ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 25th SESSION OF CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOOD (CCRVDF25)

12 – 16 and 20 July 2021 Virtual Meeting

Substances/MRLs Submitted for Approval

AGENDA ITEM 7:
Discussion paper on extrapolation of maximum residue limits to one or more species (including a pilot on extrapolation on MRLs identified in Part D of the Priority List – REP18/RVDF, App. VI)

Objectives

This document offers an analysis of agenda items to support participation to the 25th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF25), taking place virtually in July 2021. The document is intended for possible use by the Codex communities of practice promoted by GFoRSS and PARERA, as part of their contribution to enhancing awareness and supporting effective participation in international food standard setting meetings (Codex meetings) by representatives from members and observers, in particular in **the Middle East and North Africa.**

The analysis provided in this document offers a factual review of agenda items, their background and a discussion of some considerations. This analysis is indicative in nature and does not represent an official position of the organizations mentioned above (PARERA and GFoRSS), their membership or their management.

This analysis is prepared as part of the **Codex Initiative for the Middle East and North Africa**: ***MENA Codex Initiative***, implemented by PARERA and GFoRSS and funded by the US Codex Office, US Department of Agriculture.

**It is important to note that experts – members of the Expert Working Group (EWG) – do not represent the organizations and / or jurisdictions to which they are affiliated. The selection and participation in the EWG proceedings is based on each expert's own credentials and experience which should not be misconstrued as the country's / delegation's / organization's position to which they belong.*

Agenda Item 7: Discussion paper on extrapolation of maximum residue limits to one or more species (including a pilot on extrapolation on MRLs identified in Part D of the Priority List – REP18/RVDF, App. VI)

Documents: CX/RVDF 21/25/8 and CX/RVDF 21/25/8-Add.1

Background

CCRVDF22 (2015) requested JECFA to assess whether, on the basis of data from one or more fish species, it was possible to establish MRLs for finfish, crustaceans or molluscs in general, or for multiple similar groups. In response, the 81st JECFA (2015) requested further information on appropriate groupings of fish species so that representative species could be identified from which MRLs could then be extrapolated to other similar species. The current CCRVDF policy is that MRLs could only be recommended where the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had identified that it is scientifically justifiable and the uncertainties have been clearly defined.

CCRVDF23 (2016) agreed to establish an electronic working group to prepare a discussion paper on the feasibility of establishing MRLs for groups of fish species for veterinary drugs being considered by JECFA/CCRVDF. The electronic working group discussed many factors which could be used to group fish species including temperature, salinity, phylogeny, common physiology, and common behavior.

CCRVDF24 (2018) discussed a proposed step-wise approach to extrapolating MRLs for fish. The Committee agreed to establish a new electronic working group to prepare a discussion paper exploring pragmatic ways for CCRVDF to extrapolate MRLs to more species in its role as a risk manager. This electronic working group would look at extrapolation in fish as well as more broadly. The Committee also identified 10 veterinary drugs in ruminant species and 3 veterinary drugs in fish species for the electronic working group to consider for further extrapolation (see Table 1).

Table 1

Amoxicillin MRLs to ruminants in muscle, fat, liver, kidney and milk
Benzylpenicillin MRLs to ruminants in muscle, fat, liver, kidney and milk
Tetracyclines MRLs to ruminants in muscle, liver, kidney and milk
Cyhalothrin MRLs to ruminants in muscle, fat, liver, kidney and milk
Cypermethrin MRLs to ruminants in muscle, fat, liver, kidney and milk
Deltamethrin MRLs to ruminants in muscle, fat, liver, kidney and milk
Moxidectin MRLs to ruminants in muscle, fat, liver and kidney
Spectinomycin MRLs to ruminants in muscle, fat, liver, kidney and milk
Levamisole MRLs to ruminants in muscle, fat, liver and kidney
Tilmicosin MRLs to ruminants in muscle, fat, liver and kidney
Deltamethrin MRLs to bony fish in muscle
Flumequine MRLs to bony fish in muscle

The electronic working group has proposed criteria for extrapolation of existing Codex MRLs in one species to additional species and recommended extrapolation of 12 of the 13 veterinary drugs identified by the CCRVDF24 (2018). Teflubenzuron in fish was not considered by the EWG due to potential metabolism issues.

The 41st Session of the Codex Alimentarius Commission (CAC41, 2018) approved the amendment of Section 3.4, paragraph 30 of the Risk Analysis Principles* applied by CCRVDF as proposed by CCRVDF24. Namely, to provide for more autonomy to risk managers to propose extrapolation of MRLs to one or more species as opposed to the current policy. CAC41 further noted the clarification from the JECFA Secretariat that the proposed amendment would not modify the intent of the work or the safety evaluation for residues of veterinary drugs in foods, but serve instead to clarify how CCRVDF could approach its proposed work to develop extrapolation of MRLs as a risk-management decision and from the Codex Secretariat that, until such an amendment as proposed was made by CCRVDF, MRLs for minor species already requested by developing countries would not be available.

Subsequently, a discussion paper was prepared by an EWG (chaired by the European Union and co-chaired by Costa Rica) with a goal to address the following terms of reference:

- Explore pragmatic ways on how CCRVDF in its role as risk manager could extrapolate MRLs to one or more species;
- Prepare and contrast such approaches with the revised Option C for aquatic species;
- Conduct a pilot on extrapolation of MRLs identified in Part D of the Priority List.

