codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

JOINT OFFICE: Viale delle Terme di Caracalla 00153 ROME Tel: 39 06 57051 www.codexalimentarius.net Email: codex@fao.org Facsimile: 39 06 5705 4593

ALINORM 08/31/31
September 2007

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

31st Session

Geneva, Switzerland, 30 June – 5 July 2008

REPORT OF THE 17th SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS

Breckenridge, Colorado, USA

3-7 September 2007

NOTE: This report contains Codex Circular Letter CL 2007/37-RVDF

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CX 4/60.2 **CL 2007/37-RVDF**
September 2007

TO: - Codex Contact Points
- Interested International Organizations

FROM: Secretary, Codex Alimentarius Commission
Joint FAO/WHO Food Standards Programme,
Viale delle Terme di Caracalla
00153 Rome, Italy

SUBJECT DISTRIBUTION OF THE REPORT OF THE 17TH SESSION OF THE CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOODS (ALINORM 08/31/31)

The report of the Seventeenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods will be considered by the 31st Session of the Codex Alimentarius Commission (Geneva, Switzerland, 30 June-5 July 2008).

PART A – MATTERS FOR ADOPTION BY THE 31ST SESSION OF THE CODEX ALIMENTARIUS COMMISSION

1. Draft and proposed draft Maximum Residues Limits (MRLs) for Veterinary Drugs, at Step 8 and 5/8, respectively (paras 45, 47, 49 and Appendices II and III)

Governments and international organizations wishing to submit comment on the above texts should do so in writing, preferably by E-mail, to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00153 Rome, Italy (Email: codex@fao.org, telefax : +39 06 57054593) **before 31 March 2008.**

PART B – REQUEST FOR COMMENTS AT STEP 6

2. 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, at Step 6 (para. 75 and Appendix VI)

Governments and interested international organizations wishing to comment on the above draft Guidelines should do so in writing, preferably by E-mail, to the 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 (E-mail: uscodex@usda.gov, telefax: +1 202 720 3157) with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00153 Rome, Italy (Email: codex@fao.org, telefax : +39 06 5705 4593) **before 30 November 2008.**

PART C – REQUEST FOR INFORMATION

3. Information on current practices and suggestion for the scope of further work by CCRVDF on: i) Use of the Estimated Daily Intake (EDI); ii) Utilization of full ADI; iii) Starter cultures; and iv) Appending risk management recommendation(s) to MRLs (para. 132)

Governments and interested international organizations wishing to provide information on the above topics should do so in writing, preferably by E-mail, to the 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 (E-mail: uscodex@usda.gov, telefax: +1 202 720 3157) with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00153 Rome, Italy (Email: codex@fao.org, telefax : +39 06 5705 4593) **before 31 March 2008.**

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SUMMARY AND CONCLUSIONS

The Seventeenth Session of the Codex Committee on Residues of Veterinary Drugs in Foods reached the following conclusions:

MATTERS FOR ADOPTION/CONSIDERATION BY THE 31ST SESSION OF THE CODEX ALIMENTARIUS COMMISSION

Adoption of draft and proposed draft Standards and Related Texts at Step 8 and 5/8 of the Uniform Procedure

The Committee agreed to forward to the Commission:

- Draft MRLs for colistin and ractopamine for adoption at Step 8 and proposed draft MRLs for erythromycin for adoption at Step 5/8 (paras 44, 46, 48 and Appendices II and III).

Proposal for New Work

The Committee agreed to forward to the Commission, through the Executive Committee:

- the priority list of veterinary drugs for evaluation or re-evaluation by JECFA (para. 89 and Appendix VII);
- a project document for new work on the development of risk management recommendations for veterinary drugs without ADI and/or MRLs due to specific health concerns (para. 115 and Appendix VIII).

Others

The Committee agreed:

- to discontinue work on the draft and proposed draft MRLs for flumequine in Black tiger shrimp and in shrimps (para. 34 and Appendix V).

MATTERS REFERRED TO CODEX COMMITTEES AND TASK FORCES

Executive Committee (CCEXEC)

- With regard to Activity 3.3 “Develop committee-specific decision making and priority setting criteria” of the Strategic Plan 2008-2013, the Committee agreed to refer to the Executive Committee and the Commission the outcome of its discussion under Agenda Item 8 “Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation” and Agenda Item 10 “Discussion Paper on Risk Management Topics and Options for the CCRVDF” (paragraph 9).

Task Force on Foods Derived from Biotechnology (TFFBT)

- The Committee was of the opinion that the subject of recombinant-DNA vaccines was beyond its mandate and that it was necessary not to duplicate the work undertaken by OIE on this subject. Therefore, it agreed to indicate the Task Force that it had no specific advice on the matter of recombinant-DNA vaccine (paragraph 16).

OTHER MATTERS

The Committee:

- confirmed that the sentence in paragraph 3, point (d) of the *Risk Analysis Principle Applied by the Codex Committee on Residues of Veterinary Drugs in Foods* should be consistent with point (d) of the Terms of Reference of the CCRVDF, as contained in the Procedural Manual (paragraph 14);
- agreed to retain the draft MRLs for melengestrol acetate (MGA) in cattle’s tissues at Step 7 with the understanding that the European Community would provide new data for re-evaluation of MGA by JECFA (paragraph 42 and Appendix IV);

- agreed to return the proposed draft MRLs for triclabendazole in cattle, sheep and goat tissues to Step 2 and to consider the MRLs recommended by the next JECFA meeting at its 18th Session (paragraph 51);
- agreed to circulate 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 for comments at Step 6 (paragraph 74 and Appendix VI);
- agreed to suspend work on the *Compendium of methods of analysis identified as suitable to support Codex MRLs*, on the understanding that comments submitted in response to CL 2007/04-RVDF would be considered at a later date, if required (paragraph 78);
- agreed to establish an electronic Working Group, under the chairmanship of Canada and United Kingdom, to prepare a discussion paper to address: i) the future of the Compendium; ii) the link between analytical methods and advancing Codex MRLs to Step 8; and iii) the criteria necessary for analytical methods to be assessed and considered acceptable (paragraph 79);
- agreed to request the Codex Secretariat to prepare a Circular Letter requesting members and observer organizations to: i) provide comments and information on the priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA; and ii) provide and comments on Annex 1 of document CX/RVDF 07/17/12 "Starting point for a priority list of veterinary drugs for discussion at the 17th CCRVDF" (paragraph 90);
- agreed to establish an electronic Working Group on Priority, under the chairmanship of Australia, to: i) prepare a Priority list of veterinary drugs for evaluation or re-evaluation by the JECFA with a view to reaching a decision on the safety of residues in food by developing maximum residue limits (MRLs) or by informing risk managers on the safety of residues in food, if it is likely that an ADI or MRL cannot be recommended; and ii) prepare a working document listing veterinary drugs of potential interest, based Annex 1 to document CX/RVDF 07/17/12 "Starting Point for a Priority List of Veterinary Drugs for Discussion at the 17th CCRVDF" (paragraph 92);
- agreed to have further discussion on the establishment of a complete summary of the evaluations and decisions made on veterinary drugs at its 18th Session (paragraph 104);
- agreed to establish an electronic Working Group, under the chairmanship of the European Community and Mexico that, pending the formal approval of new work by the Commission, would prepare proposed draft risk management recommendations/guidance for veterinary drugs for which no ADI and/or MRL has been recommended by JECFA due to specific human health concerns (paragraph 117);
- agreed to request FAO and WHO to convene an expert group to "*develop a general decision tree approach for the evaluation of veterinary drugs, which could identify different options for hazard identification and characterization, and exposure assessment"* (paragraph 119);
- agreed on criteria for prioritization of compounds without ADI and/or MRLs to be evaluated by JECFA (paragraph 120);
- agreed to consider establishing a procedure to commit potential sponsors to join forces in order to share costs and efforts to facilitate submission of data for evaluation by JECFA, with a view to closing data gap and ensuring commitment for data availability (paragraph 123);
- agreed to encourage a global approach for the evaluation of consignments containing residues of veterinary drugs that should not be used in food producing animals (paragraph 125);
- agreed to request the Codex Secretariat to prepare a Circular Letter requesting members and observer organizations to provide detailed information on their current practices and suggestion for the scope of further work by the Committee for each of the following topics: (B-1) Use of the Estimated Daily Intake (EDI) concept; (C-1) Utilization of full ADI; (E-2) Starter culture; and (E-7) Appending risk management recommendation(s) to MRLs (paragraph 131);

- agreed to establish an electronic Working Group, under the chairmanship of France, to prepare a discussion paper that: i) would review the information provided in response to the Circular Letter, to be prepared by the Codex Secretariat; ii) assess whether it would provide sufficient ground for further work by the Committee and, where appropriate, would prepare a project document for new work or recommend to delay further action. The discussion paper should also address possible changes in the status of the proposals listed in document CX/RVDF 07/17/13, make appropriate recommendations to the Committee for further consideration and action and collate new proposals with relevant background information and appropriate recommendations to the Committee (paragraphs 133-134);
- noted that its 18th Session was tentatively scheduled to be held in 2009 (paragraph 137).

LIST OF ABBREVIATIONS USED IN THIS REPORT

ADI	Acceptable Daily Intake
ALARA	As Low As Reasonable Achievable
bw	body weight
CAC	Codex Alimentarius Commission
CAC/GL	Codex Alimentarius Commission / Guidelines
CCEXEC	Executive Committee of the Codex Alimentarius Commission
CCFICS	Codex Committee on Food Import and Export Inspection and Certification Systems
CCMAS	Codex Committee on Methods of Analysis and Sampling
CCRVDF	Codex Committee on Residues of Veterinary Drugs in Foods
CL	Circular Letter
CRD	Conference Room Document
DNA	Deoxyribonucleic acid
EC	European Community
EDI	Estimated Daily Intake
EMEA	European Agency for the Evaluation of Medicinal Products
FAO	Food and Agriculture Organization of the United Nations
GLP	Good Laboratory Practice
IAEA	International Atomic Energy Administration
IFAH	International Federation for Animal Health
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
MGA	Melengestrol acetate
MoE	Margin of Exposure
MRL	Maximum Residue Limit
MRLVD	Maximum Residue Limit for Veterinary Drug
OIE	World Organization for Animal Health
TDS	Total Diet Studies
TFFBT	*ad hoc* Codex Intergovernmental Task Force on Foods Derived from Biotechnology
TRS	Technical Report Series
USA	United States of America
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organization

INTRODUCTION

1. The Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) held its Seventeenth Session in Breckenridge, Colorado (USA) from 3-7 September 2007, at the kind invitation of the Government of the United States of America. Dr Stephen Sundlof, Director of Center for Veterinary Medicine, United States Food and Drug Administration, presided over the Session. The Session was attended by 153 delegates from 46 Member countries and one Member organization and Observers from 7 international organizations. A list of participants, including the Secretariat, is given in Appendix I to this report.

2. Dr F. Edward Scarbrough, Manager of the US Codex Office, United States Department of Agriculture, opened the Session. Mr. Dan Gibbs, Colorado State Representative, House District 56, also addressed the Committee on behalf of the State of Colorado.

Division of Competence

3. The Committee noted the division of competence between the European Community and its Member States, according to paragraph 5, Rule II of the Procedure of the Codex Alimentarius Commission, as presented in document CRD3.

ADOPTION OF THE AGENDA (Agenda Item 1)[1]

4. The Committee adopted the Provisional Agenda as its Agenda for the Session.

5. The Committee, upon the proposal of the Delegation of France, Chair of the electronic Working Group on Risk Management Topics and Options for the CCRVDF, and with a view to facilitating the Committee's discussion of the subject matter under Agenda Item 10 "Discussion Paper on Risk Management Topics and Options for the CCRVDF", agreed to convene an in-session working group under the chairmanship of France, opened to all interested members and observers and working in English only, to review document CX/RVDF 07/17/13 and written comments submitted, to prioritize the recommendations in the document and to consider ways to advance the work further.

6. The Committee agreed to discuss Agenda Item 9 "Report of the physical Working Group on Residues of Veterinary Drugs without ADI/MRL" prior to Agenda Item 8 "Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation" to make the discussion more efficient. In addition, it was agreed to discuss Agenda Item 5(a) "Draft MRLs for Veterinary Drugs at Step 7" and Agenda Item 5(c) "Proposed Draft MRLs for Veterinary Drugs at Step 4" together because they were interrelated.

MATTERS REFERRED BY THE CODEX ALIMENTARIUS COMMISSION AND OTHER CODEX COMMITTEES AND TASK FORCES (Agenda Item 2)[2]

MATTERS FROM THE CODEX ALIMENTARIUS COMMISSION AND OTHER CODEX COMMITTEES AND TASK FORCES

7. The Committee noted information in documents CX/RVDF 07/17/2 and CX/RVDF 07/17/2 Add.1. In particular, the Committee commented and/or made decision as follows:

Strategic Plan 2008-2013 of the Codex Alimentarius Commission

8. The Committee drew its attention to Activities 1.1, 1.6, 2.2, 2.3 and 3.3 of the Strategic Plan 2008-2013, which identified the CCRVDF as one of the responsible parties for implementation, and noted the written comment submitted by the European Community, as presented in CRD13.

9. With regard to Activity 3.3, the Committee noted that this Activity required that decision making and priority setting criteria be completed by 2008 and agreed to refer to the Executive Committee and the Commission the outcome of its discussion under Agenda Item 8 "Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation" and Agenda Item 10 "Discussion Paper on Risk Management Topics and Options for the CCRVDF".

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1 CX/RVDF 07/17/1

2 CX/RVDF 07/17/2; CX/RVDF 07/17/2 Add.1; CRD13 (comments of the European Community)

10. With regard to Activity 1.1, one delegation raised questions on how the specific needs of developing countries, related to infrastructure, resources and technical and legal capability, could be addressed in the course of review and development of Codex standards and related texts for food safety. The Committee suggested that the specific concerns of developing countries should be identified in advance so that they could be taken into account during the elaboration of draft standards.

