codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 12(a) **CX/RVDF 01/12**
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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS
Thirteenth Session, 4-7 December 2001
Charleston, South Carolina, USA

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

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 1 November 2001** as follows: U.S. Codex Office, Food Safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th and Independence Avenue, S.W., Washington, DC 20250, USA (Fax No: +1.202.720.3157; e-mail: uscodex@usda.gov), with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

BACKGROUND

1. At the 12th session of the CCRVDF, the Committee agreed that a drafting group (Australia, Canada, Costa Rica, France, Netherlands, United States, COMISA) would consider the criteria for the selection of methods of analysis contained in the *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drugs in Foods (CAC/GL 16-1993)* in the light of recent developments in method validation at the international level, and prepare proposals for consideration at the current meeting.[1]

DISCUSSION

2. At the present time, there is no clear and unequivocal guidance document on method validation within a single laboratory that has been established as an international standard by an independent scientific organisation, such as the International Union of Pure and Applied Chemistry (IUPAC). However, two expert consultations (Vienna, 1998; Miskolc, 1999) have recommended that such an approach should be recognised as a viable means to identify methods which should be suitable for use in a regulatory program to support recommendations for Maximum Residue Limits (MRLs) specified by the Codex Alimentarius Commission. Furthermore, these consultations not only recommended the technical specifications that should be considered in the evaluation of analytical methods in a single laboratory, but also recognised that laboratories using methods must be able to demonstrate the capability to acceptably perform analytical methods. A key feature of the single laboratory evaluation procedure is the laboratory should be able to demonstrate its analytical expertise, quality assurance procedures and qualifications that will support the authority of their analytical conclusions. The single

[1] ALINORM 01/31, paras. 98-101.

laboratory procedure considers that method performance is a direct result of the competence of the laboratory providing the analytical service.

3. While the use of an interlaboratory study is the traditional approach to evaluating the performance of analytical methods, the evaluation of methods in a single laboratory does not imply that such methods are inherently unreliable or unsuitable for use in a regulatory program. It means simply that the methods have not been subjected to a performance characterisation through an interlaboratory trial as defined by the harmonised protocol for the design, conduct and interpretation of method performance studies.

4. At the 23rd Session of the Codex Committee on Methods of Analysis and Sampling in Budapest from February 26 – March 2, 2001, the Committee was informed[2] of the progress of a guideline document on single laboratory validation within IUPAC, but could not adopt these guidelines by reference because they were not yet published in their final form. It was also noted that these guidelines did not provide practical guidance on how to proceed with single laboratory validation.

5. It was considered that the lectures presented at the AOAC/FAO/IUPAC/IAEA Workshop on Principles and Practices of Method Validation (4 - 6 November 1999, Budapest, Hungary) had been published in the scientific literature[3], including the Guidelines for Single Laboratory Validation of Analytical Methods for Trace-Level Concentrations of Organic Chemicals, which were subsequently finalized by the FAO/IAEA/AOAC Expert Consultation on Practical Procedures to Validate Methods Performance of Analysis of Pesticide and Veterinary Drug Residues and Trace Organic Contaminants in Food (8-11 November 1999, Miskolc, Hungary).[4]

6. The Committee (CCMAS) generally recognised that single laboratory validation could be used for Codex purposes and agreed that the inclusion of a specific text in the Procedural Manual would be considered at the next session.

7. The Codex Committee on Pesticide Residues (CCPR), at its 33rd meeting in April, 2001, recalled that the revision to the Guidelines on Good Laboratory Practice had been approved as new work by the 47th CCEXEC and agreed that the proposed draft Revised Guidelines should be appended to the report and circulated for comments at Step 3.[5]

8. While there currently is no agreed procedure for the validation of analytical methods in a single laboratory, consensus appears to be developing on the general technical details that should be evaluated in laboratories evaluating analytical methods. This can be inferred from a consideration of the confluence of ideas on this issue that have independently emerged from the various consultations referenced above. The specifications for the evaluation of analytical methods as laid down in CCRVDF are consistent with the views elaborated by these more recent consultations.

