# codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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**Agenda Item 11 (a)** **CX/RVDF 03/10 – Add. 1**

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**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

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

**Fourteenth Session**

**Arlington, VA. 4 - 7 March 2003**

## REVIEW OF PERFORMANCE-BASED CRITERIA FOR METHODS OF ANALYSIS FOR VETERINARY DRUG RESIDUES IN FOODS

## COMMENTS

Comments have been received from United States and European Community

### UNITED STATES

**General Comments:**

The United States recognizes the resource problems associated with enlisting the services of multiple laboratories to validate regulatory methods. We question if the resources necessary to initiate and maintain the quality control systems for an effective single laboratory validation program with appropriate reference materials would be less. This document should include a proposal for a quality assurance program that will validate a method in the appropriate laboratory environment.

Laboratories are often requested to test for residues in matrices for which no suitable method is available. A process to ensure that methods are properly validated at a standard acceptable across the international community is needed. However, it appears that this document sets a very high and possibly unattainable standard for validating a method with regard to resources in some countries. The purpose of having methods validated to international standards is both to facilitate trade and to provide for the public health of consumers in the member nations by allowing them to monitor for veterinary drug residues in food animal products. The level of validation proposed in this document creates problems. Specifically, the resources required to fulfill the requirements of the validation process may minimize the number of methods available for use, particularly in developing nations with limited resources.

- The U.S. wishes to make note that while the document adequately addresses the concepts for performance-based criteria for methods of analysis for veterinary drug residues, we suggest that it needs to more adequately address the analytical methods validation needs for developing countries. We draw attention, for example, to the extensive comments in chapter 6, re., capacity building, in the *Report of the Evaluation of the Codex Alimentarius and other FAO and WHO Food Standards Work.* The report indicates that "trade facilitation is seen as the most useful function of Codex standards in low-income countries". Part of this need is a means to have appropriately validated methods that support their trade opportunities. The validation needs of these Member States need to be addressed, particularly when the availability of all the recommended resources may not be available either locally or regionally. We note as well the agenda item 3(a) (CX/RVDF 03/2) with particular reference to the comments from CCASIA where they noted that CCRVDF (and other Codex Committees) give urgent attention to the resolution of the problems of abrupt changes in analytical techniques and changes in detection limits.

**Specific Comments:**

Paragraph 6 - There is a conflict between "The acceptability of results obtained using single laboratory validated methods can be demonstrated through calibration using reference materials, comparison with other methods which have a well-defined performance or systematic participation in proficiency tests." and Paragraph 6.ii. - "The single-laboratory validated methods *must* fulfill the following criteria: "…by calibration using reference materials and comparison of results with those obtained using other methods." Method proficiency schemes do not exist for many matrices. Nor are many reference materials available for veterinary drug residues in animal products. Given the large number of drugs that can be used in veterinary medicine and the large number of matrices, this sets a standard that may not be attainable for many analyte/matrix combinations. In addition, the availability of multi-laboratory validated methods for many drug classes is limited.

Paragraph 6.i. - Please clarify the requirement "No inter-laboratory validated method is *appropriate*." It is a very broad statement and can be read to allow the user to reject using a validated method for any reason, however trivial. The possibility of no available method would provide a reason for development of additional methodology, but what determination is used for concluding the inappropriateness of a method versus the unavailability of such a method.

Paragraph 11 - A definition for recovery compared to extraction efficiency (paragraph 13) and accuracy (Paragraph 9) is needed.

Paragraph 13, 17, 21.i., & 23.ix. - This document defines specificity and selectivity as the same parameter, while the AOAC/FAO/IAEA/IUPAC document from which this criteria list was derived defines *specificity* as the "extent to which a method provides responses from the detection system which can be considered exclusively characteristic of the analyte," while *selectivity* is defined as the "measure of the degree to which the analyte is likely to be distinguished from other sample components, either by separation (e.g., chromatography) or by the relative response of the detection system." This dichotomy should be addressed.

Paragraph 18 - This requires that quantitative information always be available. For unapproved substances, such as chloramphenicol, the use of a well characterized screening test followed by confirmation should be adequate. As long as the limit of confirmation is known for the confirmatory method, it is not necessary to have definitive quantitative information.

Paragraph 21 - Many screening tests are commercially available. What is needed is guidance to implement a screening test that has successfully been through a third party validation, such as the AOAC-RI program, into a laboratory testing program.