11. The Committee was informed of the various types of training and technical assistance, such as laboratory test and analysis, provided by FAO and WHO, as well as by other organizations, which aimed at enhancing capacity of developing countries in complying with Codex standards.

Review of Codex Committee Structure and Mandates of Codex Committees and Task Forces

12. It was noted that the decision made by the Commission on Proposal 3 (interval of meetings) and Proposals 4 (duration of meetings) would be taken into account when considering Agenda Item 12 "Date and Place of Next Session".

Risk Analysis Principles Applied by the Codex Committee on Residues of Veterinary Drugs in Foods

13. The Committee was informed that the sentence in paragraph 3 point (d) of the Risk Analysis Principle Applied by the Codex Committee on Residues of Veterinary Drugs in Foods, which was adopted by the Commission at its 30th Session, appeared to be incorrect.

14. The Committee confirmed that the sentence should be consistent with point (d) of the Terms of Reference of the CCRVDF, as contained in the Procedural Manual.

Safety Assessment of Food Derived from Animal Exposed to Protection against Diseases through Gene Therapy or Recombinant-DNA Vaccine

15. With regard to the matter referred by the Codex *ad hoc* Intergovernmental Task Force on Foods derived from Biotechnology, the Committee noted the information provided by the Observer from OIE that issues of animal health associated with the use of recombinant-DNA vaccine was the responsibility of OIE and that a report on OIE's activities in that area would be presented at the forthcoming 7th Session of the Task Force, to be held in September 2007.

16. The Committee was of the opinion that the subject of recombinant-DNA vaccines was beyond its mandate and that it was necessary not to duplicate the work undertaken by OIE on this subject. Therefore, it agreed to indicate the Task Force that it had no specific advice on the matter of recombinant-DNA vaccine.

MATTERS OF INTEREST ARISING FROM FAO AND WHO (Agenda Item 3)[3]

17. The Committee noted information contained in document CX/RVDF 07/17/3. In particular, the Committee's attention was drawn on the following points:

Provision of scientific advice

18. The Committee was informed that the examination of the applications for the new roster of experts on veterinary drug residues to serve on JECFA for the period 2007-2011 had been finalised and would be published shortly on the FAO and WHO JECFA websites.

19. The Committee was also informed that work on the FAO/WHO Framework of Scientific Advice had been completed and was available on the FAO website[4]. The Framework contained detailed information on the legal framework, core principles and procedures followed by the organizations for all activities related to scientific advice to Codex.

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[3] CX/RVDF 07/17/3; CRD5 (FAO/IAEA Information on activities of the food and environmental safety sub-programme related to residues of veterinary drugs in foods)

[4] http://www.fao.org/ag/agn/files/Final_Draft_EnglishFramework.pdf

Update on the Joint FAO/WHO activities on containment of antimicrobial resistance due to non-human use of antimicrobials

20. The WHO Representative informed the Committee of FAO/WHO activities on antimicrobial resistance arising from use of antimicrobials in food producing animals. Special mention was made of two upcoming joint FAO/WHO/OIE events in this area: (i) the first session of the newly established Codex *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance to be held 23-26 October 2007 in Seoul, Republic of Korea; and (ii) a Joint FAO/WHO/OIE Expert Meeting on Critically Important Antimicrobials to be held 26-29 November 2007 in Rome, Italy.

Expert Consultation on the use of 'active chlorine' in the food industry

21. The Committee was informed that FAO and WHO had launched a new project on the use of chlorine containing compounds in food processing, in response to requests from the Committees on Food Additives and Contaminants and on Food Hygiene. The scope of the project included the evaluation of risk of chemical residues, including disinfection by-products, resulting from such treatment; the assessment of the benefit with respect to microbiological safety; assessment of current practices and alternative methods; nutritional and organoleptic impact would be also briefly covered. The project would focus on fresh produce, meat and poultry, fish and seafood. The Committee was informed that a call for experts and a call for information had been published on the internet, and the Committee was encouraged to provide relevant information, in particular regarding current practices.

Fourth International Workshop on Total Diet Studies (TDS)

22. The Committee was informed of on-going efforts in promoting TDS via workshops held in countries and regions. TDS were a cost-effective method to assess mean exposure of population and sub-populations to chemicals in food, which helped to identify problem areas and to direct targeted interventions. Further workshops were planned in Africa, Europe and the Eastern Mediterranean, with the objective to promote and support TDS, to report on recent developments and exchange international 'best practices'.

FAO/IAEA Information on activities of the food and environmental safety sub-programme related to residues of veterinary drugs in foods

23. The Committee noted the information provided in CRD5 and thanked FAO/IAEA for the information.

66TH MEETING OF THE JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (Agenda Item 3a)[5]

24. The Committee recalled that a summary of the outcomes of the 66th JECFA had already been presented at its 16th Session[6] and that several points would be discussed under other agenda items.

25. The Delegation of the European Community raised concern regarding the new method for estimation of chronic dietary exposure of residues that had been implemented at the 66th JECFA and its possible implication on the derivation of MRLs. The Delegation also raised concern regarding the process that JECFA and the JECFA Secretariat had followed and that this new method had been adopted without consultation with the Committee. The JECFA Secretariat clarified that the development of the method for a more realistic exposure assessment was an improvement of the risk assessment methodology and that it had been developed in response to specific requests from previous CCRVDF sessions and as a follow-up to the recommendations from the international expert workshop held on MRL setting for pesticide and veterinary drug residues, which were presented at the 16th CCRVDF and published in detail in the summary report and in the final report of the 66th JECFA meeting. The improvement of the dietary exposure assessment method was also in line with the *Risk Assessment Policy for the Setting of Maximum Limits for Residues of Veterinary Drugs in Foods*, adopted by the 30th Session of the Commission[7], which stated that risk assessment should be based on realistic exposure scenarios.

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5 66th JECFA Report: Evaluation of certain veterinary drug residues in food : http://whqlibdoc.who.int/publications/2006/9241209399_eng.pdf ; Toxicological Monographs: Toxicological evaluation of certain veterinary drug residues: http://whqlibdoc.who.int/publications/2006/9241660570_eng.pdf ; Residue monographs (FAO JECFA Monographs 2, 2006): ftp://ftp.fao.org/docrep/fao/009/a0652e/a0652e00.pdf; CRD13 (Comments of the European Community)

6 ALINORM 06/29/31 paras 23-30

7 ALINORM 07/30/REP, para. 34 and Appendix III

26. Some delegations raised concern about lack of transparency and insufficient communication between JECFA and CCRVDF and highlighted the need to ensure that the risk analysis process be fully transparent and thoroughly documented, as stated in the *Risk Analysis Principles applied by CCRVDF*, adopted by the 30th Session of the Commission. The Committee agreed to have this point, as well as possible impact of the new exposure assessment method on MRL derivation, discussed by the in-session Working Group on Agenda Item 10.

REPORT OF THE OIE ACTIVITIES, INCLUDING THE HARMONIZATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF VETERINARY MEDICINAL PRODUCTS (VICH) (Agenda Item 4)[8]

27. The Observer from OIE, referring to document CX/RVDF 07/14/4, drew the Committee's attention to four main points: the cooperation between the OIE and the Codex Alimentarius Commission; the OIE and VICH activities; antimicrobial resistance; and the OIE network of reference laboratories and collaborating centres.

28. With regard to the first point, the Observer from OIE mentioned the ongoing and upcoming activities of the OIE Working Group on Animal Production Food Safety (WGAPFS), which also included experts from Codex, FAO and WHO, and the contribution of the Working Group, within its field of competence, to strengthening the institutional capacity of veterinary services in OIE Member States, in particular in developing countries.

29. With regard to VICH, the Committee was informed of three specific actions of interest: i) the establishment of a Working Group on residue metabolism and kinetics; ii) the potential establishment of a Working Group on the development of an Acute Reference Dose; and iii) the support of all measures intended to refine, reduce or replace animal experimentation.

30. With regard to antimicrobial resistance, the Observer from OIE provided information on ongoing and upcoming activities; he stated the OIE's appreciation for the establishment of the Codex Task Force on Antimicrobial Resistance and the wish that substantial progress be made in this area in collaboration with FAO, WHO and OIE.

31. The Committee was also informed of the first International Conference of OIE Reference Laboratories (RL) and Collaborating Centers (CC), held in December 2006. The intended objective was to strengthen and expand the network of such structures and to promote international harmonization.

32. The Observer from IFAH acknowledged the support of OIE to VICH activities; he welcomed the improved OIE communication with its Member States on this topic and highlighted the importance of the OIE work on antimicrobial resistance.

33. The Committee expressed its appreciation to the informative OIE report.

CONSIDERATION OF MAXIMUM RESIDUES LIMITS (MRLs) FOR VETERINARY DRUGS (Agenda Item 5)[9]

DRAFT AND PROPOSED DRAFT MRLS FOR VETERINARY DRUGS (AT STEP 7 AND STEP 4) (Agenda Item 5a and 5c)[10]

Flumequine (at Step 7 and Step 4)

34. The Committee recalled that at its 16th Session it had agreed to retain the MRLs for flumequine in muscle of Black tiger shrimp and shrimps at Steps 7 and 4 respectively and to ask the Codex Secretariat to issue a Circular Letter[11] requesting information on registered use of flumequine with the understanding that, if this information was not provided, it would discontinue work on these MRLs at its 17th Session[12].

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8 CX/RVDF 07/17/4

9 CX/RVDF 07/17/5

10 ALINORM 06/29/31 Appendices III and V; CX/RVDF 07/17/6 (Comments of Australia, Canada and United States of America); CRD4 (Comments of Philippines); CRD11 (Comments of Indonesia); CRD12 (Comments of South Africa); CRD13 (Comments of European Community)

11 CL 2006/16-RVDF, part C

12 ALINORM 06/29/31 para. 54

35. In noting that no information had been provided on the registered use of flumequine in Black tiger shrimp and in shrimps, the Committee agreed to discontinue work on the draft and proposed draft MRLs.

Melengestrol acetate

36. The Committee recalled that at its 16th Session, as consensus could not be reached on the advancement of the MRLs for melengestrol acetate (MGA), it had agreed to retain the MRLs at Step 7 for further consideration at its next Session[13].

37. The Delegation of the European Community, referring to its written comments, as contained in CRD13, stated that MGA was evaluated by JECFA for growth promotion. This use was prohibited in the European Community. The prohibition was based on the evaluations of the EC Scientific Committee on Veterinary Public Health and the European Food Safety Authority of 1999, 2000, 2002 and 2007. In this process the JECFA evaluation was also considered. The EC scientific committees criticised in particular that some of the original data in the JECFA review and the references had not been published in peer reviewed scientific literature. The 54th JECFA report moreover stated that "*Most of the studies were conducted before 1979 according to the standards in existence at the time and were not carried out in compliance with GLP*" (page 65, 3rd paragraph of the 54th JECFA report). The 62nd JECFA evaluated only new information regarding the structure and activity of the metabolites of MGA (see page 22 of the 62nd JECFA report).

38. The Delegation further said that the EC scientific committees had considered more recent studies. These indicated that amongst others: i) MGA has a very strong potential to bind to bovine progesterone receptors; ii) in utero or pre and peripubertal exposure to hormones may effect pubertal development; iii) newer experiments identify a risk for excessive exposure of consumers to residues from incorrect dose regimes (MGA is given orally); iv) in the absence of surveillance data it is difficult to quantify the exposure to residues of hormones used as growth promoters; v) the available data on the metabolism of MGA in cattle and the amount and nature of the residues in animals following continuous use in cattle are too incomplete to be assessable. The Delegation of European Community concluded that JECFA evaluation had not considered most recent scientific developments. Therefore, the European Community could not support the adoption of the proposal for MRLs of MGA and suggested that the substance be reconsidered by JECFA taking into account more recent scientific data. This position was supported by other delegations.

39. The Delegation of the United States of America made reference to the scientific review by the 66th JECFA in its MRL recommendations. It noted that the relevant studies involved identification of the MGA metabolites from treated animals and determination of their individual progestogenic activity compared to the progestogenic activity of melengestrol acetate. The Delegation noted that the biological activity for each of the identified metabolites was less than 15% when compared to MGA. The recommended MRLs were based on the consideration of parent drug and these metabolites in each tissue. The recommended MRLs were consistent with the upper bound of the ADI and therefore the United States recommended the advancement of MGA to Step 8. This position was supported by other delegations.

40. The JECFA Secretariat noted that the same arguments that the European Community brought forth had been discussed at the last session of the Committee. In particular, the quote from the 54th report regarding old and non-GLP compliant data used in the JECFA evaluation was incomplete and, as indicated in the JECFA report, some newer GLP compliant studies had also been considered.

41. As there was not enough support to advance the MRLs for MGA to Step 8, the Committee discussed the extent and nature of new data that had been considered by the EC scientific committees.

42. The JECFA Secretariat summarized that the new data available were not specific data for MGA, but rather general data on effects of hormonally active compounds. She further noted that these data were controversially discussed in the scientific community and conclusions on these data might not be possible. The JECFA Secretariat said that a re-evaluation of MGA could be considered, provided the European Community submits to the JECFA Secretariat written information on the exact nature of their concern and provision of all the relevant data for JECFA evaluation. The Committee therefore agreed to include MGA in the priority list (see paragraph 88).

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13 ALINORM 06/29/31 para. 73

43. The Committee agreed to retain the draft MRLs for MGA in cattle's tissues at Step 7 with the understanding that the European Community would provide new data for a re-evaluation of MGA by JECFA. If JECFA reaffirm its decision, MGA would be advanced to Step 8 at its next Session.

DRAFT MRLS FOR VETERINARY DRUGS (AT STEP 6) (Agenda Item 5b)[14]

44. The Committee noted that the 29th Session of the Commission had adopted at Step 5 and advanced to Step 6 the draft MRLs for colistin and ractopamine, as proposed by the Committee[15].