9. For example, the Codex Alimentarius, Volume 3 (2nd Edition, 1994) describes the set of attributes or properties which were considered to determine the usefulness of a given method. The usefulness of an analytical method was to be determined through an inter-laboratory trial involving a minimum of three analysts. The scientific issues to be evaluated were as follows:

a. specificity
b. precision
c. bias or systematic error
d. accuracy

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2 ALINORM 01/23, paras. 65-84; also see document CX/MAS 01/9

3 Principles and Practices of Method Validation, Royal Society of Chemistry, Cambridge, 2000.

4 A Summary Report of the Workshop, relevant information concerning the Workshop and Consultation, and the Guidelines developed by the Consultation are available on the IAEA website at: http://www.iaea.org/programmes/rifa/trc/pest-qa_val.htm

5 ALINORM 01/24A, paras. 204-205 and Appendix VII.

e. limit of detection
f. method sensitivity
g. practicality of use
h. tissue/species applicability
i. limit of quantitation
j. false positive/false negative responses

10. The Codex Alimentarius Commission Procedural Manual (11th edition, 2000, page 73) lists the following criteria for the selection of analytical methods, which were normally to be derived through a formal inter-laboratory collaborative study:

a. specificity
b. accuracy
c. precision; repeatability intra-laboratory; reproducibility inter-laboratory
d. limit of detection
e. sensitivity
f. practicality and applicability under normal laboratory conditions
g. other criteria which may be selected as required.

11. Criteria identified by FAO/IAEA/AOAC Consultation in Miskolc, which was considering criteria for validation of a method within a single laboratory, included the following:

a. specificity
b. analytical range, including recovery through extraction, clean-up, derivatization and measurement
c. calibration range for determination of analyte
d. limit of detection
e. limit of quantitation
f. reporting limit, or lowest calibrated level (LCL)
g. analyte stability in sample extracts
h. analyte stability during sample storage and processing
i. analyte homogeneity in samples
j. accuracy
k. trueness
l. precision
m. selectivity
n. extraction efficiency
o. purity of reagents and materials

12. In addition, the Consultation provided specific guidance on what experiments should be conducted to determine adherence to these criteria in the two situations of pesticide residues and veterinary drug residues in foods. The expanded criteria recommended for inclusion in the validation address some issues which normally would be resolved prior to a collaborative or inter-laboratory trial (analyte stability, sample homogeneity, purity specifications for reagents and materials), as well as introducing the practical considerations of the specifications for calibration range required. The support of an MRL requires that a method perform in good statistical control within the analytical range that brackets the MRL.

13. In such cases, performance of the method within that range and the inclusion of appropriate calibration points (including the lowest calibrated level, or LCL) may be more important than a characterisation of a limit of detection or limit of quantitation. The issue of method selectivity and in particular the ability of a method to provide unequivocal identification of an analyte was also seen as critical and recognised recent work to establish a minimum number of identification points which should be required to provide confidence in a confirmatory result.

14. One can see that there is a commonality of views on the crucial technical items that should be considered in the evaluation of an analytical method. It is also apparent, however, that the various consultations on the analytical method validation issue are also evidencing a jointly evolving common understanding of what should encompass single laboratory evaluation of analytical methods. More work and concurrence on specific technical details must be done, but it is clear that these specific technical details are beginning to emerge.

15. Considering the array of activity on the single laboratory method evaluation procedure that has occurred and is on-going, the opportunity for a harmonised analytical method evaluation procedure across Codex Committees is a good possibility. In view of this, rather that initiate a separate, new initiative within CCRVDF to develop analytical criteria, the following recommendations are set forth for discussion and concurrence of the WG.

RECOMMENDATIONS:

16. In consideration of the deliberations of the CCMAS and CCPR earlier in 2001, the following recommendations should be considered by the *Ad hoc* Working Group on Analytical Methods and Sampling:

a. That the Committee (CCRVDF) support attempts to harmonise procedures for the identification of suitable methods of analysis to support MRL recommendations with those recommended by CCMAS and CCPR.

b. That the Committee (CCRVDF) take note of the intention for CCMAS to include text on single laboratory validation of methods in a future revision of the Procedural Manual.

c. That the Committee (CCRVDF) consider the attachment of a document developed from the recommendations of AOAC/FAO/IAEA Consultation in Miskolc with respect to the criteria and practical guidance for the validation of analytical methods for residues of veterinary drugs in foods to the Report of the 14th Session, to seek government comments through the Codex procedure, as has been done by the 33rd Session of the CCPR. This document is the product of a drafting group assignment (Australia, Canada, Costa Rica, France, Netherlands, United States, COMISA) by the 12th Session of the CCRVDF.