CODEX ALIMENTARIUS COMMISSION E

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World Health Organization

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Agenda Item 8 (b) **CX/RVDF 12/20/10 Add. 1**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Twentieth Session

San Juan, Puerto Rico, 7-11 May 2012

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

Comments at Step 3 of Australia, Brazil, Chile, Costa Rica, Kenya, Philippines and United States of America

AUSTRALIA

General Comments

The proposed draft Appendix to CAC/GL 71-2009 contains significant duplication of text from CAC/GL 71-2009. Australia does not consider it appropriate that text from Codex documents be duplicated in Appendices.

Whilst copying text from CAC/GL 71-2009, the proposed draft Appendix (appearing in CX/RVDF 12/20/10 as Annex 1) contains some additional commentary. Much of the additional commentary is not focussed on multi-residue methods, but often relates to single analyte and multi-residue methods. Therefore, the document appears to be a duplication of information in CAC/GL 71-2009 and this may lead to confusion.

Suggestions are made below to remove unnecessary duplication and better focus the text of the appendix on performance characteristics for multi-residues methods.

Specific Comments

Annex 1, Paragraph 1

The premise of this work, as stated in the Background is that CAC/GL 71-2009 was designed to include general guidance on the validation of analytical methods for use with single analytes under single laboratory validation conditions. Australia believes that CAC/GL 71-2009 pertains to both single analyte and multi-residue methods.

On reading CAC/GL 71-2009 it is not clear that it only relates to single analyte methods. Paragraph 1 of the Background needs to be reworded to clearly state its purpose in relation to CAC/GL 71-2009.

Annex 1, Paragraph 7

Paragraph 7 refers to CAC/GL 71-2009 as pertaining only to single laboratory validation of single analyte methods. Australia's comments in relation to paragraph 1 of the annex also relate to paragraph 7.

Noting the above concerns and that the document is intended to be an appendix to CAC/GL 71-2009 it is suggested the title of the appendix is sufficient to alert the reader to its content and that paragraphs 1-9 are superfluous and could be deleted with the document starting with paragraph 10, the scope.

Annex 1, Paragraph 12

Suggest deletion of paragraph 12.

Rationale: This paragraph is a reworded copy of paragraph 160 in CAC/GL 71-2009 and is unnecessary as paragraph 160 in CAC/GL 71-2009 is written generically and does not specify only single analyte methods.

If it is not deleted, the Committee should consider the following anomaly in the first sentence:

MRMs for screening analysis are usually either qualitative or semi-quantitative in nature and often cover a range of analytes. If they are an MRM they must by definition cover more than one analyte, so this sentence adds no value and should be deleted.

The second sentence in this paragraph introduces a term "detection concentration" whereas in CAC/GL 71-2009 the term used was "target concentration". The use of two terms with the one meaning is confusing to the reader.

Annex 1, Paragraph 13

Suggest deletion of paragraph 13.

Rationale: This paragraph is a modified copy of text in paragraph 162 of CAC/GL 71-2009 and does not pertain specifically to multi-residue methods.

Annex 1, Paragraph 14

Suggest deletion of paragraph 14.

Rationale: This paragraph is a modified copy of text in paragraph 163 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 17

Suggest deletion of paragraph 17.

Rationale: This paragraph is a modified copy of text in paragraph 164 of CAC/GL 71-2009 and the original can be taken to cover both single analyte and multi-residue methods.

Annex 1, Paragraph 18

Suggest deletion of paragraph 18.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 165 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 19

Suggest deletion of paragraph 19.

Rationale: This paragraph should be deleted as it clearly states that the original CAC/GL 71-2009 pertains to MRM and the paragraph is redundant. Sentence two states that "These standards" (i.e. Performance standards in Table 1) "are the same as the current limits applied for single analyte veterinary drug residues in CAC/GL 71-2009", however Table 1 is not identical to Table 3, paragraph 166, in CAC/GL 71-2009.

Annex 1, Paragraph 20

Suggest deletion of paragraph 20

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 167 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 21

Suggest deletion of paragraph 21.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 168 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 22

Suggest deletion of paragraph 22.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 169 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 23

Suggest deletion of paragraph 23.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 171 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 25

Suggest deletion of paragraph 25.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 172 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 26, 3rd Sentence

The description (definition) given for Limit of Detection is incorrect and is inconsistent with the definition given in CAC/GL 72-2009 (refer to page 7 of CAC/GL 72-2009).

