codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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**Agenda Item 9** **CX/RVDF 04/15/7-Add.1**
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**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

**CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS**

**Fifteenth Session**

***Washington, DC (metro area), (United States of America), 26- 29 October 2004***

# PROPOSED DRAFT REVISED PART II "GENERAL CONSIDERATION ON ANALYTICAL METHODS FOR RESIDUE CONTROL" OF THE CODEX GUIDELINES FOR THE ESTABLISHMENT OF A REGULATORY PROGRAM FOR THE CONTROL OF VETERINARY DRUG RESIDUES IN FOODS

**Comments submitted by Argentina, European Community, United States of America, Venezuela, and AOAC International**

## ARGENTINA

Argentina would like to thank the Committee Secretariat for the opportunity to submit comments regarding this document.

Argentina recommends eliminating the definition and use of the term "specificity," and to refer only to the term "selectivity", as defined by the International Union of Pure and Applied Chemistry (IUPAC) and the CCMAS in paragraph 69 of Alinorm 04/27/23.

The IUPAC definition for selectivity is as follows: *SELECTIVITY (IN ANALYSIS): Qualitative: The extent to which other substances interfere with the determination of a substance according to a given procedure*. [IUPAC Compendium of Chemical Technology, 1987]

Paragraph 69, Alinorm 04/27/23, REVIEW OF THE ANALYTICAL TERMINOLOGY FOR CODEX USE IN PROCEDURAL MANUAL, states the following:

*Specificity*

*69) The Delegation of Austria noted that the definition of "specificity" was quite similar to "selectivity" and that its use created some confusion especially as "specificity" defined in Codex did not include the words "of similar behavior" which were necessary for gaining and quenching effects of matrix substances. The Committee was informed about recently published statistical approaches for estimation of selectivity, based on the IUPAC definition. As "selectivity" was well defined in IUPAC, the Committee agreed to delete the definition of "specificity" and in the future to refer only to "selectivity" as defined in IUPAC.*

## EUROPEAN COMMUNITY

The European Community supports the general principles of the document considering the quality and applicability of analytical methods to be used in residue control. Nevertheless, the document contains many repetitions and redundancies; it could therefore be considerably shortened without loosing out on details. It would moreover make the document more readable if the definitions explained and used in the document were listed in a glossary or in one list. Definitions for the different types of methods (screening, determinative, confirmatory etc.) should be included in such a list.

Overlaps with document CX/RVDF 04/15/7 *Codex Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* should also be avoided (see in particular points 1, 2, 3, 38, 39-42) and "*Method Development Considerations*" do, in our view, not fall under the scope of this document (point 16).

The outcome of the discussions of *Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL* (Bangkok, 24 – 26 August 2004) should be considered before redrafting points 6 and 38.

The European Community can support the principle of single laboratory validation (points 15 and 43).

Point 4 and 8: We agree that methods of analysis used in regulatory programmes for control should be fit for purpose. The purpose of individual parts of regulatory programmes differs, in particular with respect to type and detail of information they focus on. The requirements for methods of analysis will therefore depend on the type of the regulatory programme they are employed in (e.g. *System Verification Programmes* or *Targeted Programmes*, see page 7 of CX/RVDF 04/15/7).

Point 5 and 42: We would not completely rule out the use methods for screening which do not provide information on the chemical structure of the residues such as "*plate tests*" linking bacterial growth inhibition patterns to specific antimicrobials. However, here the method determines the result and how it is communicated (e.g. "*growth inhibition observed*"). Therefore these methods have to be described in detail, agreed and to be implemented precisely as documented in order to produce widely acceptable and comparable results. They may also be used alone, but procedures should allow the rebuttal of "positive" test results on reversal of the burden of proof.

Point 11: If particular historical methods are to be accepted, the criteria should be better defined. It is not clear what is required if the "*method performance has been demonstrated through successful use in various laboratories over time*".

Point 27: While the *AOAC Performance Test Program* may be a reliable procedure to validate screening test, an international standard should avoid exclusive reliance on programmes of one provider. We would consider it more appropriate if the required performance of a screening method (e.g. the maximal percentage of false results) could be defined.

Further details are necessary to provide the guidance which allows laboratories to clearly identify what Codex Alimentarius considers acceptable. It should, for example, be indicated what is the *required sensitivity* (point 20), what combined information is necessary to make a statement on sensitivity (point 20 and 26), what would be an appropriate *level of interest* (point 24 and 31) and what would be a *suitable level of performance* (point 22).

**UNITED STATES OF AMERICA**

The U.S. thanks Canada for the preparation of the document. Our comments are intended to expedite the advancement of the document so that it might be incorporated into an updated Codex Alimentarius Volume 3 when the other major components are available.

Specific comments

Paragraph 1. The U.S. suggests that on line 2, to insert "important for residue or regulatory control" to assure that methods considerations are focused on assays of a specific marker or series of metabolites rather than methods for residues that may not be known or assayed.