Paragraph 21.i. - While the use of six different sources of tissue is a good idea, it may impede the ability of laboratories in developing countries to validate methods. This requirement occurs in several places throughout the document.

Paragraph 21.vi. - In addition, the response of the screening test for each approved analyte in the same drug class should be monitored at its respective MRL.

Paragraph 23.i. - For single laboratory validated methods, comparison to authentic samples should be a requisite, as determination of recovery from analyte fortified control tissue does not provide sufficient information.

Paragraph 23.iii. - Clarify the purpose and use of the blank in the calibration curve and what is done with the information collected. It is inappropriate for any value obtained from a "zero" level standard to be used for the calibration statistics. Additionally, many methods use a four-point standard curve. The use of one less standard does not appear to negatively impact on the performance of these methods

Paragraph 23.iv. - Depending on when and how a tissue standard curve is created, it may or may not correct for recovery. Methods exist where the standard is added before extraction (which will correct for recovery), and where the standard is added to the final extract (which will not correct for recovery). The use of a standard curve prepared in matrix should be used in conjunction with the analysis of batch stored quality control samples, so that the method recovery may be evaluated. This is especially critical when standardized reference materials, and even incurred residues, are unavailable to test method performance.

Paragraph 23.v. - Clarification is needed for the statement "(generally taken to be 1%)." This appears to be an overly rigorous standard.

Paragraph 23.vi. & vii. - Limit of Detection (LOD) and Limit of Quantitation are variable parameters, depend on the conditions under which they are obtained, and may be estimated using multiple equations. In many cases, the LOD cannot be calculated from the y-intercept of the standard curve. The useful range of a standard curve is between the concentrations evaluated, and it is not uncommon for the y-intercept to be negative, preventing the calculation of LOD from this parameter. Therefore, it is recommended that the minimum concentration for a validated method be restricted to the lowest calibration standard to adequately evaluate the range of critical concentrations.

Paragraph 23.viii. - If the method is to be tested in only one laboratory, it should be a requisite that the method is performed by more than one independent analyst. In addition, as precision has both inter- and intra-laboratory components, it is necessary for the intra-laboratory component (repeatability) be presented as one of the method parameters for comparison purposes. We agree, the inter-laboratory component of the method may only be determined from multiple laboratory testing.

Paragraph 23.x. - The use of the Youden approach to determine analytical method critical control points is good, and widely used. However, there are cases where it is not the best approach to use. One of the requirements of this test is that the factors be independent of each other. This is not always the case, and therefore, other valid approaches to the evaluation of critical control points should be allowed. In addition, once ruggedness testing is completed, these measurement variations should be listed in the method standard operating procedure (SOP).

Paragraph 25.i. - Only the EU guidelines for confirmation are given. Alternate criteria are available and should also be considered.

**EUROPEAN COMMUNITY**

The European Community supports the CX RDVF's attempts to harmonise performance criteria for methods to be employed for the control of residues and to develop guidance for single laboratory validation. The EC therefore agrees that the "*Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Food*" and in particular "*Part II, General Considerations on Analytical Methods for Residue Control"* should be revised to introduce these concepts. However, the EC feels that the concept underlying the draft "*Codes Guidelines on Good Practice in Pesticide Residue Analysis*" should only be considered with caution. This is because this draft largely covers issues that are already covered by ISO-17025 (e.g. laboratory equipment) and is routed on OECD Good Laboratory Practice (GLP). GLP, however, focuses more on the traceability of the results of studies on specific substances than on the trueness of analytical results established in routine laboratories. In this respect particular attention should be given to acceptable recovery rates.

The EC's understanding is that laboratories involved in residue testing programmes for regulatory purposes should be requested to implement quality assurance systems according to international standards such as ISO-17025. This is also a key feature of the single laboratory evaluation procedure.

At its 13th meeting the CCRDVF agreed that further work on the performance of analytical methods would be based on the work in progress in the EU, AOAC and IUPAC (paragraph 100 of ALINORM 01/31). The EC would like to point out that the work in Europe has considerably progressed with the adoption of *Commission Decision 2002/657/EC of 12 August 2002 implementing Council Directive 96/23/EC concerning the performance of analytical methods and the interpretation of results*. A copy of this document which covers all aspects addressed in CX RDVF 03/10 is available on http://europa.eu.int/comm/food/fs/sfp/fcr/labanalysis_en.html. It has also been published in the *Official Journal of the European Communities L 221, 17/08/2002 P. 0008 – 0036.*