

CODEx ALIMENTARIUS COMMISSION



Food and Agriculture
Organization of the
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World Health
Organization

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Agenda Item 7

CX/RVDF 21/25/8-Add.1

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

25th Session
(Virtual)
12-16 and 20 July 2021

COMMENTS / INFORMATION ON:

- (i) **The approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species and**
- (ii) **Proposals for maximum residue limits based on the approach for extrapolation of maximum residue limits to one or more species**

Comments received from Brazil, Ecuador, European Union, Japan, Peru,
Thailand, Uganda, United Kingdom and United States of America

Brazil

I. The approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species

Brazil agrees with the proposed approach. It gives clear guidance to CCRVDF on how to advance in this specific issue of extrapolation of MRLs, which is of utmost importance so that Codex increases the number of approved MRLs for veterinary drugs.

II. The proposals for MRLs based on the approach proposed for extrapolation of MRLs to one or more species

Brazil agrees that the MRLs recommended in Annex II should be considered at Step 4 by CCRVDF25, subject to confirmation of the approach by CCRVDF25, in order to proceed with the advancement of these MRLs in the Step Procedure, and in accordance to the amendment already approved for the Risk Analysis Principles applied by CCRVDF.

Ecuador

ANNEX I. THE PROPOSED APPROACH FOR THE EXTRAPOLATION OF MRLs FOR VETERINARY DRUGS TO ONE OR MORE SPECIES

General criteria for extrapolation

- 2.1 the reference and concerned species are related:

It is necessary to specify and differentiate between animal species (e.g. cows, sheep, horses, etc.), classes of animals (e.g. mammals), and/or suborder of animals (e.g. ruminants), given that the term "related species" refers to species that have one or more shared characteristics or qualities. As is, the approach for concerned species for MRL extrapolation could be misunderstood.

- 2.2 the marker residue in the reference species is the parent compound only or the MRL status in the reference species is 'unnecessary' and there is an expectation that the active substance will be used under the same conditions (i.e. by the same administration routes and at similar doses) in both species:

For substances in which the marker residue does not include the parent compound, the presence of the marker residue should be confirmed in the species/food product in question.

Based on the foregoing, this information should be considered and this point in the document in question should be amended, if possible.

Additionally, we request more specific classification for the reference species and the concerned species, since describing a species as a "non-ruminant mammal" would determine if the MRLs for swine could be extrapolated to rabbits or guinea pigs and vice-versa, as these animal species have different physiologies for eliminating drugs from their systems.

- An additional significant point could be added to the general criteria for extrapolation:
 - o When extrapolation between unrelated species is considered, the similarity of the metabolic profiles between the reference species and the concerned species should be established.

Specific criteria for extrapolation

- (ii) Where identical M:T values have been used in JECFA calculations for two related species but the MRLs recommended (by JECFA) differ, **the most conservative set of MRLs (i.e. the MRLs from the species associated with the lowest consumer exposure estimate)** can be extrapolated to other related species (e.g. where different MRL values have been established for cattle and sheep and extrapolation is considered to goats, **the lowest set of MRLs should be used** for extrapolation):

If I may, the underlined sentences have opposite meanings.

On the one hand, the sentence: “The most conservative set of MRLs (i.e. the MRLs from the species associated with the lowest consumer exposure estimate)” implies that, given the case, the highest MRL values will be selected to ensure the lowest consumer exposure. However, it then states that “the lowest set of MRLs should be used.”

ANNEX II: MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS EXTRAPOLATED TO ONE OR MORE SPECIES

- Based on the comments for the previous paragraph, in ANNEX II.7 Moxidectin – proposed extrapolation to ruminants, the proposed MRLs for extrapolation in muscle is 20 ug/kg. Whereas, according to (ii) of the specific criteria for extrapolation, the recommendation is to select the most conservative set of MRLs, in which case the MRL for muscle established for sheep (50 ug/kg) should be selected.
- Lastly, in ANNEX II.8 Spectinomycin – proposed extrapolation to ruminants, the justification for extrapolating the MRLs to ruminants does not mention that, given that the M:T for cow’s milk is 1, the MRL can be extrapolated to milk for other ruminants.

European Union

European Union Competence

European Union Vote

The European Union (EU) would like to thank Codex members and observers for a very active and constructive participation in the electronic working group on the extrapolation of MRLs for veterinary drugs.

The EU supports the proposed approach for the extrapolation of MRLs for veterinary drugs to one or more species as presented in Annex I of CL 2020/42-RVDF. It provides a solid basis for CCRVDF in its role as a risk manager to recommend MRLs for species for which no residue data is available to allow JECFA to recommend MRLs. It will enable increased availability of Codex MRLs for veterinary drugs for trade while maintaining the protection of the consumer.