Colistin

45. The Committee agreed to advance the draft MRLs for colistin in cattle, sheep goat, pig, chicken, turkey and rabbit's tissues, in cattle and sheep's milk and chicken's eggs to Step 8.

Ractopamine

46. Several delegations supported the advancement of the MRLs for ractopamine to Step 8 in view of the positive outcome of the completed JECFA evaluation. In this regard, the importance of the JECFA evaluation for those countries that had not adequate resources to conduct their own safety evaluation was noted. The Delegation of the European Community, making reference to their written comments in CRD13, stated that they could not support the advancements of the MRLs to Step 8 in view of the fact that their legislation did not allow for the use of beta-agonists for growth promotion.

47. The Committee, noting that the justification for not supporting the advancement of the MRLs to Step 8 was not based on scientific arguments, agreed to advance the draft MRLs for ractopamine in cattle and pig tissues to Step 8, while noting the strong reservation of the Delegations of the European Community, Norway and Switzerland to this decision.

PROPOSED DRAFT MRLS FOR VETERINARY DRUGS (AT STEP 6) (Agenda Item 5d)[16]

48. The Committee recalled that at its 16th Session, in view of the need to consider in detail the full JECFA re-evaluation, it had agreed to circulate the MRLs for erythromycin and triclabendazole for comments at Step 3 and further consideration at its next Session[17].

Erythromycin

49. The Committee agreed to advance the proposed draft MRLs for erythromycin in chicken and turkey tissues to Step 5/8.

Triclabendazole

50. The Delegation of Australia expressed concern on the MRLs for triclabendazole because it was not clear to what degree the data on bioavailability had been taken into consideration by the 66th JECFA when recommending these MRLs.

51. The JECFA Secretariat provided clarifications on the conclusion reached by JECFA on triclabendazole at its 66th meeting with respect to the data on bioavailability of residues. The studies available to JECFA comprised studies in rats given lyophilized tissue from cattle or sheep treated with a single dose of radiolabel led triclabendazole and slaughtered after 28 days. JECFA reviewed these studies, but it did not consider the bioavailability factors from these studies in the determination of the MRLs for cattle and sheep.

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[14] ALINORM 06/29/31 Appendix IV; CX/RVDF 07/17/7 (Comments of Australia, Canada, European Community, United States of America and Vietnam); CRD4 (Comments of Philippines); CRD11 (Comments of Indonesia); CRD13 (Comments of European Community)

[15] ALINORM 06/29/41 para. 97 and Appendix V

[16] ALINORM 06/29/31 Appendix VI; CX/RVDF 07/17/8 (Comments of Australia, Canada and United States of America); CRD4 (Comments of Philippines); CRD11 (Comments of Indonesia); CRD13 (Comments of European Community)

[17] ALINORM 06/29/31 paras 67, 76 and Appendix VI

52. The JECFA Secretariat, noting that new residue data would be made available for evaluation by JECFA, expressed the willingness to re-evaluate triclabendazole, including data on bioavailability (see paragraph 84). The Committee agreed to return the proposed draft MRLs for triclabendazole in cattle, sheep and goat tissues to Step 2 and to consider the MRLs recommended by the next JECFA meeting at its 18th Session.

Status of the Draft and Proposed Draft Maximum Residue Limits for Veterinary Drugs

53. Draft and proposed draft MRLs to be forwarded to the 31st Session of the Commission for adoption at Step 8 and Step 5/8 are attached as Appendices II and III, respectively. Draft MRLs retained at Step 7 are attached as Appendix IV. Discontinued draft and proposed draft MRLs are attached as Appendix V.

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 (Agenda Item 6)[18]

54. The Committee noted that the 29th Session of the Commission had adopted at Step 5 and advanced to Step 6 the draft Guidelines, as proposed by the Committee, with the understanding that the comments of Brazil would be considered by the next Session of the Committee[19].

55. The Chairperson recalled that this work had been considered by the Committee for a long time and that the Committee needed to take a decision on the future of the document; he highlighted the broad range of issues covered by the revised Guidelines and their complexity and noted the extensive written comments that had been submitted for consideration at this Session. The Chairperson asked the Committee to discuss how to proceed with the document and proposed three options: i) to consider the document section by section; ii) to establish an in-session Working Group to revise the draft Guidelines for consideration of the plenary; iii) to discontinue work on the revised draft Guidelines and to establish an electronic Working Group to prepare a discussion paper proposing ways to revise the current Guidelines (CAC/GL 16-1993) for consideration at the 18th Session of the Committee.

56. Several delegations were in support of option (i); they highlighted: the importance of the focus of the Guidelines on primary production and on the prevention of chemical risks entering in the food chain; the shift of responsibility for ensuring food safety to the producers; the changed role of Competent Authorities in the control and use of veterinary drugs; and the broad impact that the revised Guidelines would have on their regulatory framework, private industry and consumers. They were of the opinion that considering the document section by section would allow a better appreciation of the impact and consequences of the provisions in their national regulations. However, these delegations recognised that an in-session Working Group would allow the Committee to work more efficiently and progress the revised Guidelines further. It was also noted that several delegations had prepared their position on the basis of the document contained in Appendix VII of the report of the 16th Session of CCRVDF and that they had not enough time to consider the revised text contained in the comments of the European Community and the United States of America.

57. Other delegations were in support of option (ii) and asked for clarification on which document (i.e. Appendix VII of ALINORM 06/29/31 or the proposal contained in the comments of the European Community and the United States of America in document CX/RVDF 07/17/9 Add.1) should be considered as a starting point for the revision. It was highlighted that the Committee had previously noted that the revised draft Guidelines, as contained in Appendix VII of ALINORM 06/29/31, had needed further work to improve paragraphs ordering and readability and that the revised text in the European Community and United States of America' comments had addressed these issues while maintaining the provisions of the revised draft Guidelines (as in Appendix VII). It was further noted that the European Community and United States of America's comments included a table that allowed tracking the changes in their proposal from the text in Appendix VII.

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[18] ALINORM 06/29/31 Appendix VII; CX/RVDF 07/17/9 (Comments of Australia, Canada, European Community, Peru and United States of America); CX/RVDF 07/17/9 Add.1 (Comments of European Community, New Zealand and United States of America); CRD4 (Comments of Philippines); CRD12 (Comments of South Africa); and CRD15 (Report of in-session Working Group on Agenda Item 6)

[19] ALINORM 06/29/41 para. 115 and Appendix V

58. The Committee agreed to establish an in-session Working Group[20], under the Chairmanship of the United Kingdom, to prepare revised draft Guidelines that meet the needs of Codex Members, based on the proposal of the European Community and the United States of America and agreed to base its discussion on the revised draft. It was agreed that the in-session Working Group would work in English, French and Spanish, when interpretation service was available, and in English only, when interpreters were at lunch.

59. The Delegation of the United Kingdom, speaking as the Chairperson of the in-session Working Group, introduced the revised draft Guidelines to the plenary and congratulated the members of the Working Group for their excellent work. He explained that the Working Group had considered both Appendix VII of ALINORM 06/29/31 and the proposal contained in the comments of the European Community and the United States of America; and that the introduction of the revised Guidelines and the Annexes were based on Appendix VII and the remaining parts on the European Community and the United States of America's proposal.

Specific Comments

60. The Committee considered the document in detail and, in addition to some editorial changes and other changes to improve the clarity of the document, agreed to the following:

Introduction

61. In paragraph 3, the Committee agreed to refer to "programme" in relation to residues verification instead of "system" as it was more appropriate. It agreed to make the same change in other paragraphs, where appropriate. A new paragraph was added after paragraph 4 to recognize the need of some countries, in particular developing countries, for a transition period and technical assistance to implement the Guidelines.

General Principles

62. The Committee deleted bullet (iv), which related to the identification and justification of standards for veterinary drugs, which scope were outside the mandate of Codex, and added a sentence regarding this point in paragraph 7, which recognized that veterinary drugs could be regulated for a variety of reasons, such as animal health, animal welfare, etc.

Approach based on risk

63. The Committee amended the first sentence of paragraph 12 to recognize that animal and production systems could be exposed to other chemicals than veterinary drugs. The Committee noted that the in-session Working Group had put paragraphs 16-18 into square brackets for discussion during plenary. It amended the last sentence of paragraph 16 to read "Competent Authorities should verify correct implementation of programmes and, where necessary, if action has been taken". It amended the last sentence of paragraph 17 to refer to quality management principles; and it deleted the last sentence of paragraph 18 to avoid possible misinterpretation. The Committee agreed to move the revised paragraphs, without square brackets, to the end of section "General Principles".

Definitions

64. In paragraph 19, the Committee removed the square brackets around "organization/agency(ies)" noting that the square brackets had been put there because of a translation problem in the Spanish version. In paragraph 26, it deleted "animal" and "at time of slaughter" because the Guidelines also applied to animal products, such as honey and milk. The Committee added the definition for Quality Management System that was missing.

Regulatory Framework

65. In paragraph 40, the Committee added "regional" to "national regulations" and agreed to apply this change throughout the document. It amended point (a) of paragraph 40, to read "Requiring all sales to be subject to a prescription from veterinarians or other professionals with approved competencies" to recognize differences among countries' regulations concerning prescription of veterinary drugs.

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[20] The following members and organizations attended the in-session Working Group: Argentina, Australia, Austria, Brazil, Canada, Colombia, Costa Rica, Egypt, European Community, France, Germany, Guatemala, India, Japan, Kenya, Mexico, New Zealand, Republic of Korea, Thailand, United Kingdom, United States of America, Uruguay, FAO/IAEA and IFAH

66. The Committee agreed to move: paragraph 44 under section "Responsibilities of business operators"; and paragraph 46 before paragraph 45 to improve the logical flow of the document.

67. The Committee added a new paragraph 47 to encourage producers to seek advice of veterinarians or other competent professionals on the application of the correct withdrawal time, when label directions were missing or unclear.

Verification programmes

68. The Committee agreed to refer to "traceability/product tracing" for consistency with Codex terminology. In paragraph 98, it deleted the example as it could be misleading.

Regulatory action

69. In paragraph 114, which listed possibilities to be considered when an MRL was exceeded at the point of entry, "sample contamination" was added to the bullet on analytical method problem or analytical error. Paragraph 127 was modified to recognize the role of the Competent Authority to ensure that appropriate corrective action is taken at the relevant point where investigation identifies failure.

Appendix A

70. In paragraph 134, the text in parenthesis was deleted as too prescriptive. The header in Table 2 was amended to refer to both animals and units of product in samples tested.

General Consideration of Analytical Methods for Residues Control/Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods

71. The Committee agreed to delete all references to the Codex Committees on Residues of Veterinary Drugs in Foods (CCRVDF) and on Methods of Analysis and Sampling (CCMAS), such as work undertaken by the Committee, terms of reference, etc, as the Guidelines were intended for use of Governments. Similarly, it agreed to replace the terminology used in CCRVDF for analytical methods for residue control, i.e. Level I, Level II and Level III methods, with Confirmatory, Quantitative and Screening methods, throughout the document.

72. In paragraph 208 (precision) the text "as repeatability" was deleted for consistency with the ISO definitions; the term "preferably" was added to "different equipment" to allow for more flexibility in the procedures for single laboratory validation. In paragraph 210, the numerical values for the determination of response for blank sample material (known and fortified) were changed to "a range of concentration above and below the MRLVD".

73. The Committee corrected several errors in Table 2 "Performance requirements for relative ion intensities (sample compared to standard) using various mass spectrometric analytical techniques".

74. The Committee expressed its appreciation to the Working Group for the excellent work that had resulted in a comprehensive text, highlighting the food chain and based on risk approaches and the shifting of responsibilities to ensure food safety onto producers. Some delegations were in favour of advancing the text to Step 8, while others emphasized the need to have some additional time to consider the text in consultation with their national authorities and private sector. There was a wide scale acceptance by the Committee that the Guidelines would be both a necessary and very important document to help countries to better manage the potential risks posed by the use of veterinary drugs.

Status of 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

75. In recognising the need, especially for developing countries, to consider in detail the revised Guidelines, to analyse the specific provisions and to evaluate the implication for their implementation with the national authorities and private sectors, the Committee agreed to circulate the draft Guidelines for comments at Step 6, with a view to further consider the document at its 18th Session and then forward it to the Commission for final adoption.

METHODS OF ANALYSIS FOR RESIDUES OF VETERINARY DRUGS IN FOODS (Agenda Item 7)[21]

76. The Committee recalled that at its 16th Session, it had agreed to reconvene the Working Group on Methods of Analysis and Sampling, under the co-Chairmanship of Canada and the United Kingdom, prior to its next Session to continue work on the identification of suitable methods of analysis for residues of veterinary drugs in food on the basis of information received in response to Circular Letter CL 2007/04-RVDF[22].

77. The Delegation of the United Kingdom, speaking as the co-Chairperson of the Working Group on Methods of Analysis and Sampling[23], introduced the report of the Working Group, held prior to the Session, as presented in CRD1.

78. The Committee noted that the Working Group had considered the comments submitted in response to Circular Letter CL 2007/04-RVDF, but it 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. The Working Group had discussed 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.

79. The Committee endorsed the recommendation of the Working Group that the work on the Compendium be suspended, on the understanding that comments submitted in response to CL 2007/04-RVDF would be considered at a later date, if required.

80. On the recommendation of the Working Group, the Committee agreed to establish an electronic Working Group[24], led by the Delegations of Canada and United Kingdom, working in English only and open to all the members and observers, to prepare a discussion paper to address: i) the future of the Compendium of Methods of Analysis Identified as Suitable to Support Codex MRLs; ii) the link between analytical methods and advancing Codex MRLs to Step 8; and iii) the criteria necessary for analytical methods to be assessed and considered acceptable.

81. A delegation asked about the link between Codex MRLs and methods of analysis assessed by JECFA. The Committee noted that this would be considered together with criteria for multi-residue methods by the electronic Working Group.

82. The Committee noted that the physical Working Group on Methods of Analysis and Sampling would not be re-established prior to its 18th Session.