The definition in the proposed guidelines is also inconsistent with the definition given in paragraph 173 of CAC/GL 71-2009. The sentence in the proposed guidelines should be changed to read:

'The detection *Limit* or *Limit of Detection* (LOD) of a method is defined in CAC/GL 72-2009 and may be described in practical terms as the lowest concentration of the analyte in the sample that can be detected ~~but may not be positively identified/confirmed~~ **and positively identified**'.

Annex 1, Paragraph 27

Suggest deletion of paragraph 27.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 174 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 29

Suggest deletion of paragraph 29.

Rationale: This paragraph should be deleted as it is a modified copy of text in CAC/GL 72-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 31

Suggest deletion of paragraph 31.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 175 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 35

Suggest deletion of paragraph 35.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 178 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 38

Suggest deletion of paragraph 38.

Rationale: This paragraph should be deleted as it is a modified copy of text in paragraph 179 of CAC/GL 71-2009 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraphs 40 to 43

Suggest deletion of paragraph 40 - 43.

Rationale: These paragraphs should be deleted as they are a modified copy of text in paragraphs 182 to 185 of CAC/GL 71-20 and the edits do not pertain specifically to multi-residue methods.

Annex 1, Paragraph 44

Delete the first two sentences of paragraph 44.

~~44. Ideally, a method of analysis for veterinary drug residues should be developed and characterised for the analysis of the four major tissues generally classed as "edible tissues", which are fat, liver, kidney, and~~

~~muscle. In addition, milk, eggs and honey are traded internationally and methods of analysis may also be required for these matrices.~~

Annex 1, Table 1

Suggest deletion of table 1.

Rationale: This table is a modified copy of Table 3 in CAC/GL 71-2009, does not pertain specifically to multi-residue methods.

Annex 1, Tables 2 and 3

Suggest deletion of tables 2 and 3.

Rationale: These tables are widely available in European Commission Decision 2002/657/EC and have already been endorsed Codex in CAC/GL/71-2009.

Annex 1, Table 4

Suggest deletion of table 4.

Rationale: This table is a modified copy of Table 4 in CAC/GL 71-2009, does not pertain specifically to multi-residue methods.

Annex 1, Table 5

Suggest deletion of table 5.

Rationale: This table is a copy of Table 5 in CAC/GL 71-2009, does not pertain specifically to multi-residue methods and is duplication.

Annex 1, Table 6

Add liver as a target tissue under 'Fat Soluble'.

Change 'Non ruminant (e.g. pig)*' to mammals and add liver to the column Fat-soluble for mammals and also poultry.

Suggest liver be added to footnote ** so that it would read:

"…. Fat-soluble compounds are usually present as residues at highest concentrations in fat **and liver**, so in such instances the selection of test matrices is typically fat, **liver** and muscle…"

Rationale: fat-soluble chemicals may be found at high levels in liver

BRAZIL

General comments

Brazil congratulates Canada and the United Kingdom for its work and supports the advance of the proposed draft.

The Guide is very well prepared with useful and essential principles about Performance Characteristics for Multiresidues Methods and some important aspects to provide reliable results. For instance, Paragraph 5 specifies recommendations that "laboratories engaged in regulatory analyses must be compliant with ISO/IEC 17025:2005"; "participate in appropriate proficiency testing schemes"; "use internal quality control procedures" and (Paragraph 29) specifies "Measurement uncertainty". Therefore, it is indispensable for a laboratory to consider the traceability as a background to apply the proposed Guidelines (which can be approached using some ISO/IEC 17025:2005 requirements).

Specific Comments:

Brazil proposes after paragraph 5 the inclusion of the text below in order to clarify and to remark the general ideas expressed in the text.

Paragraph 5 of the Guideline - Text to be included after the paragraph:

During the evaluation on Performance Characteristics for Multiresidues Methods, it is essential to consider the traceability, which is encompassed by the Accreditation Quality Assurance Cycle - AQAC (Figure 01)

[REFERENCE: Igor Renato Bertoni Olivares, Fernando Antunes Lopes. Essential steps to providing reliable results using the Analytical Quality Assurance Cycle. Trends in Analytical Chemistry, 2012, DOI http://dx.doi.org/10.1016/j.trac.2012.01.004]. This cycle shows that validation will verify if the method is fit for the purpose for which it is to be used, promoting the traceability of the method. Uncertainty will show the traceability of a result by offering a confidence level. Finally, QC of a routine analysis will evaluate if the method is capable of providing reliable measures that will produce results corroborating the validation and uncertainty. These items (validation, uncertainty and QC) need to be evaluated using calibrated equipment (traceability of the equipment) and certified standards (standard traceability). Equipment (e.g., balances, micropipettes and other generally calibrated instruments) in ISO/IEC 17025-accredited laboratories ensure traceability. The RM producer has to demonstrate that it operates in adequate conditions (e.g., it should be certified by ISO Guide 34).

