codex alimentarius commission E

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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Agenda Item 7 **CX/RVDF 09/18/7**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Eighteenth Session

Natal, Brazil, 11-15 May 2009

DISCUSSION PAPER ON CONSIDERATION OF METHODS OF ANALYSIS AND SAMPLING IN CCRVDF

(Report of the electronic Working Group on Methods of Analysis and Sampling)

Governments and international organizations wishing to submit comments on the Discussion Paper (Report of the electronic Working Group on Methods of Analysis and Sampling) are invited to do so **no later than 31 March 2009** as follows: U.S. Codex Office, Food safety and Inspection Service, US Department of Agriculture, Room 4861, South Building, 14th Independence Avenue, S.W., Washington DC 20250, USA (Telefax: +1 202 720 3157 ; or ***preferably*** E-mail: uscodex@usda.gov, with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, Viale delle Terme di Caracalla, 00153 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org, ***preferably***).

INTRODUCTION

1. At the 17th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF) in Breckenridge, Colorado, the Committee agreed to establish an electronic Working Group (eWG) under the chairmanship of the United Kingdom and Canada. The purpose of the eWG is to prepare a discussion paper for the 18th session of the CCRVDF to address the following issues:-

- The future of the compendium of analytical methods compiled by the *ad hoc* Working Group on Methods of Analysis and Sampling;
- The link between analytical methods and advancing Codex Maximum Residue Limits (MRLs) to Step 8; and
- The criteria necessary for analytical methods to be assessed and considered suitable.

2. This paper has been prepared the United Kingdom and Canada, with input from Australia, Belgium, Germany, the Netherlands, Norway, Japan, Sweden, and IFAH.

BACKGROUND

3. At the 17th Session of the CCRVDF in Breckenridge, Colorado, in 2007 the United Kingdom co-chair of the Working Group on Methods of Analysis and Sampling reviewed the background linking the MRL-setting process in the CCRVDF to the need to assess analytical methods for regulatory use. The CCRVDF had previously agreed that MRLs could not progress from Step 7 to Step 8 without the Working Group on Methods

of Analysis and Sampling assessing the suitability of analytical methods for the determination of drug residues at the MRL. Unfortunately, that practice had not been consistently followed in recent years, and the purpose of the Compendium of Analytical Methods was also unclear to many. Therefore, in order to better meet the needs of the CCRVDF, it was agreed to suspend further work on the Compendium and recommend the preparation of a discussion paper to address the issues highlighted in the introduction above.

4. The Working Group on Methods of Analysis and Sampling, therefore, agreed to recommend the formation of an eWG to be led by the UK and Canada to prepare this discussion paper for circulation and comments for the 18th CCRVDF meeting. This recommendation was endorsed by the CCRVDF.

NEED FOR ANALYTICAL METHODS

5. In 1985, the Codex Alimentarius Commission (CAC) agreed to establish a Codex Committee on Residues of Veterinary Drugs in Foods with the following Terms of Reference:

- to determine priorities for the consideration of residues of veterinary drugs in foods;
- to recommend Maximum Residue Limits (MRLs) or Maximum Residue Limits for Veterinary Drugs (MRLVDs) of such substances;
- to develop codes of practice as may be required;
- to determine criteria for analytical methods used for the control of veterinary drug residues in foods.

6. The Commission recommended that the new Committee should liaise closely with the Committee on Methods of Analysis and Sampling (CCMAS) in carrying out its mandate, and that the work already undertaken by other bodies, such as the Council of Europe, should be taken into account.

7. In establishing this new Committee it was recognised that there was a need for methods to be classified as screening methods, quantitative methods and confirmatory methods with performance characteristics demonstrated by evaluating their accuracy, precision, reliability, cost effectiveness, ruggedness and sensibility in multi-laboratory validation studies.

8. In 1987, a paper, "Criteria for Analytical Methods", was developed as a framework for general criteria. It was also emphasized that it was necessary to characterise analytical methods by their attributes to give broadest consideration to the scope of analytical methods to be considered for specific substances of interest to CCRVDF.

9. In 1989, consideration was given to the development of simpler methods accessible to developing countries as well as to the international validation of methods and regional validation was proposed as a means to minimize possible problems related to the shipment of biological samples across borders. Methods would be classified as either having “recommended and adopted status” or “provisional status”.

