CODEX ALIMENTARIUS COMMISSION E

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World Health Organization

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Agenda Item 7 **CX/RVDF 13/21/7add.1**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twenty-first Session

Minneapolis, Minnesota, United States of America, 26 – 30 August 2013

PROPOSED DRAFT GUIDELINES ON PERFORMANCE CHARACTERISTICS FOR MULTI-RESIDUES METHODS (APPENDIX TO CAC/GL 71-2009) (N01-2011)

Comments at Step 3 Submitted by:

Brazil, Chile, Costa Rica, European Union, Peru, Philippines and United States of America

BRAZIL

Brazil thanks Canada and the United Kingdom for providing the report of the EWG and wishes to acknowledge the work done during the EWG and the overall improvement of the document since its very first version.

Specific comments

Annex1

Brazil understands that considering the definitions of **measurement principle** [VIM3-2012 §2.4], **measurement method** [VIM3-2012 §2.5] and **measurement procedure** [VIM3-2012§2.6] (note that the last two terms are also defined in the [CAC/GL 72-2009] in perfect agreement with the definitions in the [VIM3-2012]), the adequate term to be used in the document is not “analytical method” but **analytical procedure**. Any change in the analytical procedure can also change its metrological properties and make it not fit for purpose. For this reason we recommend substituting the expressions “analytical method” or “method” by **analytical procedure** or **procedure**, respectively, where these expressions are not in the citation of the title of another document.

Paragraph 4 (c) (ii)

(c) Reliability of results

(i) Recovery

(ii) ~~Accuracy (trueness, bias)~~ **Trueness**

(iii) Precision and Measurement uncertainty

(iv) Robustness (ruggedness) testing including identification of critical control points and possible stopping points

Rationale: Brazil understands that item (ii) should be substituted only by the term “trueness”, because according to definitions in [VIM3 2012 §2.13] both trueness and precision are encompassed by the definition of accuracy, as emphasized in Note 2 of [VIM3 2012 §2.13]: *The term “measurement accuracy” should not be used for measurement trueness and the term “measurement precision” should not be used for “measurement accuracy”, which, however, is related to both these concepts.*

Paragraph 12

Brazil requests clarification regarding to the nature of the “**six different sources of blank material**” mentioned in paragraph 12, and whether or not this represents tissues from six different animals to be obtained at every validation study conducted by the laboratories.

CHILE

Chile supports the advancement of the work on the Proposed Draft Guidelines on Performance Characteristics for Multi-Residue Methods.

Nevertheless, we suggest to review the Spanish translation all throughout the document, because both the language and technical terms used could confuse the reader, as those are not the usual terms in the technical language, like,

Paragraph 10 Analytes fortified, is translated as "analitos fortalecidos", and it should be translated as, "**analitos fortificados**".

Paragraph 12 *Blank matrix,* in some sections is translated as "matriz objetivo", but it should be translated as "**matriz blanco**".

I. Specific Comments

Comment 1. We suggest to change the last phrase to the beginning of the sentence. So it would give more clarity to

paragraph 5. **To avoid repetitions, in this Appendix it will only point out those differences to consider for a single analyte.** It should be understood that the performance characteristics listed in paragraph 4 should be defined and measured for every single analyte listed in the scope of the fully optimized multi-residue method. Esto se logra mejor luego de que se ha determinado que el desarrollo y/o modificación del método ha sido finalizado y que el método analítico no estará sujeto a ~~ningún~~ **algún** cambio o modificación adicional. [This comment only applies to the Spanish version]. In this regard, the concepts involved are very similar to those for determining the performance characteristics of an analyte in a single analyte method elaborated, as it is explained in CAC/GL 71-2009, paragraphs 160 – 181. To avoid repetition, only differences from single analyte consideration will be highlighted in this Appendix.

Comment 2. The meaning of the beginning of the paragraph is not clear, we request to clarify the reason to include it.

Paragraph 6 The requirement on MRMs to successfully detect residues of a variety of different veterinary drugs in a complex food matrix can be expected to result in an increased risk of interference by other material from the sample matrix compared to single analyte methods. If the MRM is required to analyze different matrices or a matrix from different species the risk is increased. Considering the 4 MRMs functionality in CX/RVDF 13/21/7 and as previously stated, this necessitates particular emphasis on performance characteristics related to detection capability and selectivity when considering the performance of MRMs.

Comment 3. On paragraph 8, we request to clarify what it is referring to, and what are those veterinary drugs not approved for use.

Also, we request to point out the base of the selectivity rate for the stated MRMs in the paragraph, because these are more stringent than those presented in CAC/GL 71-2009 (par. 162) for a single analyte.

Paragraph 8 Screening methods for approved veterinary drugs should demonstrate a selectivity rate of 95% with 95% confidence and a sensitivity rate of 90% with 95% confidence limit. For regulatory purposes, these screening methods can tolerate a small number of “false positive” results, as any screen “positive/presumptive positive/suspect positive” sample should be carried forward for additional confirmatory and/or quantitative analysis to verify the presence of the “suspect” residue. For all other veterinary drugs which are NOT approved for use, this appendix may be used to inform decisions on the performance criteria which may need to be developed.

Comment 4. This paragraph is giving all responsibility to the analyst, so we suggest to add a phrase at the end, with the purpose of considering other factors influencing the results.

Paragraph 14 The necessary steps to positive identification are a matter of expert judgment on the analyst’s part and particular attention should be paid to the choice of a method that would minimize the effect of interfering analytes. **The laboratory and the equipment should comply with the required standards for these kind of determinations.** Ultimately, it is the responsibility of the analyst to make choices, provide supporting data, and interpret results according to scientific principles and qualified judgment (6).