PRIORITY LIST OF VETERINARY DRUGS REQUIRING EVALUATION OR RE-EVALUATION (Agenda Item 8)[25]

83. The Committee recalled that at its 16th Session, it had agreed to reconvene the Working Group on Priority, under the Chairmanship of Australia, prior to its next Session, to consider proposals for compounds to be evaluated or re-evaluated by JECFA and the report of the physical Working Group on Compounds without ADI/MRL[26].

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21 CX/RVDF 07/17/10 (Comments of Australia, Norway, Sweden and United States of America); CX/RVDF 07/17/10 Add.1 (Comments of Canada, European Community and Indonesia); CRD1 (Report of the Working Group on Methods of Analysis and Sampling; CRD10 (Comments of Thailand), CRD11 (Comments of Indonesia)

22 ALINORM 06/29/31 para. 121

23 The following members and organizations attended the physical Working Group: Australia, Brazil, Canada, Czech Republic, the European Community, France, Germany, Japan, Netherlands, New Zealand, Norway, Republic of Korea, South Africa, Sweden, Switzerland, Thailand, United Kingdom, United States of America, Uruguay, OIE, IFAH, FAO and WHO

24 Australia, Brazil, China, France, Germany, Indonesia, Japan, Malaysia, Netherlands, Norway, Republic of Korea, Sweden, Thailand, United States of America, IFAH and FAO expressed their willingness to participate in the electronic Working Group

25 CX/RVDF 07/17/11 (Comments of Brazil, Canada, Germany, United States of America and IFAH); CRD2 (Report of the Working Group on Priorities); CRD7 (A proposal for streamlining activities of the Working Group on Priority – prepared by Australia); CRD8 (Comments of Republic of Korea); CRD9 (Risk assessment of malachite green residues – Literature study); and CRD14 (An Outline of the Modus Operandi for Activities of the Proposed Electronic Working Group on Priority)

26 ALINORM 06/29/31 para. 135

84. The Delegation of Australia, speaking as the Chairperson of the Working Group on Priority, introduced the report of the Working Group[27], held prior to the Session, as presented in CRD2. The Committee noted that the recommendations related to the report of the physical Working Group on Compounds without ADI/MRL would be considered under Agenda Item 9. The Committee noted that the Working Group had prepared a revised Priority List of Veterinary Drugs for evaluation or re-evaluation by JECFA; had a discussion on the literature review provided by the Delegation of Germany on the risk assessment of malachite green (CRD9); and had considered a proposal for streamlining the activities of the Working Group on Priority, based on a proposal of the Delegation of Australia (CRD7).

85. The Committee considered the priority list prepared by the Working Group, which included: dexamethasone (proposed by Canada); tylosin (proposed by Germany and IFAH); avilamycin (proposed by Brazil and IFAH); malachite green (proposed by Germany); tilmicosin (proposed by United States of America); monensin (proposed by United States of America and IFAH); narasin (proposed by United States of America and IFAH); and triclabendazole (proposed by Australia).

86. The Committee noted that the Working Group had not included the following compounds in the priority list because the data were not available or insufficient for a JECFA evaluation: kanamycin (proposed by the Republic of Korea); bacitracin (proposed by Brazil); xylazine (proposed by Germany and New Zealand); and sulfathiazole (proposed by the Republic of Korea).

87. The Committee was informed that the next JECFA meeting on veterinary drugs was tentatively planned in autumn 2008, subject to resource availability. Upon request of the JECFA Secretariat, delegations confirmed the time by which the data would be made available to JECFA for their evaluation.

88. The Committee agreed to add melengestrol acetate (see paragraph 42) and malachite green to the priority list.

89. With regard to malachite green it was noted that the preliminary risk assessment, as presented in CRD9, based on a literature study, indicated that available data were probably not sufficient to derive an ADI and MRLs. Other approaches to advise risk managers about the safety of use in food producing animals might be necessary, e.g. applying the Margin of Exposure (MoE) approach. The JECFA Secretariat noted that JECFA had developed in detail an approach to estimate the margin of exposure for contaminants in food, however JECFA clearly indicated that this should not be applied to compounds that are intentionally added to foods, such as food additives. Moreover, the MoE was a tool to indicate a level of concern to risk managers for setting priorities for actions.

90. The Committee agreed to forward the Priority List of Veterinary Drugs for Evaluation or Re-evaluation by JECFA to the 31st Session of the Commission, as attached in Appendix VII.

91. The Committee agreed to request the Codex Secretariat to prepare a Circular Letter requesting members and observer organizations to: i) provide comments and information on the priority list of veterinary drugs requiring evaluation or re-evaluation by JECFA; and ii) provide and comments on Annex 1 of document CX/RVDF 07/17/12 “Starting Point for a Priority List of Veterinary Drugs for Discussion at the 17th CCRVDF”.

92. With regard to the activities of the Working Group on Priority, the Committee endorsed the recommendation of the Working Group to change the physical Working Group on Priority to an electronic one.

[27] The following members and organizations attended the physical Working Group: Australia, China, Czech Republic, the European Community, Germany, Japan, New Zealand, Norway, Republic of Korea, Sweden, Switzerland, Thailand, United Kingdom, United States of America, OIE, IFAH, FAO and WHO

93. Based on the proposal of the Delegation of Australia, as presented in CRD14, the Committee agreed to establish an electronic Working Group[28], under the chairmanship of Australia, working in English only and open to all the members and observers. The Committee agreed that the electronic Working Group, based on the replies to the Circular Letter (see paragraph 91), would:

i. Prepare a Priority List of Veterinary Drugs for Evaluation or Re-evaluation by the JECFA with a view to reaching a decision on the safety of residues in food by:

- developing maximum residue limits (MRLs); or
- informing risk managers on the safety of residues in food if it is likely that an ADI or MRL cannot be recommended.

ii. Prepare a working document listing veterinary drugs of potential interest, based Annex 1 to document CX/RVDF 07/17/12 "Starting Point for a Priority List of Veterinary Drugs for Discussion at the 17th CCRVDF".

94. The Committee requested the electronic Working Group to include the proposal submitted by the Delegations of Guatemala and Japan, as contained in document CX/RVDF 07/17/12 Add.2, in the working document listing veterinary drugs of potential interest. It agreed that the report of the electronic Working Group should be made available in a timely manner to allow consideration and comments by all members and observer organizations.

REPORT OF THE PHYSICAL WORKING GROUP ON RESIDUES OF VETERINARY DRUGS WITHOUT ADI/MRL (Agenda Item 9)[29]

95. The Committee recalled that at its 16th Session, it had agreed to re-establish the physical Working Group on Residues of Veterinary Drugs without ADI/MRL, under the Chairmanship of the European Community, to consider Annex III "Starting Point for a Priority List of Veterinary Drugs Requiring Evaluation or Re-evaluation by JECFA" of document CX/RVDF 06/16/13[30].

96. The Committee also recalled that the physical Working Group had been asked in particular:

- to give further consideration to the prioritization of compounds on the list and update it;
- to consider management options for compounds to be evaluated by JECFA where a management decision was pending; and
- to provide guidance on practical analytical methods suitable for use by national regulatory authorities.

97. The Delegation of the European Community, as the Chairperson of the physical Working Group, referring to the Report of the Working Group, as contained in document CX/RVDF 07/17/12, highlighted that the report summarized the problems of substances without ADI and/or MRLs and identified possible options to solve these problems. The Report also included six Recommendations (A-F, as presented in paragraphs 42-56 of document CX/RVDF 07/17/12), which were discussed by the Working Group on Priority (see paragraph 84).

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[28] Australia, Brazil, Canada, Colombia, European Community, France, Germany, Guatemala, Hungary, Indonesia, Japan, Malaysia, Mexico, New Zealand, Norway, Republic of Korea, Sweden, United Kingdom, United States of America, IAEA, IFAH, FAO and WHO expressed their willingness to participate in the electronic Working Group

[29] CX/RVDF 07/17/12; CX/RVDF 07/17/12 Add.1 (Comments of Brazil, Canada, Ghana, United States of America and IFAH); CX/RVDF 07/17/12 Add.2 (Comments of Guatemala and Japan); CRD2 (Report of the Working Group on Priorities); CRD6 (Comments of FAO/WHO JECFA Secretariat); CRD9 (Risk Assessment of Malachite Green Residues – Literature Study, submitted by Germany); CRD10 (Comments of Thailand); CRD17 (proposed project document submitted by European Community); CRD17bis (Revised proposed project documents submitted by European Community)

[30] ALINORM 06/29/31, para. 134

98. The Delegation of Australia, speaking as the Chairperson of the Working Group on Priority, referring to the report of the Working Group, as presented in CRD2, briefly reported that significant discussion was held on the above six Recommendations. He noted that further discussion should be held at the plenary, in particular, on Recommendations A (Complete list of evaluations made publicly available) and B (Specific veterinary drugs) since the Working Group could not reach conclusions on these Recommendations.

99. The Committee considered the six Recommendations, noting the outcomes from the Working Group on Priority. Discussion held and decisions made were as follows:

Recommendation A: Complete list of evaluations/decisions made publicly available

100. The Committee considered Recommendation A, which suggested that Codex should establish in collaboration with JECFA a complete summary of the evaluations and decisions made on veterinary drugs. This Recommendation was aimed at facilitating the development of a global approach in Codex for veterinary drugs with or without ADI and/or MRLs for use in food producing animals.

101. The Representatives of FAO and WHO, speaking as JECFA Secretariats, referring to CRD6, clarified that summaries of all JECFA's evaluations of veterinary drugs, including information on ADIs and MRLs as well as toxicological and residue monographs, already existed and were publicly available on FAO and WHO JECFA websites, also as databases[31,]. Therefore, the Representatives suggested that the Committee should primarily need to assess the applicability of this information and, where necessary, recommend possible further improvement.

102. The Codex Secretariat clarified that all the information related to Codex MRLs for veterinary drugs were available on the Codex website, including a searchable database on Codex MRLs for veterinary drugs[32], as well as the *Compendium of methods of analysis identified as suitable to support Codex MRLs*[33].

103. Considering the above information, the Committee was asked to clarify which were the need and objectives of developing such a list that would contain information already searchable through internet. In reply, the Delegation of the European Community, speaking as the Chairperson of the physical Working Group on Residues of Veterinary Drugs without ADI/MRL, clarified that this Recommendation was proposing to establish a single point of access to both information on JECFA's evaluations and decisions of Codex for veterinary drugs and reiterated that such a complete single list would help to facilitate public awareness in the status of all veterinary drugs in Codex.

104. As a way forward, the Codex Secretariat proposed adding to document CX/RVDF 07/17/5 a third part to include all substances evaluated by JECFA for which an ADI and/or MRLs could not be established and listing any relevant decision of the Committee.

105. After some discussion, the Committee agreed to have further discussion on this issue at its 18th Session, with a view to exploring possibility on how to proceed with implementation of this Recommendation, including resource availability and design of the list.

Recommendation B: Specific veterinary drugs

106. The Committee considered Recommendation B on how to address specific veterinary drugs for which no ADI and/or MRLs were recommended by JECFA due to specific health concerns.

107. The Delegation of Australia, referring to the outcome of the Working Group on Priority, stated that, as this Recommendation was linked to Recommendation A, it would not be necessary to develop a list of compounds for which no ADI and/or MRLs were recommended by JECFA if a complete list of the evaluations and decision made on veterinary drugs would be made available.

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31 http://www.fao.org/ag/agn/jecfa-vetdrugs/search.html?lang=en; http://jecfa.ilsi.org/

32 http://www.codexalimentarius.net/mrls/vetdrugs/jsp/vetd_q-e.jsp

33 http://www.codexalimentarius.net/mrls/vetdrugs/vetd_ref/MAS-RVDF_2006_e.pdf

108. The Delegation of the European Community, speaking as the Chairperson of the physical Working Group on Residues of Veterinary Drugs without ADI/MRL, pointed out that the above clarification, made by the Delegation of Australia, misinterpreted the intention of Recommendation B and clarified that Recommendation B did not propose to develop a list of such substances, but that the Committee considers developing risk management recommendations and provides risk management advice to national and regional authorities on substances for which ADI and/or MRLs could not be recommended due to specific heath concerns. The Delegation proposed to start new work on this topic.

109. The Committee agreed to take up this recommendation and considered a draft project document for new work, prepared by the Delegation of the European Community, as presented in CRD17bis.

110. In presenting CRD17bis, the Delegation of the European Community stressed that the objective of the proposed new work was not to establish a negative list of veterinary drugs, but to develop risk management recommendations for veterinary drugs without ADI and/or MRLs due to specific health concerns, including suggestion for the use of these substances if their unavailability would create animal health concerns.

111. With regard to project documents for new work, the Committee was informed that the 30th Session of the Commission had noted that some project documents submitted in the past years were of low quality and not addressing all criteria with ample explanation/justification and had requested that in the future all project documents should be prepared correctly in accordance with the provisions in the Procedural Manual[34].

112. Concerns were expressed by some delegations as to whether the proposed new work would develop a negative list, which might have potential implication for national food safety systems as well as enormous negative economic impact on livestock sectors. Therefore, further discussion would be necessary to clarify the context of the work. Other delegations were of the view that they did not have sufficient time to consider the proposal and to consult with relevant stakeholders at national level.

113. The Representative of WHO, speaking as JECFA Secretariat, recalled that the Committee had not yet taken action on some substances for which JECFA had completed its evaluation and had identified a clear human health concern. For instance, for chloramphenicol, evaluated by JECFA at its 62nd Meeting in 2004 upon the CCRVDF's request, it was concluded that it was not appropriate to establish an ADI, due to toxicological concerns regarding potential carcinogenicity via a genotoxic mechanism and aplastic anemia. Moreover, for carbadox, re-evaluated by JECFA at its 60th meeting in 2003 upon the CCRVDF's request, an ADI could not be established and the MRLs recommended at the 36th meeting were withdrawn due to concerns regarding the persistence of carbadox and its main metabolite desoxycarbadox and their carcinogenicity, where a genotoxic mechanism could also not be excluded. The Representative of WHO, therefore urged the Committee to support the project document and to take its responsibility for public health protection and consider means to act on JECFA's assessment of such compounds.