The discussion paper underwent 2 rounds of comments by the EWG before being finalized and submitted to the Codex Secretariat for consideration by Codex members and observers (CX/RVDF 20/25/8).

Summary

The approach on extrapolation proposed in CX/RVDF 20/25/8 relies on there being confidence that metabolism in the concerned (extrapolation) species will be similar to that in the reference species, i.e., that major metabolic pathways are comparable and major metabolites are produced in comparable proportions. As a rule, this can be considered to be the case when the reference and concerned species are related species (species belonging to the same category of food producing species of ruminant (cattle, sheep, goats, buffalo, deer, elk, giraffes and camels) and non-ruminant mammals (pigs, horses and rabbits), birds or bony fish). 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 the EWG document but could be considered in the future following agreement on the principles to be applied in the most straight forward cases.

Extrapolation of MRLs should take place where it can be assumed that the ratio of marker to total residues (M:T) used in the intake calculation undertaken for the reference species can also be safely applied to the concerned species.

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 MRLs already exist and which were established on the basis of the recommendations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). The proposal is specifically aimed at those situations where species-specific data for the concerned species are not available.

The main comment of a number EWG members was about the uncertainty that exists with regard to the similarity of metabolism between the reference and the extrapolation species, even when these are related, and suggested the need for evidence to support similarity of metabolism on a case-by-case basis. While acknowledging that the availability of such evidence would certainly provide additional assurance, the EWG Chairs noted that the relevant data is not routinely available. They further reminded that the idea behind extrapolation at CCRVDF is precisely to

address those situations where species specific data are not available and to provide a pragmatic, risk management approach based on general principles.

Proposed Approach

Criteria for Extrapolation

1. the reference and concerned species are related.
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.
3. the M:T established for the reference species can be applied to the concerned species.
    a. Where identical MRLs have been established in at least two related species on the basis of JECFA recommendations, these MRLs can be extrapolated to other related species (e.g., extrapolate from cattle and sheep to all ruminants).
    b. 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).
    c. Where the M:T established by JECFA is 1 in all tissues (substance not metabolized) in a single reference species, the same MRLs can be extrapolated to related species.

If or when CCRVDF agrees to extrapolate MRLs, it should be clear that these MRLs were established by extrapolation rather than on the basis of a substance/species specific JECFA assessment. An appropriate symbol should be included next the relevant values reported in the Codex MRL database.

Proposed MRL extrapolations

From Reference Species	To Concerned Species
Ruminant (cattle, sheep, goats)	Tissues of all ruminants if the marker residue is the parent only and one of the following apply: i. identical MRLs already exist in 2 ruminant species ii. identical M:Ts exist in 2 ruminant species iii. MRLs have been established in only 1 ruminant species but the M:T = 1 in all tissues.

Pilot Examples on Extrapolation

Benzylpenicillin – proposed extrapolation to ruminants

1. MRLs exist for cattle (muscle, liver, kidney, milk), sheep (muscle, liver, kidney), pig (muscle, liver kidney); MRLs are identical.
2. MRLs were established on the basis of a full evaluation undertaken by JECFA
3. The marker residue is the parent compound

4. JECFA report uses a M:T of 1 for all tissues (limited/no metabolism)
5. MRLs can be extrapolated to all ruminants as criteria have been met
6. MRLs proposed for all ruminants would be the same as those already established for cattle, sheep and pigs.

Teflubenzuron – proposed extrapolation to all bony fishes

1. MRLs have been established for salmon
2. MRLs were established on the basis of a full evaluation undertaken by JECFA
3. The marker residue is the parent compound
4. JECFA report uses a M:T of 0.8 for both muscle and fillet
5. MRLs can not be extrapolated to all bony fishes because the M:T is not 1 (i.e., there is metabolism) and as the MRLs are not based on the LOQ.

Criteria was not met as MRLs have been established in only 1 specie and the M:T is not 1 in the reference and is not based on the LOQ.

Recommendation

There will likely be support by CCRVDF25 delegates for continuing the work associated with extrapolation of MRLs based on the identified criteria and agreement with the proposed approach.

***Proposed Amendment to the Procedural Manual (SECTION 3.4 - EVALUATION OF RISK MANAGEMENT OPTIONS)**

30. The CCRVDF may:

- recommend the MRLs based on the JECFA assessment;
- recommend extrapolation of MRLs to one or more other species, ~~where JECFA has identified that is scientifically justifiable and the uncertainties have been clearly defined~~;
- modify the MRLs in consideration of other legitimate factors relevant to the health protection of consumers and for the promotion of fair practices in food trade;
- request JECFA to reconsider the evaluation for the veterinary drug in question;
- decline to advance the MRLs based on risk management concerns consistent with the Risk Analysis Principles of the Codex Alimentarius and the recommendations provided by JECFA;
- develop risk management guidance, as appropriate, for veterinary drugs for which JECFA has not been able to establish an ADI and/or to recommended a MRL, including those with specific human health concern. As a result of this consideration, the CCRVDF may refer a range of risk management options to JECFA to obtain guidance on the attendant risks and likely risk reductions.