Finally, it is possible to understand the association of all of the items shown in the AQAC – validation, uncertainty, and QC – because all of these aspects when applied, while utilizing calibrated equipment and certified standards, promote traceability and produce reliable results.

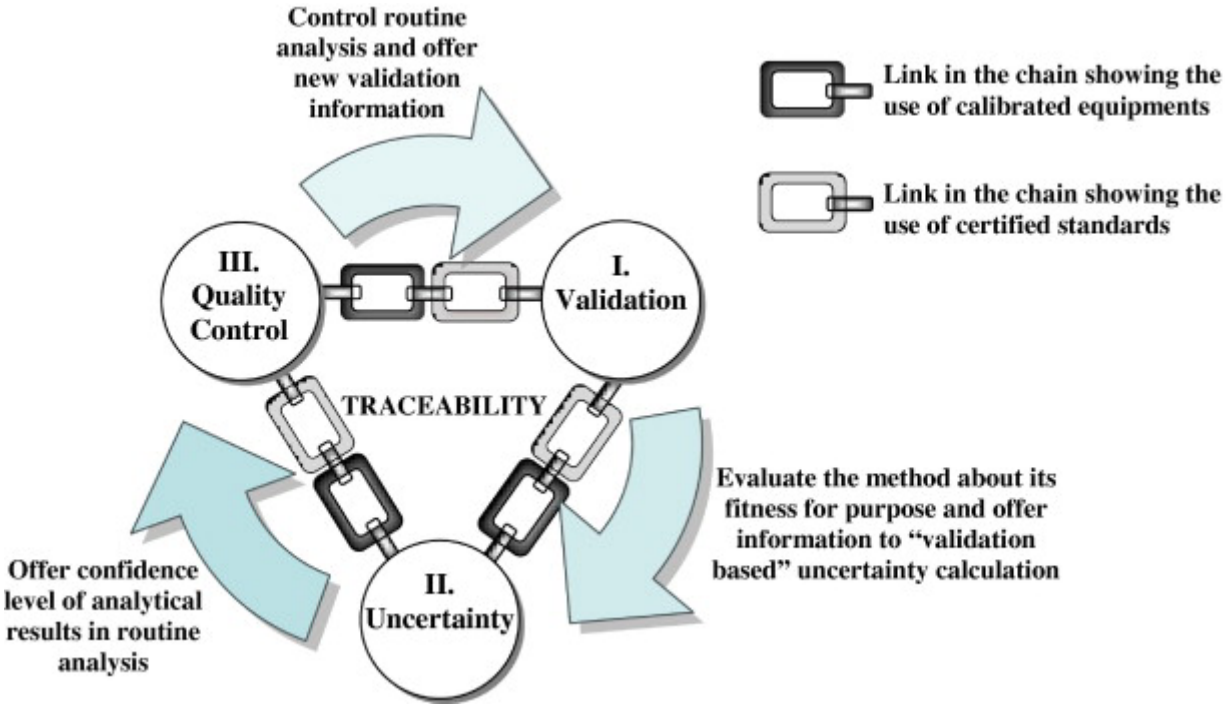

Figure 01. Analytical Quality Assurance Cycle [REFERENCE: Igor Renato Bertoni Olivares, Fernando Antunes Lopes. Essential steps to providing reliable results using the Analytical Quality Assurance Cycle. Trends in Analytical Chemistry, 2012, DOI http://dx.doi.org/10.1016/j.trac.2012.01.004]

Correction in Paragraph 9 – There are references to document SANCO 10684/2009, but the document SANCO/10684/2009 is now superseded by the new update: Document N° SANCO/12495/2011.

CHILE

General Comments

We support the draft.

Specific Comments

We want to present some specific comments to the Proposed Draft to paragraphs 20, 21, 22, 24, 26, 29, 31, 41, 42, 47, Table 1 and the Glossary of Terms, as follows:

20. The ~~accuracy~~ **Veracity** (~~trueness, bias~~)

"...The accuracy requirements of methods will vary depending upon the planned regulatory use of the results. The **veracity** ~~accuracy~~ should be carefully characterized at concentrations around the MRL or target concentration for regulatory action to ensure that regulatory action..."