114. The Representative of FAO, speaking as JECFA Secretariat, stated that the six compounds in the Table at paragraph 46 of document CX/RVDF 07/17/12 should be considered by the Committee for developing risk management options, consistently with the decisions made at the present Session under Agenda Item 8 and with the mandate given to the Working Group on Priority to also cover decisions on the safety of residues in food by "informing risk managers if it is likely that an ADI and/or MRL could not be recommended" (see paragraph 93). The Representative of FAO stated that it would be unlikely that an ADI could be established and MRLs recommended for malachite green, which was added to the priority list. She questioned why the Committee had included malachite green in the priority list if there was no agreement on how to act for compounds without ADI and/or MRLs due to specific health concerns.

115. After some discussion, the Committee agreed to add the section on "Main aspects to be covered" of the draft project document, a point regarding consideration of options for communicating risk management recommendations on veterinary drugs without ADI and/or MRLs due to health concerns and a paragraph to clarify that the outcomes of this work would not be to establish a negative list, but to develop risk management recommendations

116. The Committee agreed to forward the project document as amended above, proposing new work to the Executive Committee for critical review and for approval by the 31st Session of the Commission in July 2008 (see Appendix VIII).

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34 ALINORM 07/7/REP para. 97

117. The Committee also agreed to establish an electronic Working Group[35], under the chairmanship of the European Community and Mexico, open to all members and observers and working in English and Spanish. It further agreed that, pending the formal approval of new work by the Commission, the Working Group would prepare proposed draft risk management recommendations/guidance for veterinary drugs for which no ADI and/or MRL has been recommended by JECFA due to specific human health concerns, for circulation for comments at Step 3 and its consideration at Step 4 at the 18th Session of the Committee.

118. The Delegations of Australia, New Zealand and the United States of America opposed to the proposal for new work as in CRD17bis because of a lack of clarity of the objectives, parameters and the likely form of the final product and how it could be used. These Delegations alternatively proposed to prepare a discussion paper that would be taken up in context and jointly with Recommendations A of document CX/RVDF 07/17/12 for consideration at the 18th Session of the Committee. This position was supported by the Delegation of Mexico.

Recommendation C: scientific evaluation

119. The Committee endorsed Recommendation C requesting FAO and WHO to convene an expert group to "*develop a general decision tree approach for the evaluation of veterinary drugs, which could identify different options for hazard identification and characterization, and exposure assessment*"[36].

120. The Representative of WHO, speaking on behalf of JECFA Secretariats, reiterated that resource constraints would not allow convening the above expert group and encouraged members to mobilize necessary funds.

Recommendation D: prioritization (criteria for the prioritization of veterinary drugs without ADI and/or MRLs)

121. The Committee considered Recommendation D on criteria for prioritization of compounds without ADI and/or MRLs to be evaluated by JECFA.

122. The Committee agreed that the following criteria should be considered for prioritization of these compounds:

- Consumer health protection: Veterinary drugs used in food producing animals, but completely prohibited by at least one Codex member for reasons related to consumer health, should be given priority on approach based on risk.
- Trade concerns: Trade disruptions may occur when food safety decisions differ between countries leading to a number of problems including rejection of consignments due to the detection of residues, added compliance costs in the exporting country to meet the different requirements or complete cessation of trade. Priority should be given to evaluation of those veterinary drugs that have led to the rejection of consignments in the past.
- Necessity for the treatment of animals: Priority should be given to the evaluation of veterinary drugs that are needed to avoid unnecessary suffering or disease in animals (i.e. morbidity and mortality). Moreover those veterinary drugs that are needed by Codex members that rely on the Codex safety evaluation should be given priority. Additionally the extent to which the veterinary drugs are used for the treatment of animals should be considered. (Spanish translation for mobility).
- Agronomic impact: The availability of veterinary drugs can have a profound impact on the agricultural economy of Codex members. In consequence, consideration should be given to the economic impact of the use or non-use of a veterinary drug and the extent of its use when weighing the risks against the benefits in risk management decisions, including the prioritization of these drugs for further consideration.

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[35] Australia, Austria, Belgium, Brazil, Canada, China, Colombia, Germany, Guatemala, Hungary, Indonesia, Italy, Japan, Malaysia, Norway, New Zealand, Republic of Korea, Sweden, Thailand, United Kingdom, United States of America, Vietnam, and IFAH, FAO and WHO expressed their willingness to participate in the electronic Working group

[36] Recommendation of the 66th JECFA

- Availability of data and/or evaluation: Priority should be given to the evaluation of veterinary drugs for which sufficient data are available to support a decision on their use in food producing animals. Veterinary drugs can only be evaluated for use in food producing animals if sufficient data is available. Therefore, subject to the previous criteria being satisfied, priority should be given to the evaluations of drugs which have already been evaluated at national/regional level employing procedures similar to those used by JECFA/CCRVDF.

Recommendation E: closing data gap

123. The Committee considered Recommendation E on establishment of a procedure to facilitate submission of data for evaluation by JECFA, with a view to closing data gap and ensuring commitment for data availability.

124. The Committee made some changes to the text in order to align with procedure on participation of members and observers in Codex and agreed to the following Recommendation:

The CCRVDF should consider establishing a procedure to commit potential sponsors to join forces in order to share costs and efforts and that Codex members should make an effort to also contact the generic drugs industry which is not represented by IFAH.

Recommendation F: Evaluation of consignments

125. The Committee considered Recommendation F and made some amendments to the text to avoid duplication of work and mandate with the Committee on Food Inspections and Certification Systems (CCFICS).

126. The Committee agreed that *the CCRVDF should encourage a global approach for the evaluation of consignments containing residues of veterinary drugs that should not be used in food producing animals to be as guidance and more transparency to facilitate fair practices in food trade.*

DISCUSSION PAPER ON RISK MANAGEMENT TOPICS AND OPTIONS FOR THE CCRVDF (Agenda Item 10)[37]

127. The Committee recalled that at its 16th Session, it had agreed to establish an electronic Working Group, under the chairmanship of France, to identify risk management topics and options to be considered at the next Session of the Committee[38].

128. The Delegation of France, speaking as the Chairperson of the in-session Working Group on Agenda Item 10[39], introduced relevant recommendations of the Working Group, as contained in CRD16.

129. The Committee noted that the in-session Working Group had classified the proposals listed in document CX/RVDF 07/17/13 into four mains categories:

- Topics that should be taken up immediately for consideration by the Committee**:** (B-1) Use of the Estimated Daily Intake (EDI) concept; (C-1) Utilization of Full ADI; (E-2) Starter Cultures; and (E-7) Appending Risk Management Recommendation(s), to MRLs.
- Topics that the Committee should address in the future: (B-2) Expression of Risk Assessment Results in Terms of MRLs; (B-4) Scientific evaluation; (B-5) Recommendations from the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL (Bangkok, 24-26 August 2004): CCRVDF should develop a risk assessment policy that would allow extrapolation of risk assessments from species to species; and (C-3) Residues at Injection Sites.

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37 CX/RVDF 07/17/13; CX/RVDF 07/17/13 Add.1 (Comments of Canada, Costa Rica, Ghana and IFAH); CRD16 (Report of the in-session Working Group on Agenda Item 10)

38 ALINORM 06/29/31, para. 113

39 The following members and organizations attended the in-session Working Group: Australia, Austria, Brazil, Canada, France, Germany, Ireland, Japan, Malaysia, Netherlands, New Zealand, Republic of Korea, Sweden, Thailand, United Kingdom, United States of America, IAEA, IDF, IFAH, FAO and WHO

- Topics for which no further work was required**:** (A). Substances recognised of toxicological concern; (B-5) Recommendations from the Joint FAO/WHO Technical Workshop on Residues of Veterinary Drugs without ADI/MRL (Bangkok, 24-26 August 2004): Recommendation to undertake work on a threshold of toxicological approach for residues of veterinary drugs; (C-2) Rounding of the ADI; (C-4) Definition of Good Agriculture Practices; (D-1) Risk Management Options; (D-2) ALARA (As Low As Reasonably Achievable); (E-1) Withholding Time Calculations; (E-3) Data Protection; and (E-6) Threshold of Toxicological Concern for Veterinary Drugs (CX/RVDF 07/17/13, para.83).
- Topics for which further clarification should be provided at the next session of the Committee**:** (B-3) Use of Regional Consumption Factors (recommendation by the Bilthoven Workshop); (E-5) Old Drug Policy; and (E-6) Threshold of Toxicological Concern for Veterinary Drugs (CX/RVDF 07/17/13, para. 85).

130. The Committee endorsed the recommendations of the in-session Working Group that the following topics should be taken up immediately for consideration:

- (B-1) Use of the Estimated Daily Intake (EDI) concept: The work should focus on two issues: i) the means to improve communication between JECFA and CCRVDF on changes in risk assessment methodology, in advance of their implementation; and ii) the impact on the risk management process of the changes, introduced by the 66th JECFA in its method for the evaluation of residues of veterinary drug in foods;
- (C-1) Utilization of full ADI;
- (E-2) Starter cultures. The work should be based on constructive comments to be submitted by members and/or observers before the next session of the Committee;
- (E-7) Appending risk management recommendation(s) to MRLs. The work should consider whether additional recommendations on risk management could be provided by the Committee when it establishes MRLs.

131. The Committee also endorsed the recommendation of the in-session Working Group that proposal (C-3) “Residues at injection sites” be taken up for consideration in the future taking account of the estimation of acute reference doses published by JMPR, the work on the same topic planned by JECFA and the consideration planned by VICH, when they become available.

132. Based on the recommendation of the in-session Working Group, the Committee agreed to request the Codex Secretariat to prepare a Circular Letter requesting members and observer organizations to provide detailed information on their current practices and suggestion for the scope of further work by the Committee for each of the topics listed above (see paragraph 130).

133. To the request of one delegation to consider the issue related to the harmonisation of withdrawal period’s calculation, it was noted that information on methods for calculation of withdrawal period were included in the guidance available on the EMEA webpage; and that the VICH Expert Working Group on Metabolism and Residue Kinetics was considering the issue around harmonisation of statistical methods for calculation of withdrawal period as one of its major topics and that draft guidelines would be discussed at the next meeting of the Working Group in October 2007 and the output would be reported at the 18th Session of the Committee, if available.

134. The Committee agreed to establish an electronic Working Group, under the chairmanship of France[40], working in English only and open to all members and observers, to prepare a discussion paper that would:

(i) review the information provided in response to the Circular Letter (see paragraph 132);

(ii) assess whether it would provide sufficient ground for further work by the Committee and, where appropriate, would prepare a project document describing possible new work for consideration by the Committee or recommend delaying further action.

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[40] Australia, Brazil, Canada, China, Colombia, Costa Rica, European Community, Guatemala, Hungary, Indonesia, Japan, Netherlands, New Zealand, Norway, Republic of Korea, Sweden, Thailand, United Kingdom, United States of America, Vietnam, IDF, IFAH, FAO and WHO expressed their willingness to participate in the electronic Working Group

135. The discussion paper should address possible changes in the status of the proposals listed in document CX/RVDF 07/17/13 and make appropriate recommendations to the Committee for further consideration and action and collate new proposals with relevant background information and appropriate recommendations to the Committee.

136. The Committee agreed that the discussion paper be made available in a timely manner in order to allow consideration and comments by all members and observer organizations.

OTHER BUSINESS AND FUTURE WORK (Agenda Item 11)

137. The Committee noted that no other business had been put forward.

DATE AND PLACE OF NEXT SESSION (Agenda Item 12)

138. The Committee noted that its 18th Session was tentatively scheduled to be held in 2009, subject to further discussion between the Codex and United States Secretariats and taking into consideration the schedule and the availability of the report of the next JECFA meeting on veterinary drugs residues in foods.

139. The Committee noted the kind offer of the Delegation of Brazil to co-host its next Session.

SUMMARY STATUS OF WORK

SUBJECT MATTER	STEP	ACTION BY:	DOCUMENT REFERENCE (ALINORM 08/31/31)
Draft Maximum Residue Limits for: - Colistin - Ractopamine	8	31st CAC	Paras 45, 47 and Appendix II
Proposed draft Maximum Residue Limits for: - Erythromycin	5/8	31st CAC	Para. 49 and Appendix III
Draft Maximum Residue Limits for: - Melengestrol acetate	7	18th CCRVDF	Para. 43 and Appendix IV
Draft Guidelines for the design and implementation of national regulatory food safety assurance programmes associated with the use of veterinary drug residues in foods	6	18th CCRVDF	Para. 75 and Appendix VI
Proposed Draft Maximum Residue Limits for: - Triclabendazole	2	Members/ Observers	Para. 52
Proposed draft Risk management recommendation/guidance for veterinary drugs for which no ADI and MRL has been recommended by JECFA due to specific health concerns	1/2/3	31st CAC and electronic Working Group	Para. 116 and Appendix VIII
Priority list of veterinary drugs requiring evaluation of re-evaluation by JECFA	1	31st CAC	Para. 90 and Appendix VII
Draft and proposed draft Maximum Residue Limits for: - Flumequine (Black tiger shrimp and shrimps)	discontinued	31st CAC	Para. 35
Discussion paper on consideration of methods of Analysis and Sampling in CCRVDF (Report of the electronic Working Group on Methods of Analysis and Sampling)	-	electronic Working Group	Para. 80
Draft Priority list of veterinary drugs requiring evaluation of re-evaluation by JECFA and working document listing veterinary drugs of potential interest (Report of the electronic Working Group on Priority)	-	electronic Working Group	Para. 93
Discussion paper on current practices and needs for further work by the Committee on: the Use of the Estimated Daily Intake (EDI) concept; Utilization of full ADI; Starter culture; and Appending risk management recommendation(s) to MRLs (Report of the electronic Working Group on Risk Management Topics and Options for the CCRVDF)	-	electronic Working Group	Paras 134-135

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Appendix II

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 8 of the Elaboration Procedure)

Colistin (antimicrobial agent)

Acceptable Daily Intake: 0-7 µg/kg bw (66th JECFA, 2006)

Residue Definition: Sum of colistin A and colistin B

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	150	8	66	16IV
Cattle	Liver	150	8	66	16IV
Cattle	Kidney	200	8	66	16IV
Cattle	Fat	150	8	66	16IV
Cattle	Milk	50	8	66	16IV
Sheep	Muscle	150	8	66	16IV
Sheep	Liver	150	8	66	16IV
Sheep	Kidney	200	8	66	16IV
Sheep	Fat	150	8	66	16IV
Sheep	Milk	50	8	66	16IV
Goat	Muscle	150	8	66	16IV
Goat	Liver	150	8	66	16IV
Goat	Kidney	200	8	66	16IV
Goat	Fat	150	8	66	16IV
Pig	Muscle	150	8	66	16IV
Pig	Liver	150	8	66	16IV
Pig	Kidney	200	8	66	16IV
Pig	Fat	150 [(a)]	8	66	16IV
Chicken	Muscle	150	8	66	16IV
Chicken	Liver	150	8	66	16IV
Chicken	Kidney	200	8	66	16IV

Keys for List of MRLs for Veterinary Drugs

Step: (r), revised MRL; (a), amended MRL, T, temporary MRL.

