2. For those injectable substances for which depletion of injection site residues when compared to the muscle MRL would result in extended (prohibitive) withdrawal periods, an Injection Site Residue Reference Value ('ISRRV') shall also be established by the Agency. The ISRRV shall be set at a level that ensures that, at the likely withdrawal period, a standard food basket including 300g of injection site muscle would contain residues below the ADI.

II.7.3. The ISRRV shall not be published in the Annex to Regulation (EU) No 37/2010; the value shall only be available in the European Public MRL Assessment Report ('EPMAR') and shall be used when deriving a withdrawal period for the veterinary medicinal product.

III. CONSIDERATIONS ON POSSIBLE EXTRAPOLATION OF MRLs

III.1. The extrapolation of MRLs shall be considered in line with the requirements as set out in the Commission Regulation (EU) 2017/880[(4)].

III.2. Data that may be useful in relation to the extrapolation considerations shall be submitted as part of the dossier, where available.

(**1**) Safety and residue data requirements for veterinary medicinal products intended for minor use or minor species (MUMS)/limited market (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001536.jsp&mid=WC0b01ac058002dd38).

(**2**) Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (OJ L 311, 28.11.2001, p. 1).

(**3**) Risk characterisation and assessment of maximum residue limits (MRL) for biocides (http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_001541.jsp&mid=WC0b01ac05804aca04).

(**4**) Commission Regulation (EU) 2017/880 of 23 May 2017 laying down rules on the use of a maximum residue limit established for a pharmacologically active substance in a particular foodstuff for another foodstuff derived from the same species and a maximum residue limit established for a pharmacologically active substance in one or more species for other species, in accordance with Regulation (EC) No 470/2009 of the European Parliament and of the Council (OJ L 135, 24.5.2017, p. 1).