The EU also supports the proposals for MRLs extrapolated based on the proposed approach as presented in Annex II of CL 2020/42-RVD and their advancement in the Step Procedure.

Japan

Japan would like to thank the Chairs and the members of the Electronic Working Group (EWG) for their efforts on finalizing the discussion paper on the extrapolation of maximum residue limits for veterinary drugs to one or more species. The EWG has adopted the approach that minimizes the risk in setting the MRL for the concerned species without relevant data. While considering the differences in metabolism among different species, general and specific criteria for extrapolation proposed by the EWG seem to be appropriate. Therefore, Japan supports the proposals from the EWG and has no comments on the Annexes I and II of this circular letter.

Peru

Position of Peru on the consultation made on circular letter CL 2020/42-RVDF.

Whose annexes are:

- i. Approach for extrapolation of MRLs for veterinary drugs to one or more species.
- ii. Proposals for MRLs based on the proposed approach for extrapolation of MRLs to one or more species

In this regard, we state the following about the CL 2020/42-RVDF as well as the CX/RVDF 20/25/8, the approach for the extrapolation of MRLs is confirmed as well as the proposal of MRLs based on the proposed approach.

Thailand

Thailand would like to thank chair and co-chair of EWG for their hard work. We have considered the approach for the extrapolation of maximum residue limits (MRLs) for veterinary drugs to one or more species and the proposals for MRLs based on this approach. We would appreciate this opportunity to share our comments for further discussion in the CCRVDF meeting as follows:

General comments

1. In principle, Thailand has no objection to the concept of the work on the extrapolation of MRLs for veterinary drugs to one or more species as long as the proposed approach is based on a sound scientific evidence.
2. We are of the view that the establishment of extrapolated MRLs should be based on “Codex MRLs” rather than “MRLs recommended by JECFA as “Codex MRLs” considered and adopted by CCRVDF are clearly referable. In this regard, we propose to change “MRLs” to “Codex MRLs” throughout the document. In relation to the comments provided above, the proposed extrapolation of MRLs for Tilmicosin in cattle and sheep muscle to all ruminant species muscle should be revised because the Codex MRL for Tilmicosin in sheep is not established.

The proposed texts for some amendments, for example, are as follows:

(1) Introduction, paragraph 1

1. ... The proposal aims to provide a pragmatic approach based on general principles that can be applied in order to allow establishment of maximum residue limits (MRLs) in species related to those for which **Codex** MRLs already exist and which were established on the basis of the recommendations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

(2) A note on terminology

‘Reference species’ is used to refer to a species in which **Codex** MRLs have been established based on a scientific evaluation by JECFA.

(3) General criteria for extrapolation, paragraph 2, point 2

2. the marker residue in the reference species is the parent compound only or the **Codex** MRL status in the reference species is ‘unnecessary’ and there is an expectation that the active substance will be used under the same conditions (i.e. by the same administration routes and at similar doses) in both species.

(4) Specific criteria for extrapolation, paragraph 3, point i-iv

- (i) Where identical **Codex** MRLs have been established in at least two related species on the basis of JECFA recommendations, these **Codex** MRLs can be extrapolated to other related species (e.g. extrapolate from cattle and sheep to all ruminants).
- (ii) Where identical M:T values have been used in JECFA calculations for two related species but the **Codex** MRLs recommended (by JECFA) differ, ...
- (iii) Where the M:T established by JECFA is 1 in all tissues in a single reference species, the same **Codex** MRLs can be extrapolated to related species.
- (iv) For fish, where the **Codex** MRL in muscle/fillet recommended by JECFA was established based on the limit of quantification (LoQ) (e.g., twice the LoQ), the **Codex** MRL can be extrapolated to all bony fish.
- (v) For milk and eggs, where the M:T established by JECFA is 1 (in milk or eggs of a reference species), the milk/egg **Codex** MRL of the reference species can be extrapolated to milk of other ruminants and eggs of other domesticated poultry species, respectively, even if the M:T is not 1 in tissues.

(5) Table summarizing proposed MRL extrapolations

- The term “MRLs” should be replaced with “Codex MRLs”.

Specific comments:

1. Introduction, paragraph 3

We are of the view that there are high uncertainty of metabolism, distribution and depletion of veterinary drug residues between unrelated species. Therefore, we propose to delete the entire text in paragraph 3.