Rationale

According to what has been proposed in this paragraph, only the veracity is being referenced, therefore it wouldn't correspond, in accordance with the official Codex terminology (CAC/GL, 72-2009), to use the veracity or bias as a synonym for accuracy.

21. *Recovery* is usually ~~expressed~~ **determined** as the percentage of analyte experimentally determined after fortifying of sample material at a known concentration and should be assessed over concentrations that cover the analytical range of the method.

22. *Precision*, ~~which quantifies the variation between replicated measurements on test portions from the same sample material~~, is also one of the important considerations in determining when a residue in a sample should be considered to exceed an MRL or other regulatory action limit. ~~Precision of a method is usually expressed in terms of the within-laboratory variation (repeatability) and the intra-laboratory variability (reproducibility) when the method has been subjected to a multi-laboratory trial.~~

Rationale

The relevance of introducing this phrase in the guidelines should be evaluated, as repeatability is within the laboratory, the reproducibility can be either within or between laboratories, since what has been pointed out is not quite right.

For a single laboratory method validation, precision should be determined from experiments conducted on different days, using a minimum of six different tissue pools, different reagent batches, preferably different equipment, etc., and preferably by different analysts. Precision of a method is usually expressed as the standard deviation. **Similarly to the relative standard deviation (RSD) or (RSD%).** ~~Another useful term is relative standard deviation (RSD), or coefficient of variation/variability (the standard deviation divided by the absolute value of the arithmetic mean). The RSD may be reported as a percentage by multiplying by 100.~~

Rationale

The scope mentioned about the synonym for RSD is already covered in the Codex definition. To this effect and maybe to avoid making this guidance too long, it might not be necessary to mention it. Or it could also be incorporated in the annexes.

24. There can be some degree of ambiguity in the scientific literature around the terms “matrix fortified” and “matrix matched”. Terminology has been proposed to clarify this position (REFERENCE: Wang, J., Cheung, W., & Grant, D. (2005) Determination of pesticides in apple-based infant foods using liquid chromatography electro spray ionization tandem mass spectrometry, J. Agric. Food Chem. 53. 528-537) and the definitions below will be used in this text.

Remarks

We suggest clarifying these terms by the MSCC for all the methods, not only for RMV, as this could cause some worries in other areas like pesticides.

26. ~~The accepted definition for sensitivity (CAC/GL 72-2009) is: “the quotient of the change in the indication of a measuring system and the corresponding change in the value of the quantity being measured”, a property associated with the slope of the calibration curve and the ability to discriminate changes in concentration of the analyte. It is necessary to establish the lower limits at which reliable detection, quantification or confirmation of the presence of an analyte may be performed using a particular analytical method.~~

Rationale

We do not consider it necessary to duplicate the definition, as it is already in the guideline (CAC/GL, 72 2009), so it is better to have it as an annex.

29. *Measurement uncertainty* is defined in CAC/GL 72-2009 as the “non-negative parameter characterizing the dispersion of values being attributed to a measurand, based on the information used”. There is no agreed standard approach to calculating measurement uncertainty and a number of approaches have been published

on this [REFERENCE: CAC/GL 59-2006: Guidelines on estimation of uncertainty of Results (Annex, amended 2011). ~~REFERENCE: Technical Specification ISO/TS 21748:2004: Guidance for the repeatability, reproducibility and trueness estimates in measurement uncertainty estimation. First edition 2004-03-15.].~~ ISO/IEC 17025:2005 requires laboratories to determine and make available the uncertainty associated with analytical results. SANCO/10684/2009 suggests a practical approach for a laboratory to estimate its uncertainty measurement and to verify its estimation based on its own within-laboratory data is by evaluating its performance during proficiency tests.

Remarks

It the topic of measurement uncertainty is going to be commented on, the Codex only points out non-specific, general guidelines, as internationally there is not just one way to determine it, therefore we suggest mentioning SANCO as a footnote rather than in the text.

31. *Selectivity*, ~~the ability of the method to identify unequivocally a signal response as being exclusively related to a specific analyte, is the primary consideration for confirmatory methods~~ ***is a method's*** **ability of the to determine specific analytes in mixtures or matrixes without the interference of other components of similar behavior.** Certain instrumental techniques, such as Fourier infrared transform spectroscopy or mass spectrometry, may be sufficiently selective to provide unambiguous identification. These are often the techniques on which confirmatory methods are based.

Rationale

We suggest using the selectivity definition already agreed on Codex, and to not mention it in the guideline but rather as an annex (just like all the other definitions mentioned above).