JECFA: Meeting number of the Joint FAO/WHO Expert Committee on Food Additives where the MRL was recommended/considered.

CCRVDF: Session number of the CCRVDF where the MRL was considered and Appendix number of its report where the MRL is contained.

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Chicken	Fat	150 [(a)]	8	66	16IV
Chicken	Eggs	300	8	66	16IV
Turkey	Muscle	150	8	66	16IV
Turkey	Liver	150	8	66	16IV
Turkey	Kidney	200 [(a)]	8	66	16IV
Turkey	Fat	150	8	66	16IV
Rabbits	Muscle	150	8	66	16IV
Rabbits	Liver	150	8	66	16IV
Rabbits	Kidney	200	8	66	16IV
Rabbits	Fat	150	8	66	16IV

[(a)] The MRL includes skin + fat.

Ractopamine (production aid)

Acceptable Daily Intake: 0–1 µg/kg bw (62nd JECFA, 2004)

Residue Definition: Ractopamine

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	10	8	62, 66	15VI, 16IV
Cattle	Liver	40	8	62, 66	15VI, 16IV
Cattle	Kidney	90	8	62, 66	15VI, 16IV
Cattle	Fat	10	8	62, 66	15VI, 16IV
Pig	Muscle	10	8	62, 66	15VI, 16IV
Pig	Liver	40	8	62, 66	15VI, 16IV
Pig	Kidney	90	8	62, 66	15VI, 16IV
Pig	Fat	10 [(a)]	8	62, 66	15VI, 16IV

[(a)] The MRL includes skin + fat.

Appendix III

PROPOSED DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 5/8 of the Elaboration Procedure)

Erythromycin (antimicrobial agent)

Acceptable Daily Intake: 0-0.7 µg/kg bw (66th JECFA, 2006)

Residue Definition: Erythromycin A

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Chicken	Muscle	100	5/8	66	16VI
Chicken	Liver	100	5/8	66	16VI
Chicken	Kidney	100	5/8	66	16VI
Chicken	Fat	100 [(a)]	5/8	66	16VI
Chicken	Eggs	50	5/8	66	16VI
Turkey	Muscle	100	5/8	66	16VI
Turkey	Liver	100	5/8	66	16VI
Turkey	Kidney	100	5/8	66	16VI
Turkey	Fat	100 [(a)]	5/8	66	16VI

[(a)] The MRL includes skin + fat.

Keys for List of MRLs for Veterinary Drugs

Step: (r), revised MRL; (a), amended MRL, T, temporary MRL.

JECFA: Meeting number of the Joint FAO/WHO Expert Committee on Food Additives where the MRL was recommended/considered.

CCRVDF: Session number of the CCRVDF where the MRL was considered and Appendix number of its report where the MRL is contained.

Appendix IV

DRAFT MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

(at Step 7 of the Elaboration Procedure)

Melengestrol Acetate (production aid)

Acceptable Daily Intake: 0-0.03 µg/kg bw (54th JECFA, 2000)

Residue Definition: Melengestrol acetate

Species	Tissue	MRLs (µg/kg)	Step	JECFA	ALINORM
Cattle	Muscle	1	7	66	16III
Cattle	Liver	10	7	54, 58, 66	16III
Cattle	Kidney	2	7	66	16III
Cattle	Fat	18	7	54, 58, 66	13V, 14IV, 16III

Keys for List of MRLs for Veterinary Drugs

Step: (r), revised MRL; (a), amended MRL; T, temporary MRL.

JECFA: Meeting number of the Joint FAO/WHO Expert Committee on Food Additives where the MRL was recommended/considered.

CCRVDF: Session number of the CCRVDF where the MRL was considered and Appendix number of its report where the MRL is contained.

Appendix V

DISCONTINUATION OF WORK ON THE DRAFT AND PROPOSED DRAFT CODEX MAXIMUM RESIDUE LIMITS FOR VETERINARY DRUGS

Flumequine (antimicrobial agent)

Acceptable Daily Intake: 0-30 µg/kg bw (48th JECFA, 1997)

Residue Definition: Flumequine.

Species	Tissue	MRL (µg/kg)	Step	JECFA	ALINORM
Black tiger shrimp (*P. monodon*)	Muscle	500 T [(a)]	7	62	15V, 16III
Shrimps	Muscle	500 T [(a)]	4	66	16V

[(a)] The MRL is temporary; the following information is requested: Information on the approved dose for treatment of shrimps and the results of residue depletion studies conducted at the recommended dose.

Keys for List of MRLs for Veterinary Drugs

Step: (r), revised MRL; (a), amended MRL; T, temporary MRL.

JECFA: Meeting number of the Joint FAO/WHO Expert Committee on Food Additives where the MRL was recommended/considered.

CCRVDF: Session number of the CCRVDF where the MRL was considered and Appendix number of its report where the MRL is contained.

Appendix VI

DRAFT GUIDELINES FOR THE DESIGN AND IMPLEMENTATION OF NATIONAL REGULATORY FOOD SAFETY ASSURANCE PROGRAMME ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS

(at Step 6 of the Elaboration Procedure)

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Appendix B Sampling of commodities

DRAFT GUIDELINES FOR THE DESIGN AND IMPLEMENTATION OF NATIONAL REGULATORY FOOD SAFETY ASSURANCE PROGRAMME ASSOCIATED WITH THE USE OF VETERINARY DRUGS IN FOOD PRODUCING ANIMALS

Introduction

1. Modern food production systems should be designed and managed to ensure that the exposure of food producing animals to veterinary drugs does not pose a risk to human health.

2. The commercial entities involved in the production and marketing of food have the primary responsibility for ensuring food safety. The role of competent authorities is to control the use of veterinary drugs and to verify that appropriate practices are being applied and effective measures are in place within the veterinary drug distribution and food production systems to provide effective protection for consumers and facilitate trade, consistent with the goals of Codex Alimentarius.

3. The application of a programme based on risk to all food types should provide the controls and verification consistent with the risk that the food type may pose to consumers. The application of an approach based on risk across all food groups and hazard classes should allow a more focussed application of resources to those areas which are most likely to generate real human health protection gains.

4. Risk profiles for different hazards may vary by country, region, species and/or production system. The application of a control and verification assurance programme based on risk should provide the necessary basis for exporting countries to certify the safety of exported food, and for importing countries to have the confidence to accept such consignments.

5. It is recognized that in particular developing countries may need a transition period and/or technical assistance regarding the full implementation of these Guidelines.

Scope

6. This guide is intended to provide the overarching principles and guidance for governments on the design and implementation of national and trade related food safety assurance programmes for residues of veterinary drugs. The current and future annexes to this guide may provide a further refinement of guidance on issues which may be relevant to the control and verification programmes for products from certain species. These annexes should be read in conjunction with the principles outlined in this guide.

General Principles

7. Programmes for the control of residues of veterinary drugs in foods should:

   i. be based on risk using realistic risk profiles assessed as reasonably likely to be associated with food derived from the relevant productions system(s);

   ii. be prevention focussed based on the realistic risk profiles associated with the probable or known use of approved, non-approved and prohibited veterinary drugs in the production system;

   iii. include regulatory measures proportionate to the relative human health risk associated with these hazards compared with other food-associated hazards;

   iv. ensure all parties involved in the production, marketing and processing system of the animals and/or the food products derived from them are held accountable to ensure that unsafe animal products will not be sold as a result of their action or inaction;

   v. recognise that pre-harvest controls and practices are the primary means for ensuring safe food;

   vi. recognise that the primary role of audits and sampling programmes is to verify the implementation and effectiveness of the pre-harvest controls and practices;

   vii. focus on system and population based assurances; and

   viii. be cost effective and have the support of stakeholders.

8. It should be recognised that veterinary drugs are regulated in many countries for a variety of reasons, such as animal health, animal welfare and protection of the environment. Where these uses and the related standards do not fall under the mandate of the Codex Alimentarius Commission, they should be clearly identified and justified where, for reason of efficiency, they form part of the Competent Authority's residue control programme.

9. The Codex Alimentarius Commission's recommended sampling procedures for residues of veterinary drugs in food are exempted from the general sampling procedures of food commodities developed by the *Codex Committee on Methods of Analysis and Sampling*. Accordingly, this guideline includes sampling procedures relevant for the entire control programme.

10. The safety of foods is achieved by the implementation of appropriate rules applied from primary production or import to retail or export and requires the participation of all parties involved. Competent Authorities should verify correct implementation of programmes and, where necessary, if action has been taken.

11. The reliability of laboratory results is important for the decision making of Competent Authorities. Thus official laboratories should use methods validated as fit for purpose and work under internationally accepted (e.g. ISO 17025) quality management principles.

12. A control programme designed and implemented according to this guideline provides reassurance for importing countries to accept consignments certified as safe by the exporting country.

Approach based on risk

13. An approach based on risk applied across the entire production chain and on all food groups and potential hazards will allow Competent Authorities to focus application of resources to areas of highest risk which are most likely to have an impact on consumer health protection.

14. Continuous application of good practices and regular control contribute more significantly to food safety than end product testing.

15. Residues may exert an adverse effect on consumers in a number of ways, such as:

(a) chronic toxicological adverse effects;

(b) acute pharmacological effects on consumers and on the microflora of the gastrointestinal track of consumers;

(c) allergic reactions.

16. Different types of controls and monitoring programme may be justified where the risk assessment identifies one or more of these other end-points as being significant for human health. Detections of non-compliant residues (e.g. those exceeding applicable MRLs) justify regulatory follow up.

17. Animals and/or production systems can be exposed to a variety of veterinary drugs and other chemicals that may as a result be present in the products derived from them. Their importance for consumer health protection, however, varies with type and source.

18. An understanding of the circumstances required for each veterinary drug input to actually pose a risk to consumers of animal products, along with an estimate of the relative likelihood of this occurring, is essential to determine the appropriate controls and verification programmes which should be included in the design of national residue control and verification programmes.

19. The application of a control and verification programme based on risk should provide the necessary basis for exporting countries to certify, where required, the safety of exported food, and for importing countries, subject to any additional assessment they deem necessary, to accept such consignments.

20. The same principles should apply to export assurance programmes as are applied to the design and implementation of national assurance programmes.

Definitions (for the purposes of these guidelines)

Competent Authority(ies) means the official government organisation/agency(ies) having jurisdiction[1].

Approved means officially authorised or recognised by a competent authority.

Based on risk means focussed on and proportionate to an estimate of the probability and severity of an adverse effect occurring in consumers.

Risk profiles are defined in the Codex Manual[2] as "*The description of the food safety problem and its context.*" For veterinary drugs they relate a production system to a potential consumer health risk. They are the basis for approvals and use restrictions.

Maximum residue limit for veterinary drug (MRLVD or MRL) is defined[3] as *"the maximum concentration of residue resulting from the use of a veterinary drug (expressed in mg/kg or µg/kg on a fresh weight basis) that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food. It is based on the type and amount of residue considered to be without any toxicological hazard for human health as expressed by the Acceptable Daily Intake (ADI), or on the basis of a temporary ADI that utilizes an additional safety factor. It also takes into account other relevant public health risks as well as food technological aspects. When establishing an MRL, consideration is also given to residues that occur in food of plant origin and/or the environment. Furthermore, the MRL may be reduced to be consistent with good practices in the use of veterinary drugs and to the extent that practical analytical methods are available."*.

System verification means obtaining overall information on the extent of application of the practices and controls.

Risk targeted verification programmes means inspection/audit and/or sampling/laboratory analysis of specific suppliers or products aimed at the detection of non-compliance.

Non-biased sampling refers to the random sampling of specified populations to provide information about the occurrence of residue non-compliances, typically on an annual, national basis. Compounds selected for non-biased sampling are usually based on risk profiles and the availability of laboratory methods suitable for regulatory purposes. The results of non-biased sampling are a measure of the effectiveness and appropriateness of the controls and practices within a wider segment of the production system.

Survey refers to the collection of additional data aimed at the investigation of residues linked to a specific veterinary drug use or production type.

Withdrawal time/ Withholding time (food harvest restriction) are defined in Codex Guideline CAC/MISC 5 1993 - Glossary of Terms and Definitions (Veterinary Drugs Residues in Foods) as: "*the period of time between the last administration of a drug and the collection of edible tissue or products from a treated animal that ensures the contents of residues in food comply with the maximum residue limit for this veterinary drug (MRLVD)*". A period of time may also be represented by a combination of events or other factors.

Production system means the methods or activities used to produce food for human consumption for which the residue control programme of a Competent Authority has been designed.

Quality control (in residue laboratories) means monitoring those factors associated with the analysis of a sample by a tester.