~~3. There can be less confidence when considering possible extrapolations between unrelated species and in cases where a metabolite is included in the marker residue. Therefore, such cases are not considered in this document but could be considered in the future following agreement on the principles to be applied in the most straight forward cases.~~

2. A note on terminology

We would like to express our concern on the terms “(all) non-ruminant mammals” and “(all) ruminant mammals” used in this document as there are different consumption patterns of livestock products in different regions and country groups. We are of the opinion that these terms are too broad and may lead to different interpretations of the definitions. In this relation, we humbly suggest that “**the list of species in the categories of ruminant and non-ruminant food producing mammals**” or “**the classification criteria for such animals**” should be developed for member countries to have a mutual understanding.

3. General criteria for extrapolation in point 3 of paragraph 2

As the general criteria referring to “the M:T established for the reference species can be applied to the concerned species” is ambiguous, we would like to propose adding the criteria on how to extend established M:T of the reference species to the concerned species.

4. A pilot on extrapolation of MRLs identified in the priority list Part D

It is important to note that the Codex MRLs for benzylpenicillin are given only for cattle, chicken and pig tissues (no Codex MRLs for benzylpenicillin in sheep tissues is established) as shown in the Codex online databases and the RVDF/25 INF/01, Part A (Codex MRLs and Risk Management Recommendations (RMRs) for Veterinary Drugs) adopted by the CAC41. In this regard, the extrapolation of MRLs for such compound to ruminants should be reconsidered.

Uganda

i. The approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species

Uganda is in agreement with the approach being suggested for extrapolation for the MRLs.

ii. The proposals for MRLs based on the approach proposed for extrapolation of MRLs to one or more species

Uganda is in agreement with the proposed MRLs.

United Kingdom

The UK would like to thank the EU and Costa Rica for leading on this project and all of the participants, who put forward a clear and appropriate proposal for the principles of extrapolation of MRLs between different species.

Our comments are as follows:

Annex I. The approach for the extrapolation of maximum residue limits for veterinary drugs to one or more species: CX/RVDF 20/25/8, Appendix I, Section II

No comments from the UK. The approach is agreed.

Annex II. The proposals for MRLs based on the approach proposed for extrapolation of MRLs for veterinary drugs to one or more species: CX/RVDF 20/25/8, Appendix I, Section IV

In the pilot provided, some of the identical MRLs or M:Ts of the reference species were established by extrapolation from one species to the other, generally from cattle to sheep, supported by only limited data in sheep. Based on the principles presented in EHC 240, CCRVDF accepted that metabolism is comparable in cattle and sheep, and therefore it was considered appropriate to extrapolate the M:T from one species to the other.

The main point for clarification is whether the intention is to:

- a) have two independently evaluated reference species, the establishment of whose MRLs are/were not reliant on assumption of metabolic similarity to each other during their original evaluations, or
- b) allow for the assumption of identical M:T between the two reference species, and further assume that this will be the same for all related species.

The former option would mean that the Codex approach for MRL extrapolation could be quite restrictive, whereas the latter would effectively allow for a double extrapolation, i.e. from the reference species to the first concerned species and then to the rest of the related species.

The UK is not opposed to the principles outlined in the approach to extrapolation, but if the intended extrapolation from two independently evaluated reference species to all related species is considered by Codex to be a key tenet of the approach, then some of these MRL proposals may not be justified. This point should be clarified.

The affected compounds are:

Cyhalothrin, cypermethrin, deltamethrin, spectinomycin, levamisole, and tilmicosin.

United States of America

The United States would like to thank the European Union and Costa Rica for their leadership of the electronic working group and the development of the proposed approach to extrapolation of existing Codex maximum residue limits (MRLs) to additional species. The United States supports the proposed approach to extrapolate existing Codex MRLs following the proposed general criteria. The ability to extrapolate established Codex MRLs to other species may increase the availability of Codex standards for use by member countries.

The United States would like to offer one comment on the proposed specific criteria for extrapolation. The specific criteria give great consideration to assessing the applicability of the existing reference species Codex MRLs and the underlying M:T that those Codex MRLs are based on when determining extrapolation to a related concerned species or a broader related group. However, the specific criteria are unclear regarding whether the comparison of two or more reference species MRLs should consider if the M:Ts were calculated based on species specific data.

In some cases where JECFA has recommended the same MRLs or used the same M:T to recommend MRLs for two related species, JECFA had extrapolated the M:T from one of the reference species to the other where data to calculate a M:T were not available in the second species. The United States recommends further consideration on the comparison of M:Ts and whether the M:Ts should be supported by species specific data.