COSTA RICA

In general terms we agree with the document; we also think it's very important to harmonize the performance characteristics for Multi-Residues Methods to monitor veterinary drug residues in foods of animal origin for human consumption. Nevertheless, we would like to recommend that instead of using "six different sources" it should recommend "three different sources", because we think this number is adequate.

Also, it is important to clarify and explain the possibility of using ccβ and the Decision Limit.

EUROPEAN UNION

The European Union and its Member states (EUMS) appreciate the work done by the electronic working group led by the United Kingdom and Canada on performance characteristics for multi-residues methods.

The EUMS can largely agree with the draft text in Annex 1 of document CX/RVDF 13/21/7. In general the text is now much simplified compared to the beginning of the process some years ago and represents clear and reasonable guidelines for MRMs without going into too many details. However, there are still a few comments and questions which the EUMS would like to raise:

Paragraph 6

The problem is not an increasing risk of interference by other material from the sample matrix but different interferences on different analytes and interactions between the analytes in particular during validation of multi-residue methods with a high number of analytes (approx. >100).

Paragraph 11

It is not clear how the value “10 µg/kg” is derived. How is it justified?

Paragraph 20

Paragraph 189 of CAC/GL 71-2009 does not describe the application of incurred material for validation, but merely the application for getting more information about biological interaction during analysis. The application of incurred material for the overall validation process does not seem possible for MRMs.

Even if just a limited number of analytes are selected, the material has to be characterised at least by homogeneity tests and stability of the analytes in matrix. The application of such materials for validation purposes seems thinkable theoretically only.

Incurred samples such as in-house reference materials or better certified reference materials are more suitable for continuous control of a validated method.

PERU

The Technical Commission on Veterinary Drugs Residues does not have any comments about document CX/RVDF 13/21/7 "Proposed draft Guidelines on performance characteristics for multi-residues methods (Appendix to CAC/GL 71-2009) (N01-2011)”.

PHILIPPINES

The Philippines appreciates the Electronic Working Group’s (e-WG) efforts in ~~charge of~~ revising the draft report on performance criteria for multi-residue analytical methods ~~that~~ which was submitted to the 20th Session for inclusion as an Appendix to the Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals (CAC/GL 71-2009) and to develop a generic validation protocol for multi-residue methods.

Also, the Philippines after reviewing the draft proposes the following:

1) Reiterate its proposal to:

Reference	Proposed Change	Rationale
Paragraph No 9	Criteria for identifying cut-off or threshold limits for screening methods are given in CAC/GL 71-2009 (paragraph 163) ~~and in documents such as the EU CRL guidelines on screening method validation for veterinary drugs (4).~~	Phrase is inappropriate
Paragraph No 4.c.iii	(iii) Precision ~~and Measurement~~ (iv) Measurement Uncertainty	Precision and measurement uncertainty are two separate concepts

2) The performance criteria should apply to any technology and methods; and

3) There is a need for additional reference/documents for screening analysis and validation of Multi Residues Methods characteristics.

Therefore, recommending the advancement to Step 5/8 after the above-mentioned proposals has been considered.

UNITED STATES OF AMERICA

The United States would like to thank the United Kingdom and Canada for their chairmanship of this electronic working group and for the opportunity to provide comment on the latest draft of the Performance Characteristics of MRMs.

At the 20th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) in San Juan, Puerto Rico, (7 – 11 May 2012), the Committee agreed to establish an electronic working group.

The purpose of the group is:

- To revise the draft report on performance criteria for multi-residue analytical methods that was submitted to the 20th Session for inclusion as an Appendix to the *Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals* (CAC/GL 71-2009); and
- To develop a generic validation protocol for multi-residue methods.

The United States would like to change the wording in paragraph 8 of the proposed annex to more closely align with CAC/GL 71-2009 as suggested in our specific comments below.

SPECIFIC COMMENTS

8. Screening methods for approved veterinary drugs should demonstrate a selectivity rate of ~~95%~~ **90%** with 95% confidence and a sensitivity **at the lowest concentration at which the target analyte may be reliably detected within defined statistical limits usually** ~~rate of 90% with~~ 95% confidence limit. For regulatory purposes, these screening methods can tolerate a small number of "false positive" results, as any screen "positive/presumptive positive/suspect positive" sample should be carried forward for additional confirmatory and/or quantitative analysis to verify the presence of the "suspect" residue. For all other veterinary drugs which are NOT approved for use, this appendix may be used to inform decisions on the performance criteria which may need to be developed.

9. Criteria for identifying cut-off or threshold limits for screening methods are given in CAC/GL 71-2009 (paragraph 163) and in documents such as the EU CRL guidelines on screening method validation for veterinary drugs (4), **Type I Validations of Chemistry Methods, FSIS Laboratory-wide SOP LW-0050.00 (9) and Validation of CVDR Test Methods CVDR-S-0027.08 (2011/06) (10)**.

21. Alternative protocols may be used for validation of MRMs, adapted as necessary for individual circumstances. For example and for guidance only, the EU Community Reference Laboratories (CRL) have published a guideline (4) on screening method validation for veterinary drugs, and the SANCO Document (SANCO 12495/2011) describes a method validation and quality control procedures for pesticide residues analysis in food and feed (8)**, by the US** FSIS **in Laboratory-wide SOP LW-0050.00** (9) and **by** Canada **in Validation of CVDR Test Methods CVDR-S-0027.08 (2011/06 (10).**