Quality assurance (in residue laboratories) means independent review to ensure that the analytical programme is performing in an acceptable manner.

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[1] Definition used in the Codex Guidelines for the Production, Processing, Labelling and Marketing of Organically Produced Foods (CAC/GL 32-1999).

[2] FAO/WHO. 2006. Codex Alimentarius Commission Procedural Manual, 16th Ed., Food and Agriculture Organization of the United Nations, Rome, page 44.

[3] FAO/WHO. 2006. Codex Alimentarius Commission Procedural Manual, 16th Ed., Food and Agriculture Organization of the United Nations, Rome, page 43.

Quality management system ensures that a laboratory is managed and operated in a manner that meets the requirements of an internationally recognized quality standard to produce quality data and results (e.g. ISO 17025: 2005).

Regulatory Framework

Roles

21. Business operators/commercial entities involved in the production and marketing of food have the primary responsibility for ensuring food safety.

22. Competent Authorities regulate the use of veterinary drugs, verify that appropriate practices are applied and that effective measures are in place within the veterinary drug distribution and food production system to provide effective protection of consumers and facilitate trade, consistent with the goals of Codex Alimentarius.

23. The competent authority responsible for providing consumer assurances for foods must ensure that it has sufficient knowledge of and control over veterinary drugs that are being sold and used within the production systems and that it has sufficient knowledge of food safety.

Approval

Criteria

24. Appropriate official approval criteria should be established. These criteria may include the acceptance of the assessments of other recognised competent authorities where use patterns are likely to be similar.

25. Approval systems should:

(a) require an evaluation of the human safety of residues of the veterinary drug relying on a risk analysis and establishing, where appropriate, maximum residue limits;

(b) attempt to take into account the needs of the producers in order to reduce the temptation to use unapproved veterinary drugs or prohibited substances.

26. Approval systems should take into account that risk profiles and management options may vary substantially among production systems and regions.

Approval restrictions

27. The conditions for the approval of veterinary drugs should be specified in law.

28. To mitigate potential risk, restrictions may be imposed on:

(a) formulations;

(b) criteria of use (e.g. time, species);

(c) indications;

(d) withdrawal time/withholding time/food harvest restriction.

National register

29. All formulations of veterinary drugs approved in a country should be recorded in a national register.

Information on veterinary drugs

30. Information and/or education programmes on suitable use to provide effective treatment while affording protection of consumers should be provided for each approved veterinary product formulation.

Sale and use

31. National/regional regulations should establish which veterinary drugs may be sold domestically and how these may be used. Formulations not recorded in the national register should not be used and sanctions should be in place to act as a deterrent against such use.

32. It may be appropriate, where justified by a relevant risk profile, to impose additional conditions on the sale and use of certain veterinary drugs to ensure appropriate use and to prevent misuse or abuse.

33. Sale and use conditions may include:

(a) Requiring all sales to be subject to a prescription from a veterinarian or other professional with approved competencies;

(b) Restricting administration to individuals or professionals with approved competencies;

(c) Requiring all treated animals/production systems to be identified in specified ways;

(d) Requiring all uses to be recorded and/or notified to (a) central database(s).

34. Efficacy and the necessity of use conditions should be regularly reviewed against the local risk profile. In doing this it should be considered that the non-availability of necessary treatments may encourage use of non-approved veterinary drugs or prohibited substances.

35. Competent Authorities may establish legislation/regulation that allows, as an exception, the use of non-approved veterinary drugs off-label/extra label in accordance with direct and written veterinary advice and oversight. Such legislation should be consistent with national and/or international guidance and technical information on this issue.

36. In animals from which milk, eggs or honey, respectively, are collected for human consumption, only veterinary drugs specifically approved for use in lactating animals, laying birds and honey bees should be used. Specific exemptions may be made for off-label/extra label use.

Responsibilities of business operators (Best Practice Guidance)

37. Producers should only use veterinary drugs which have been approved for use in food producing animals. Non-approved veterinary drugs should not be used. Veterinary drugs should be used strictly in accordance with the officially approved/recognised instructions. Veterinary drugs should be used off-label only in accordance with direct and written veterinary advice. Such advice should be consistent with national and/or international guidance documents and technical information on this issue.

38. Producers should be encouraged to seek advice of veterinarians or other competent professionals on the application of the correct withdrawal time, where the label direction for use may not be available or may not be clear.

39. Records should be kept of all details of the treatment and the withdrawal time/withholding time required before the animal or product from the animal can be harvested for human consumption.

40. Business operators (whether primary producers or others) should be required to communicate food harvesting restrictions (withdrawal/withholding times) still in place on the animal or animal product at the time of sale to subsequent purchasers of the animal(s).

41. Processors should be required to ensure that they only purchase and/or process animals and/or animal products from suppliers (whether primary producer or others) who can credibly attest to the suitability/safety of the animal or animal product for the purpose intended.

42. Producers should have appropriate on-farm food safety assurance measures in place with respect to the use of and/or exposure of food-producing animals to veterinary drugs. All workers directly involved with the animals should be familiar with these measures.

43. Producers should be able to identify all food-producing animals, or lots of these animals, which have been treated with or exposed to veterinary drugs to ensure compliance with withdrawal/withholding times.

44. Continuous food safety assurance measures such as record keeping should ensure that products (e.g. milk, eggs, honey) are harvested only if appropriate withdrawal/withholding times have been respected.

45. Treated or exposed animals for which the withdrawal time/withholding time has not elapsed should be kept separate from animals that have not been treated, or be positively identified to reduce the potential for mistakes.

46. Products from animals under harvest restrictions should be obtained in such a way that ensures their product does not mix with that being harvested for human consumption. Any equipment likely to be contaminated should be adequately cleaned prior to being used on other animals.

Verification programmes

Purpose

47. A verification programme that combines audits/inspection of various control points and point of harvest testing should be implemented. This approach will reduce reliance on chemical analyses and provide a higher degree of assurance.

48. The overall objective of the verification programme is to provide an appropriate degree of confidence that the practices and controls in place are adequate and being applied to the extent necessary to ensure the health of consumers of animal products. It will therefore attempt to ensure that exposure to residues in excess of the ADI rarely occurs.

49. Verification programmes should contribute to the:

(a) verification of assumptions made in the registration process;

(b) identification of unacceptable production, marketing and/or chains of advice;

(c) evaluation of the effectiveness of veterinary drug label information as it relates to food safety;

(d) evaluation of the effectiveness education or risk reduction programmes;

(e) evaluation of quality assurance systems;

(f) verification of implementation and effectiveness of corrective actions.

General design principles

50. Verification programmes should cover, as appropriate, the entire food chain from primary production to retail or export. A combined system of inspection/audits and sampling/laboratory analysis should be implemented. The frequency, point and type of activity should be based on an assessment of the risk to provide the most effective control.

51. Verification programmes can be classified as follows according to objective and criteria applied to the sample selection:

(a) system verification programmes;

(b) risk-targeted verification programmes;

(c) surveys;

(d) port of entry testing programmes.

52. Verification programmes may focus on assessing the

(a) effectiveness of a control system; and/or

(b) compliance by individuals or groups.

System and targeted verification programme design

53. Verification programmes should:

(a) define their purpose;

(b) identify the population being sampled;

(c) state whether the sampling is non-biased or targeted (directed); and

- base the sample sizes for non-biased sampling protocols on statistics;
- pre-determine targeting criteria to direct sampling;

(d) pre-determine the criteria to be applied to the analysis of the results;

(e) define sampling and identification procedures that allow tracing each sample back to its origin and independent confirmation of the finding in case of dispute.

Risk Profiling

54. It is the responsibility of the Competent Authorities to determine the risk profiles for their country and/or production system.

55. The frequency and intensity of verification or inspection/audit of each drug residue chosen to be monitored under the system verification programme should depend on the veterinary drug and use profile.

56. Risk profile considerations concerning veterinary drugs include:

(a) the type of hazard presented;

(b) the class and severity of the adverse human health effect associated with the residue (e.g. chronic toxicity, acute pharmacological, allergic reaction, or microbiological disturbance);

(c) the use and/or production circumstances required to produce residues and the likelihood of these occurring in foods derived from the production system at concentrations and in frequencies presenting a risk to consumer health;

(d) the dietary consumption required for the residue to give rise to a realistic consumer health risk.

57. Competent Authorities should attempt to make realistic estimates of the types, quantities and use patterns of veterinary drugs in their jurisdiction.

58. Subsequently the following should be considered:

(a) circumstances required for each veterinary drug to cause an adverse health impact on consumers;

(b) likelihood of such circumstances occurring.

59. When considering and ranking the residues associated with the veterinary drugs likely to be present at some stage in the production system potential sources and exposure pathways should be described.

60. The following sources of veterinary drug residue should be considered:

(a) veterinary drugs authorised in the jurisdiction of the Competent Authority;

(b) veterinary drugs that are known to be, or suspected of being misused.

61. The exposure pathways of veterinary drug residue should be considered:

(a) intended e.g. direct administration to the animals;

(b) indirect administration to the animals through addition to feed or water;

(c) unintended contamination via e.g. feed, water, or the environment.

62. Competent Authorities should, as appropriate to the risk profiles in the country and/or production system, consider the following potential pre-harvest control points for audit/inspection in the verification programme:

(a) the sellers and purchasers of veterinary drugs to verify what is being sold and how they are being marketed;

(b) the users of veterinary drugs (including farmers, veterinarians and feed compounders) to verify how drugs are actually being used in the production systems, e.g. according to label, what records are being kept and how the treatment status of animals is identified;

(c) the animal and animal product distributors to verify that any food harvest restrictions associated with the animal or product are effectively communicated;

(d) the assurance systems used by processors and/or producers to ensure the suitability of the animals or product they are being supplied with for the purposes they intend using it for.

Choice of verification programme

System verification programmes

63. In setting up system verification programmes the following should be considered:

(a) systematic examination of the regulatory control system;

(b) non-biased sampling of a specified population with broadly similar attributes so that the results can be used to derive a statistical confidence as to the extent of control present in that population as a whole.

64. System verification programmes can focus on the degree of application of specific controls in the process or can focus on monitoring the residues in the animals/products at or close to the point of harvest.

65. Non-biased sampling programmes should be used in order to find out whether one of the controls within the system needs adjusting. They should not be relied upon for product evaluation.

66. Where the Competent Authority has linked the approval of a veterinary drug to particular use conditions/restrictions in order to avoid misuse or abuse, the appropriateness of the use conditions/use restrictions should be regularly verified with risk-targeted verification programmes as to their efficacy and necessity to manage the risk posed by the use of the veterinary drug.

67. Generally non-biased sampling protocols are not efficient in detecting low incidences of non-compliance. Where such incidences are a potential significant risk to human health other assurance programmes should be employed.

Risk targeted verification programmes

68. In setting up risk targeted verification programmes the following should be considered:

(a) previous performance, history of non-compliance;

(b) the quality management components usually relied on;

(c) potential risk factors which may be correlated with an increased use of veterinary drugs such as;

- high somatic cell counts in milk, or
- significant ante- or post-mortem findings e.g. injection site lesions or resolving pathology;

(d) any other information linked to non-compliance and drug use.

69. Competent Authorities may complement the risk-targeted pre-harvest verification programmes with established risk-targeted post-harvest verification programmes.

Surveys

70. Surveys may be performed to:

(a) assess the initial situation before a verification programme is started;

(b) evaluate the efficiency and appropriateness of specific aspects of control programmes;

(c) monitor the impact that variables, such as location, season, or age, may have on the presence, absence or concentration of a residue.

Review

71. Control and verification programmes should be regularly reviewed to ensure their continued efficacy and/or necessity, as well as to review the potential impact of changes to the risk profiles.

72. Where a significant incidence of non-compliance is identified in any one year and consequent changes to the control programme implemented, a higher standard of verification may be appropriate until the effectiveness of the corrective actions has been demonstrated. Some of the selected lower risk profile veterinary drugs should be considered for rotation in and out of the programme based on history of compliance to ensure that the scope is as wide as possible.

Sample taking

General principles

73. Appropriate mechanisms to prevent possible bias occurring in both the selection and taking of samples should be put in place.

74. Ideally, samples should be taken before animals and/or products are commingled with animals or product from other suppliers.

Traceability/product tracing

75. Competent Authorities should ensure that all samples can, throughout the sampling, storing, shipping, analysis and reporting, be traced back to their origin.

76. Each sample needs to be clearly identified so that appropriate follow-on actions can be applied in case of non-compliant results.

77. If sub-units of a consignment are sampled, care should be taken to identify those clearly. Sufficient sample should be taken to allow for unprocessed portions to be retained allowing possible independent confirmation of the findings.

Statistical considerations

General

78. The sample sizes for system verification programmes can be statistically pre-determined (see Appendix A for additional guidance).

79. In designing a sampling protocol it is essential to define both the purpose of the programme and the population of interest. It is also important to define the criteria to be applied when analysing the results with respect to the need/desirability for any further action, and especially how such criteria and reactions directly relate to the protection of human health.

80. Ultimately "a population" made up of "units of food consumed" is the most relevant to human health. However, as it is the application of appropriate pre-harvest practices and controls which ensures food safety, a sampling strategy which verifies both the appropriateness and extent of compliance of these pre-harvest practices and controls can be used to provide appropriate assurances that the health of consumers is unlikely to be negatively affected. Generally the population of interest for targeting pre-harvest compliance/appropriateness verification information will be those population units to which common practices and controls should be applied such as:

(a) the seller of the veterinary drug input into the production system;

(b) the producer;

(c) the supplier of the animals or animal product to the processor; or

(d) the processor.

81. However, because the potential consequences to human health are much larger when large production units (farms) are out of control, the usual pre-harvest population randomly sampled is a standardised unit of production sold at any one time e.g. individual animal, vat of milk, barrel of honey, or defined weight of aquaculture product. In this way the larger producers/suppliers should effectively have a greater probability of being sampled while still maintaining the randomness of the sampling protocol.