Paragraph 3. It is known that many residue control laboratories may develop their own procedures and not simply choose from a list of available methods. Therefore, we suggest inserting "and/or develop" following "residue control programmes must identify and select" on lines 4 and 5.

Paragraph 4. We suggest that a reference to definitions of limit of detection and limit of quantification be referenced in paragraphs 30 and 31.

Paragraph 6. There are reasons other than toxicology for not establishing an ADI or recommending MRLs. We suggest that following "toxicology" in line 3, that "or other relevant factors" be inserted.

Paragraph 28. While informative and prescriptive about specific concentration for fortification purposes, it should be considered to give a set of limits without being as specific, such as 30-250% of the MRL, allowing some flexibility to laboratories. Second, there is some ambiguity regarding matrix standard curves. We note that this is not a generally accepted approach supported by FDA-CVM.

Paragraph 29. On line 2, change "quality" to "quantity" of analyte to be determined.

Paragraph 31. Reference is made to Table 1, but it is not included in the document.

Finally, the U.S. suggests that a section on sources of reference standards may be appropriate. Knowing how and where to obtain standards is important for all regulatory control laboratories.

We believe these are not significant matters and, therefore, support the advancement of the document.

**VENEZUELA**

Regarding the aforementioned document, Venezuela submits the following comments:

a) In paragraph 2, the term **"zero residue" should be deleted** and replaced with the term **"undetectable residues"**.

b) In paragraph 2, **the text,** "...for the other applications of residue methods for veterinary drug residues and related substances in foods," **should be deleted and replaced with** the text "...for the methods of detection of residues and related substances."

**AOAC INTERNATIONAL**

**Section 4.** The Committee should note that there appears to be a natural limit of quantification as shown by Thompson and Lowthian J. AOAC Intl. (1997) **80**, 676-679 at about 8 ppb (ug/kg). Agreement between laboratories below this concentration is not possible unless an inordinate amount of effort is devoted to the analysis as in the case of dioxins. Commercial prices for the dioxin analysis that meet the US EPA and the EU requirements are of the order of $1000 per sample and a response time of two weeks. This economic target has been in existence for over 10 years and there is little hope that "analytical detection capabilities" will evolve to encompass lower target concentrations. As the Draft document states for requirements below the natural limit "the LOQ and linearity of response over an extended analytical range become primary considerations."

To work in this region, however, requires overcoming the natural tendency of analytical residue chemists to censor their results below the LOQ and LOD by reporting "less than the LOQ [or LOD]" or by assigning arbitrary fractional values less than the LOQ or LOD to the low values. Residue work in this region must be accompanied by instructions to report analytical signals transformed to concentrations as they are read from the calibration curve, positive, negative, or zero, and permit the law of averaging to provide a reasonably good estimate of the actual value.

**Section 6.** For those methods "where detection and confirmation of the presence of the substance as a residue is the major issue" the capability of the laboratory to provide reliable information can only be verified by presentation of accompanying performance data demonstrating proficiency in examination of unknown test materials and the existence of a continuous program of quality assurance. Such programs are expensive and there is little evidence that regulatory authorities have budgets capable of supporting such requirements. Licensing, distribution control, and auditing may be cheaper and more effective means of controlling veterinary drug residues in foods than analytical methods operated near their LODs and LOQs.

**Section 8 – 15.** These sections are directed toward justifying use of lesser validated methods but they are not accompanied by an economic analysis to demonstrate that they are cost effective. All methods in the region of the MRLVDs have typical variability of the order of 20-30% between laboratories. They require acquisition and maintenance of sensitive and expensive instruments whose cost is in the region of $10^5$ –$10^6$ dollars and operated by scientists and technicians with salaries in the upper brackets. The cost of other equipment, supplies, and reagents is ever increasing. The EU has prepared methodology for the operation of a program to control mycotoxins which requires less expensive equipment than veterinary drugs. A report of the costs and results of this program may provide a basis for justifying the program on veterinary drugs or may suggest applying auditing tools to "assure a safe and wholesome food supply.". Analytical chemistry may be pricing itself out of the enforcement market. Several articles have appeared in ***The Analyst*** during the past several years supported by the UK government developing methodology for economic analysis of analytical chemistry tools.

**Section 16-38.** Method development and reliability considerations should be accompanied by cost considerations, as well as the need for the residue control program. Analytical chemists are well aware of the method development and analytical performance requirements but they have not been sensitive to time and cost. Residue enforcement administrators should now be brought in to assess the effectiveness of analytical control. The time from collection of the sample to the reporting of the results has never been factored into the method performance evaluation.

**Section 39-42.** Screening methods are suggested for their potential to rapidly eliminate the need for testing many negative test samples. Such methods necessarily operate in a region of high variability and are prone to provide numerous false positive and false negative results. Their use should be accompanied by an evaluation tied to the safety of the drug. What is the potential for harm by the inadvertent release of false negative?

**Section 43-49.** Excellent statement of principles. It should be supplemented by cost and administrative considerations.