10. In 1995, the CCRVDF supported the proposal that greater emphasis should be given to the availability of analytical methods for compounds to be considered for JECFA evaluation. It was noted with some concern that with few exceptions inter-laboratory trials of methods of analysis for veterinary drug residues were normally conducted with only a small number of laboratories. In order to improve that situation it was recommended that the initiatives already being developed (as in EEC and IUPAC) in identifying the availability of suitable materials for study, availability of competent participant laboratories and procedures for transmission of test materials be supported.

11. Serious concerns were expressed about the proposal of the CCMAS that reference methods for Codex standards required validation by a minimum of six laboratories. The CCRVDF noted that it had been difficult for analytical methods for veterinary drug residues to be validated by a minimum of three laboratories.

ANALYTICAL METHODS LINKED TO THE CODEX ALIMENTARIUS STEP PROCESS

12. The CCRVDF’s discussion in 1995 mainly covered matters related to the availability and validation of methods, and whether an MRL needed to be set before a method could be recommended. The Committee noted

that methods of analysis included in the submission to JECFA might be suitable for regulatory purposes but were not in the public domain. Furthermore, such methods would require inter-laboratory validation and to be available to regulatory authorities to be recommended for Codex purposes. The CCRVDF agreed that MRLs should be developed independently of validated methods, but such methods should be available before the CCRVDF advances MRLs to Step 8.

13. In 1996, the CCRVDF referred to the decision made at its 9th Session (1995) that if no method of analysis acceptable to the Committee was available to monitor an MRL, that the MRL should not be advanced beyond Step 7. At that time the Committee had noted the problems of inter-laboratory validation and the difficulty of validating methods in its field of competence by at least three analysts in three laboratories. The Committee had requested that a paper be prepared on the issue and include criteria for the validation of an analytical method.

14. The need for reliable methods for use in monitoring compliance with MRLs was stressed by the CCRVDF, and there was general agreement that the identification of appropriate methods was an integral part of decision-making in a risk analysis framework. However, the practical problems of applying inappropriate or unrealistic validation criteria to the identification of methods were also recognized. The Committee noted that at a national or regional level these problems seemed not to exist and more pragmatic approaches were in use; for example, methods validated using intra-laboratory criteria combined with quality systems-based laboratory accreditation. It was further noted that performance-based methods were available for many of the MRLs retained at Step 7, the only constraint being that these methods had not been validated in inter-laboratory collaborative trials. It was noted that specific problems could arise, such as reliance on costly methods which were beyond the accessibility of many developing countries.

15. Noting that its Terms of Reference required the CCRVDF "to determine criteria for analytical methods used for the control of veterinary drug residues in foods" but did not extend to the consideration of methods of analysis *per se*, the Committee agreed that all MRLs currently retained at Step 7 should be considered for advancement to Step 8 on this occasion. It reiterated the need for monitoring methods to be available in order to meet normal residue control practices, and stated that in the future, methods conforming to established performance criteria should normally be available before advancing MRLs to Step 8.

ORIGINS OF THE COMPENDIUM OF ANALYTICAL METHODS

16. In 1998, the Delegation of the United States reported that the information on analytical methods provided by Member countries in response to CL 1998/7-RVDF showed that in total methods were reported for 50 compounds considered by Codex. The initial objective of this exercise was to catalogue methods of analysis used by national governments to ascertain the availability of methods to support Codex MRLs. The next step would be to catalogue validated methods of analysis for veterinary drug residues.

17. It was noted that JECFA would bear primary responsibility for reviewing methods for compounds on its agendas of the 50th and later meetings while the Working Group would undertake a similar exercise for compounds reviewed by the 48th and earlier JECFA meetings. To make the process more transparent, the individual compound rapporteur system was replaced by teams that would evaluate methods within four classes of compounds: anthelmintics; antimicrobials; antiprotozoals, insecticides, trypanocides; and growth promoters, *beta*-adrenoceptor blockers, and tranquilizers.

18. In 2000, the Committee was informed that the following meetings relevant to method validation had been held in November 1999:

- AOAC/FAO/IAEA/IUPAC International Workshop on Principles and Practices of Method Validation; and
- AOAC/FAO/IAEA/IUPAC Expert Consultation on Single Laboratory Validation of Analytical Methods for Trace-Level Concentrations of Organic Chemicals

19. It was agreed that the outcome of the Expert Consultation, together with the work in progress in the EU, AOAC and IUPAC could provide the basis for the criteria to be developed by the Committee.

20. The Committee agreed that, since suitable validation data existed, provisional and recommended status could be applied to the methods for a number of veterinary medicines.