41. ***Robustness*** ~~**Ruggedness (Robustness)**~~ **testing** may be conducted using the standard factorial design approach to determine any critical control points where minor variations in the method may result in a statistically different analytical result. REFERENCE: Youden, W.J. & Steiner, E.H. 1975. *Statistical Manual of the Association of Official Analytical Chemists*. Gaithersburg, USA, AOAC International.]. Typical factors to consider in a design include variations in reagent volumes or concentrations, pH, incubation or reaction time and temperature, reagent quality, and different batch or source of a reagent or chromatographic material. Ruggedness testing may also be conducted using other designs such as the Plackett-Burman approach. Ruggedness of a confirmatory method may be required if the method differs significantly from the quantitative method previously validated (e.g. if the method uses different extraction or derivatisation procedures than are used in the quantitative method).

Rationale

The correct term in Spanish is Robustness, as mentioned I the Codex, analytically it does not correspond to the term ruggedness.

42. *Cost-effectiveness* is the use of reagents and supplies that are readily available in the required purity from local suppliers and equipment for which parts and service are also readily available. The *method efficiency* is increased when multiple samples can be analyzed at the same time. This reduces the analytical time requirements per sample and usually reduces the cost per sample, as there are certain fixed costs associated with the analysis of samples whether done singly or in larger sets. The ability of a method to accommodate multiple samples in a batch is important when large numbers of samples must be analyzed in short or fixed time frames. *Portability* is the analytical method characteristic that enables it to be transferred from one location to another without loss of established analytical performance characteristics.

Rationale

The inclusion of this matter in the guideline should be evaluated, as it has more to do with matters of financing, and so in this sense evaluating the feasibility of applying a method or looking at its efficiency has nothing to do with the Codex, but rather with the laboratory that must apply it, and could be incorporated as a note, and as so not leave it as a point within the guideline.

Table 1: Performance criteria that should be met by MRMs suitable for use as quantitative analytical methods to support MRLs for residues of veterinary drugs in foods.

	Coefficient of variability (CV)		Trueness
Concentration	Repeatability (within-laboratory)	Reproducibility (between-laboratory)	Range of mean recovery*
(µg/kg)	(%)	(%)	(%)
≤ 1	36.	54.	50–120
1 a < 10	32.	46.	60–120
10 a < 100	22.	34.	70–120
100 a < 000	18.	25.	70-110
≥ 1 000	14.	19.	70-110

Comment

The Codex lays out the guidelines to set relative numeric values to the criteria to be 71.

GLOSSARY OF TERMS*

Matrix (Matrix Blank)	Sample material containing no detectable concentration of the analytes of interest.
Method matrix-matched standard calibration curve (MMSCC)	Method matrix-matched standard calibration curve (MMSCC) but also known as a matrix-fortified standard calibration curve – a calibration curve prepared by addition of standards to blank matrix prior to extraction.
~~**Method**~~	~~The series of procedures from receipt of a sample for analysis through to the production of the final result.~~ *Measurement Method:* Generic description of a logic organization operations used in a measurement. **Rationale** We consider best to leave the official Codex definition.
~~**Method Validation**~~	~~Process of verifying that a method is fit for purpose.~~ **Rationale** Clarify the meaning of this term, typically what we have are validation procedures, and not validation methods, or are they referring to validated methods? We propose to use the following definitions instead of the Validation Method that also are approved Codex definitions. ***Validation:*** **Verification that the specified requirements are suitable for their predicted use.** Reference: VIM, International Vocabulary of Metrology – Basic and general concepts and associated terms, 3rd edition, JCGM 200: 2008. ***Validated Trial Method:*** **Trial Method accepted for those validation studies that have been conducted for the purpose of determining its precision and reliability for a specific purpose.** Reference: ICCVAM Guidelines for the nomination and submission of new, revised and alternative test methods, 2003.
~~**Reference Method**~~	~~Quantitative analytical method of proven reliability characterised by well-established trueness, selectivity, precision and sensitivity. These methods will generally have been collaboratively studied and are~~

~~usually based on molecular spectrometry. The reference method status is only valid if the method is implemented under an appropriate QA regime.~~

For Codex Reference Method (Type II) is defined as that one used when Type I is not applicable.

Rationale

We don't think is convenient to include definitions which Codex already have terminology for, because it can cause confusion between different documents.

Rationale

In general, we suggest to include only those terms that are not in the Codex general guideline.