21. At the 12th Session of the CCRVDF in 2001, it was agreed that a drafting group 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, including work undertaken by the Codex Committee on Pesticide Residues (CCPR) and the CCMAS, for consideration at its 13th Session.

22. Also, the Committee agreed that the four task groups established at its previous session to evaluate the methods submitted or acquired should request additional information on methods that may be suitable to support the MRLs. The suitability of these methods would be assessed using the provisional text of any amended criteria.

23. The 13th Session of CCRVDF in 2002 agreed that the drafting group established at its previous session should continue to consider the criteria relating to the selection of methods of analysis for veterinary drugs contained in the *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* (CAC/GL 16-1993). The Committee agreed that the paper should consider developments in the international approach to method validation and continuing work in this area undertaken by the CCPR and the CCMAS.

24. In discussing the first four recommendations of the report of the Working Group on Methods of Analysis and Sampling, it was noted that in order to better address the needs of developing countries, criteria for method validation needed to be developed. In this regard, it was suggested that developing countries might wish to assess their method needs in order to include this in the exercise.

25. In 2004, general support was given for the document prepared by the Working Group on Methods of Analysis and Sampling, and it was agreed that the recommendations resulting from the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL related to methods of analysis and laboratories, could be addressed in the revision of Part II and III of the *Guidelines for the Establishment of a Regulatory Programme for the Control of Residue of Veterinary Drugs in Foods.* The Working Group on Methods of Analysis and Sampling had also discussed a suggestion to review Part I of the Guidelines concerning sampling, that would require additional expertise concerning statistics and sampling.

26. In 2006, the Chair of the Working Group on Methods of Analysis and Sampling presented the report of the meeting held prior to the Session, that had addressed the proposed draft revised Parts I, II, and III of the Codex *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drug Residues in Foods* and the list of methods of analysis identified as suitable to support the MRLs for Veterinary Drugs.

27. The list included new methods to support existing MRLs for veterinary drugs, and methods for compounds for which MRLs do not exist or for matrices for which there are no current MRLs for the substances.

28. The Working Group on Methods of Analysis and Sampling reorganised the list to include two separate Annexes with information on methods for:

- those substances and matrices for which validated methods were still required; and
- those substances or matrices without MRLs.

29. The CCRVDF endorsed the recommendation of the Working Group on Methods of Analysis and Sampling to seek comments on the list for the next CCRVDF meeting. The CCRVDF agreed to forward the Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs to the 29th Session of the CAC.

30. In 2007, the CCRVDF noted that the Working Group on Methods of Analysis and Sampling had considered the comments submitted but had decided not to take any action to incorporate them into the Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs at that time. This was because it had been agreed to seek the views of the CCRVDF on the purpose of the Compendium, the link

between analytical methods and the setting of MRLs and the needs of CCRVDF in relation to methods of analysis and sampling.

31. The Committee endorsed the recommendation of the Working Group on Methods of Analysis and Sampling that the work on the Compendium be suspended, on the understanding that comments submitted would be considered at a later date, if required.

USE AND VALUE OF THE COMPENDIUM OF ANALYTICAL METHODS

32. The Compendium of Analytical Methods (Appendix X of ALINORM 06/29/31) consists of analytical methods for about 50 different veterinary drugs including several species and matrices. In total this represents several hundred different analytical methods because of the range of species and tissues covered. The compilation represents a collection of analytical methods which were developed over a period of at least 20 years.

33. As discussed above, the purpose of the Compendium is primarily to be a link between analytical methods and the setting of MRLs to meet the needs of CCRVDF in relation to methods of analysis and sampling. The list includes fully validated methods, provisionally validated (which often means single-laboratory validated methods) and methods for substances without MRLs. However, questions have been raised over the reliability of these analytical methods and some members and delegates have proposed retaining the list of methods as an informal document that could be updated regularly for information purposes but not be adopted by the CCRVDF and the CAC as official methods for drug analysis.

34. Confidence in any analytical method used in only the developing laboratory is limited in a residue control programme unless the method has been adequately validated, e.g. to the accreditation standards of ISO/IEC-17025. However, acceptable performance in the developing laboratory does not provide an automatic assurance that the analytical method can be transferred and perform adequately in another laboratory.

35. Many national and international bodies require laboratories undertaking analytical work for the determination of veterinary drug residues to have accreditation to internationally agreed standards (such as ISO/IEC-17025) and have robust quality assurance/quality control procedures in place. In addition, laboratories may be required to participate in proficiency testing programmes and inter-laboratory trials, all of which contribute towards assessing the transferability and reliability of analytical methods.