COSTA RICA

Costa Rica appreciates the opportunity to submit comments on the "Proposed Draft Guidelines on Performance Characteristics for Multi-Residue Methods," with which, after close analysis of the document, we conclude that we agree.

KENYA

Issues and observations

The proposal from the eWG is acceptable.

Comments

The proposal should be advanced to the next step.

PHILIPPINES

(i) General Comments

- Experts from the Philippines have reviewed the proposed draft and would like to congratulate the electronic working group for a job well done. Only a few comments were made on the current draft. Philippines does not oppose the proposed performance characteristics. However, we have reservations on advancing this document in the Step process because developing countries like ours will have difficulties when working towards using these guidelines. Hence, we recommend conducting training course for developing countries to gather additional data to either support or counter the proposed performance characteristics. Meantime, the draft proposal can be retained at Step 3.
- Philippines supports the development of a database of multi-residue analytical methods to be hosted by IAEA and would gladly contribute our available methods.

(ii) Specific Comments

Reference	Proposed Change	Rationale
Paragraph # 47, Section (c) (iii)	(iii) Precision ~~and Measurement Uncertainty~~ **(iv) Measurement Uncertainty**	Precision and measurement uncertainty are two separate concepts

UNITED STATES OF AMERICA

The United States notes that the "Proposed Draft Guidelines on Performance Characteristics for Multi-Residues Methods" is a well-researched document based on established science. However, issues regarding implementation in regulatory laboratories and method development considerations must be further addressed. In particular, the way that method performance is outlined in this document does not take up method characteristics that must be considered for the use of multiresidue analytical methods (MRMs) in regulatory programs. The draft document does not provide clear guidance for the practical implementation of a validated method into an established laboratory management system, and into an overall regulatory program. A method alone is insufficient for regulatory use. Rather a laboratory regulatory system of

measurement and sample handling is needed. The two aspects that need to be included in this measurement system are the transferability of the method, determination of sample stability and long-term storage. In addition, an intra-laboratory test procedure whereby the laboratory could assess, whether the method and the analysts were operating in a state of control, and lastly, what are the elements of a system of measurement for regulatory purposes.

Specific Comments

In paragraph 8 the definition of a Multi-Residue Method states, **"For the purposes of this document, a MRM is considered to be a method which includes three or more analytes in the same class or more than one class of veterinary drugs in its scope. These MRMs are most commonly used by laboratories for screening samples for the possible presence of veterinary drugs in samples but they can also be used for both quantitative and confirmatory analyses."** The United States does not fully support this definition because it is very limiting in its scope. We consider the current definition as a practical initial start but we expect modification of this definition as our knowledge and experience in developing MRM advances.

Paragraph 18 states, **"It is recommended that methods used to support Codex MRLs should meet the performance standards for trueness and precision listed in Table 1. These standards are the same as the current limits applied for single analyte veterinary drug residues in CAC/GL 71-2009 and consideration of data from laboratories using MRM suggest they can be adopted for MRM, especially if confirmatory analysis are conducted using different analytical methods more specifically suited for individual analytes."** The United States is concerned that this definition might be too restrictive in these criteria and recommend that they be relaxed. It is our experience when validating and implementing MRMs that include analytes of different structural or chemical classes that the single analyte criteria for trueness and precision listed in table 1 cannot be met by a fully functional regulatory laboratory.

Paragraph 20 the last sentence states, "**Where no guidance is available to provide a target concentration, it is proposed that an interim value in the 1.0 to 10 ug/kg is adopted provided there can be reasonable confidence there will be no significant toxicological implications whilst more formal advice is sought."** If no guidance is available on what levels of analyte are important, the U.S. is concerned that the laboratory scientist would be burdened with making what is basically a toxicological, metabolic or physicochemical judgment for which they might not be fully qualified to make. This could result in a method that cannot measure the necessary concentrations or in the laboratory expanding both intellectual capital and funds to develop an exquisitely sensitive method that may not be needed. Our view is that the request for method development should always contain the information on the required method sensitivity and associated metabolites of interest. We would strongly recommend that the laboratory scientist have a written or oral briefing on the metabolism of the drug of interest combined with guidance from the risk managers on the appropriate concentration to target. Codex provides guidance for conducting risk analysis (**Working Principles for Risk Analysis for Food Safety for Application by Governments. WHO, First edition. 2007.)** Available at **ftp://ftp.fao.org/codex/Publications/Booklets/Risk/Risk_EN_FR_ES.pdf)** which may assist in the establishment of interim values in the absence of national or other guidance.