36. The Working Group on Methods of Analysis and Sampling and CCRVDF previously recommended that a three laboratory ring test should be a minimum number of laboratories to check a method and develop performance characteristics for residue control. This remains the currently agreed approach, but only very few methods have been tested in this way, and it is unlikely that many analytical methods will be tested in this way in the future.

37. It is also recognized that rapid changes in technology and the continuous improvement of the analytical methods lead to increased demands on the performance expected of laboratories. However, the requirements and demands for fully validated methods have changed not only because of the new technology but also because of new legislation. Whilst the Compendium of analytical methods was compiled, the performance criteria evolved to take account of scientific and technical advances in analytical science. As a result, all analytical methods contained in the compendium are not based on the same performance characteristics.

38. Based on these considerations and bearing in mind the quality assurance principles for analytical methods used in the residue control programme, it is apparent that the analytical methods in the Compendium do not provide the basis for ensuring optimum methods performance.

39. Many of the analytical methods are published in the journal FAO Food and Nutrition Papers 41/8 to 41/16. The performance of these methods is not usually described in detail. It could be argued that many of the analytical methods are not adequately validated for some purposes and they are unlikely to be readily transferable between laboratories. Many of the analytical methods in the Compendium have also been published in international scientific journals, where complete details of the analytical methods are rarely provided and are, therefore, of limited use to laboratories in their residue control programme. Nevertheless, when developed in

accredited laboratories, and based on international guidelines for analytical methods to be used in official residue control programmes, it is likely that the developing laboratory will have a detailed validation file for the analytical method. This validation file should include data on the analytical parameters and performance criteria met by the analytical method. It is also expected that the file will contain data on the method robustness which can be used to assess the potential for transferability.

40. Having reviewed many of the analytical methods in the Compendium (ALINORM 06/29/31) the electronic working group considers that some of the analytical methods in CCRVDF Compendium may not be capable of detecting and determining residues at the proposed MRLs. They are generally not fully validated to modern internationally accepted standards and it is likely that they will not be readily transferable between laboratories. Consequently, they should not be accepted and published as official methods for drug analysis. However, the analytical methods in the Compendium should provide valuable tools for laboratories and can act as an initial resource for analytical chemists working in the drug residue field.

CONCLUSIONS AND RECOMMENDATIONS

41. In 1998, the CCRVDF accepted that JECFA should be responsible for consideration of analytical methods for veterinary medicines from the 50th JECFA meeting onwards. If JECFA recommends a MRL, the method used for this purpose should be available for consideration by the CCRVDF. The electronic Working Group therefore recommends:

a. For all veterinary medicines currently being considered by the CCRVDF, or veterinary medicines submitted in the future, that a working group is established to evaluate the analytical methods provided to JECFA according to the performance criteria set out in the draft Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals[1] (paragraphs 201 – 226 of Appendix VI of ALINORM 08/31/31). If found satisfactory, the CCRVDF should be advised that the analytical method is acceptable for monitoring purposes and this method, with the co-operation of industry and JECFA, should be made available to analysts;

b. For the purposes of trade, analytical methods should not be considered as set or unalterable, but that any analytical method may be used PROVIDED it can meet the performance criteria set out in Appendix VI (paragraphs 201 – 226) of ALINORM 08/31/31;

c. It is recognised that the performance criteria given in the draft Guidelines for the Design and Implementation of National Regulatory Food Safety Assurance Programmes Associated with the Use of Veterinary Drugs in Food Producing Animals) (paragraphs 201 – 226 of Appendix VI of ALINORM 08/31/31 were primarily developed for single drug analytical methods. In practice, most veterinary drug residue testing laboratories use multi-residue analytical methods where possible for practical reasons. Consideration should be given to developing performance criteria for multi-residue analytical methods.

d. All further work on the compendium should be suspended but the compendium may continue to provide a useful initial resource to analysts working in this area; and

e. The current version of the compendium should be maintained as a resource of initial analytical methods and analytical contacts for the benefit of scientists working on veterinary drug residue surveillance programmes for a period of five years, after which the Committee should reconsider whether the compendium should be withdrawn.

[1] The draft Guidelines when adopted by the CAC will supersede CAC/RCP *Guidelines for the Establishment of a Regulatory Programme for Control of Veterinary Drugs in Foods* (CAC/GL 16-1993)