82. Generally, conclusions will be drawn from the prevalence, or lack thereof, of non-complying results in the units sampled during the production season or calendar year. However, where problems are found during the course of the production season, corrective actions may have already been applied and have started to have a positive effect well before the end of the production season or calendar year. For small populations, or for either low risk or reasonably stable exposure scenarios, several production seasons or calendar years may be used/needed to collect the number of samples statistically determined to give the required confidence.

83. Where it is possible to further refine and describe the affected population associated with defined risk factors such as season, region or specific type of production, then a correlation of the sampling protocol to such a co-variable may be justified.

84. The point at which a sample is taken depends on the objective of the specific programme. Where the objective is to verify the effectiveness of controls at the supplier stage, generally samples are taken at the point of sale/harvest where it is still possible to correlate the unit sampled with a supplier or producer.

85. On-farm sampling may also be used as part of a pre-harvest quality assurance programme or where there are concerns associated with the possible use of substances prohibited by the Competent Authority.

86. Where the objective is to verify the overall effectiveness of a system at ensuring the general population's exposure is less than the ADI then multiple sample units can be combined before analysis, or commingled product sampled and analysed.

87. Where the objective is to verify the credibility and effectiveness of the control and verification programmes present in an exporting country, samples may be taken from standardised units of export at the port of entry. Such secondary verification programmes have quite different design considerations with respect to their objective, the population of interest and the type of response to any identified incidence of non-compliance. The statistical tables in Appendix A are not relevant to such programmes and sample sizes should reflect the importing country's confidence in the performance of the exporting country.

Retention of consignments during laboratory analysis

88. Competent authorities should not routinely retain lots of production associated with randomly selected samples pending the availability of the analytical results. Competent Authorities may routinely retain lots of production where:

(a) immediate action, such as product recall, when such action is indicated by a finding in such samples; or

(b) it is considered likely that a risk targeted test will produce non-compliant results that present a potential risk for consumer health.

Result interpretation

89. A greater degree of assurance is achieved if statistically based system verification programmes based on non-biased sampling and risk targeted (e.g. specific suppliers or products) verification programmes are operated in parallel.

90. The results of risk targeted verification programmes alone do not allow conclusions on the exposure of the general population with residues of veterinary drugs.

91. Conclusions on the exposure of the general population can be drawn from the combining the results of:

(a) statistically based system verification programmes involving non-biased sampling; and

(b) risk targeted verification programmes.

<u>Port of entry testing programmes (specific requirements)</u>

92. Competent Authorities should consider port of entry testing programmes only as a secondary system verification tool.

93. The matrices used in port of entry programmes may vary from those used for national verification programmes.

94. For port of entry testing programmes the population of interest is all like product produced under a common control and verification programme. While units of product may be sampled from selected consignments, the results attained are only reflective of the discrete unit (package) sampled and the performance of the national control and verification programme as a whole. For consignments of non-homogenous products, except where there is a commonality of pre-harvest source, the results attained from the sampled unit are no more reflective of the rest of the consignment from which the sampled unit came than other similar product produced under the same national control and verification programme.

95. Except where a risk to health is suspected or detected, certified product should be subjected to non-biased sampling and release programmes at a frequency determined by the exporting country's record of compliance.

96. The application of directed or targeted sampling in port of entry sampling programmes is only appropriate where it is known or suspected that products share the same risk profile.

97. However, following the detection of non-compliant results during port of entry programmes, importing countries may increase the overall frequency of testing of directly related food of animal origin from the exporting country for a period as an added verification of the effectiveness of any additional controls being implemented by the exporting country.

98. In the interpretation of laboratory results of consignments of animal products it should be considered that these are made up of commingled product from a variety of animals, farms and processing dates and, therefore, heterogeneous. Because of this, results should not be taken to judge other units of a consignment except where units share a common pre-harvest risk factor and where a direct risk to health is suspected or detected.

99. Results of port of entry testing programmes should only be communicated if confirmed with methods fully validated for the specific matrix and analyte.

100. Laboratory reports on non-compliant results should include:

(a) a description of the method used;

(b) performance characteristics of the method of analysis (including the confidence interval of the result).

101. Laboratory reports on non-compliant results should be distributed to all parties affected by the result (e.g. the owner of the consignment and the certifying competent authority of the exporting country).

102. Competent Authorities of importing countries should provide exporting countries regularly with the results of their verification programmes including information to enable trace back.

103. In cases of non-compliance with the food safety parameters, Competent Authorities from the exporting country should conduct a trace back and apply appropriate corrective actions and provide a summary of these to the importing country.

104. Where the type, incidence and/or frequency of non-compliance detected raises concerns as to whether the imports are meeting the standard of human health protection required by the importing country, then additional assurances may be requested.

105. The importing country may also choose to increase the frequency of port of entry verification to confirm that the assurances given are in fact addressing the problem.

106. Where residues of substances that should not be used in food producing animals in either the exporting or the importing country are detected in port of entry testing, both Competent Authorities should co-operate in order to identify potentially similarly affected food of animal origin and to resolve any potential wider control problem.

107. Resolution of such problems will require an analysis in the originating country of the source of such residues, the identification of deficiencies within the country's own control and monitoring system, and subsequent application of appropriate additional controls and measures to address the situation.

108. In cases where the exporting country is a less developed nation, consideration should be given by the importing country to the provision of technical assistance to help resolve the issue.

109. The application of new sampling and testing methods may reveal the presence of types and concentrations of residues previously unknown to exist by one or both parties. The determination of the source of such residues and their significance may take some time.

110. Where the presence of such residues is associated with previously accepted production practices, the implementation of changes, should these be deemed necessary, may require an extended period of time for capacity building.

Regulatory Action

Investigation of non-compliances

111. Competent Authorities should investigate each non-compliant result to ascertain the contributing factors which lead to its occurrence and the systemic significance of the identified case.

112. An attempt should be made to identify the substances and the consumer health significance of their occurrence in food.

113. Laboratories should report all detections of substances whose identity could not be confirmed.

114. When an animal tissue/food contains residues in excess of the relevant MRL at the point of harvest the following possibilities should be considered:

(a) the veterinary drug was not used according to label or prescription instructions;

(b) a non-authorised veterinary drug or formulation was used;

(c) the recommended withholding time was not observed or is not appropriate;

(d) treated and non-treated animals were commingled;

(e) unintended exposure to feed, water or contaminated environment occurred;

(f) the food is part of the statistically predictable small percentage of animals with residues in excess of the MRL even when the required withdrawal period has elapsed;

(g) sample contamination, analytical method problems or analytical error.

Measures in case of non-compliance: Conduct

115. Competent Authorities should adjust the scale and type of response to identified non-compliances to the relative importance that the respective hazard has for consumer health protection.

116. Competent Authorities should take proportionate action when considering whether the non-compliance is the result of negligence or intent.

117. Competent Authorities should in case of isolated mistakes due to ignorance or negligence require that appropriate advice and training measures are followed.

118. In the case of proven negligence or intent punitive measures in line with the Codex member's penal system should be considered (e.g. condemnations, fines, movement controls, etc.) to act as a deterrent.

119. Competent Authorities should, in case of widespread non-compliance, advise stakeholders and motivate the respective business sector to initiate the necessary changes.

120. Competent Authorities should verify that appropriate corrective action is taken and monitor the success of these measures through inspection/audits and/or sampling/laboratory analysis.

Measures in case of non-compliance: Product

121. Non-compliant product should not be passed as fit for human consumption.

122. Where the results of samples taken on farm for risk targeted verification programmes do not provide the necessary confidence that the rest of the lot has been produced using appropriate practices and controls, the lot should not be passed for human consumption until sufficient information can be generated to provide the required degree of assurance as to its safety.

123. Where the results indicate there is a direct risk to consumer health, an attempt should be made to trace and remove all similarly affected products. In making such judgements it needs to be acknowledged that the non-compliant result may represent only a small proportion of the total production likely to be similarly affected but unidentified.

124. In non-biased sampling programmes the unidentified proportion may represent a much greater potential threat to consumers than the identified proportion. Accordingly, any actions taken with respect to the identified non-compliant lot are less significant than the actions taken on the system as a whole.

125. When pre-harvest controls are not carried out or are unreliable due to a high incidence of misuse of veterinary drugs, more frequent post-harvest verification may be appropriate to provide the required degree of consumer assurance. This should be regarded as an interim measure only until the appropriate corrective actions to the control programme have been put in place and subsequently demonstrated to be effective.

Corrective action in case of non-compliance

126. Depending on the results of such investigations local and/or systemic corrective actions may be considered appropriate to prevent reoccurrence.

127. Where the investigation of non-compliances indicates that use and distribution provisions for the substance(s) are inappropriate, Competent Authorities should take appropriate corrective action by modifying approval and distribution rules.

128. Where the investigation of non-compliances identifies local or systemic control failures, Competent Authority should ensure that appropriate corrective action is taken at the relevant points.

129. The Competent Authority should verify that the measures are taken. Respective action should be proportionate in time and intensity to the consumer health hazard, scale and frequency of the non-compliance.

130. In cases where the failure lies outside of the direct control of the business operator the Competent Authority should prevent repetition of the failure by applying appropriate measures.

Interaction between the control programmes of two Competent Authorities

131. Competent Authorities should co-operate to ensure consumer health in all countries is protected.

132. This co-operation aims at achieving better assurance than can be achieved through sole reliance on port of entry inspection programmes.

133. Trading countries should exchange copies of their control and verification programmes along with the results of these programmes from preceding years on a regular basis.

134. In order to facilitate trade from developing countries longer transition periods and technical assistance regarding all aspects of a residue control programme should be considered.

Appendix A - Sampling strategies

Non-biased sampling

Purpose

135. Non-biased sampling is designed to provide profile information, especially as to the extent of application or performance of a control or assurance system for a specified animal/food population over a defined period.

Statistical considerations on sampling population size

136. Sample sizes for non-biased sampling protocols should be statistically based and may be influenced by the size of the population (where less than 5000), the prevalence of non-compliance determined to be significant, the confidence to be placed in the results as well as economic considerations.

137. Sample size based on the binomial distribution will always be equal to or greater than the required sample size based on the hypergeometric distribution[4].

138. If the size of the population is small the effect of sampling without replacement is significant and the sampling distribution should be based on the hypergeometric distribution.

139. In populations larger than 5000 units the effect of sampling without replacement is negligible. Thus the binomial distribution can be used to determine an appropriate sample size.

140. The sample size for a defined confidence will be effectively constant for populations exceeding 5000 units.

Sampling Confidence reporting

141. Where non-compliant results are detected it is possible to derive a crude estimate of the likely prevalence in the general population.

142. However, where no non-compliant results are found then any statements about prevalence need to be stated with a defined confidence that the prevalence of non-compliant results does not exceed a specified percentage.

143. The sample size required to give a required statistical assurance can be read from Table 1. Other scientifically based statistical protocols may also be used.

Table 1: Number of samples required to detect at least one non-compliant result with pre-defined probabilities (90, 95, and 99 percent) in a population having a known non-compliance prevalence.

Non-compliant prevalence (% in a population)	**Minimum number of samples required to detect a non-compliant result with a confidence level of:**		
	90%	**95%**	**99%**
35	6	7	11
30	7	9	13
25	9	11	17
20	11	14	21
15	15	19	29
10	22	29	44
5	45	59	90
1	230	299	459
0.5	460	598	919
0.1	2302	2995	4603

[4] In the probability theory and statistics, the *hypergeometric distribution* is a discrete (consisting of unconnected distinct parts) probability distribution that describes the number of successes in a sequence of *n* draws from a finite population without replacement.

144. The probability of failing to detect a specified prevalence of non-compliant results associated with a specified targeting mechanism can be read off Table 2 below. Because of the low efficacy of sampling protocols to detect low prevalences of non-compliance, other assurance mechanisms are more important where a low prevalence of non-compliance is expected.

Table 2: Probability of failing to detect a non-compliance

Prevalence	**Number of animals/units of product in sample tested**									
(%)	**5**	**10**	**25**	**50**	**75**	**100**	**200**	**250**	**500**	**1000**
1	0.951	0.904	0.779	0.605	0.471	0.366	0.134	0.081	0.007	0.000
2	0.904	0.817	0.603	0.364	0.220	0.133	0.018	0.006	0.000	
3	0.859	0.737	0.467	0.218	0.102	0.048	0.002	0.000		
4	0.815	0.665	0.360	0.130	0.047	0.017	0.000			
5	0.774	0.599	0.277	0.077	0.021	0.006				
6	0.734	0.539	0.213	0.045	0.010	0.002				
7	0.696	0.484	0.163	0.027	0.004	0.001				
8	0.659	0.434	0.124	0.015	0.002	0.000				
9	0.590	0.389	0.095	0.009	0.001					
10	0.528	0.349	0.072	0.005	0.000					
12	0.470	0.279	0.041	0.002						
14	0.418	0.221	0.023	0.001						
16	0.371	0.175	0.013	0.000						
18	0.328	0.137	0.007							
20	0.254	0.107	0.004							
24	0.193	0.064	0.001							
28	0.193	0.037	0.000							
32	0.145	0.021								
36	0.107	0.012								
40	0.078	0.006								
50	0.031	0.001								
60	0.010	0.000								

Directed or targeted sampling

Purpose

145. Directed or targeted sampling protocols are designed to place a greater intensity of inspection/audit on suppliers or product considered to possibly have a greater potential than the general population of being non-compliant.

146. It is not possible to extrapolate from non-compliant results to draw conclusions about the general population because a sub-population which is considered to have greater chance of non-compliance is being sampled (biased sampling).

147. However, if compliant results confirm non-biased programme results, they provide increased assurance that the system is working effectively.

Appendix B - Sampling of commodities

Scope

148. This appendix applies to the following commodities: primary food commodities of animal origin and processed products of animal origin made from primary food appearing in Table A and Table B of this appendix, and honey of the following origins and/or processing method:

(a) blossom or nectar honey that comes mainly from nectaries of flowers;

(b) honeydew honey that comes mainly from secretions of or on living parts of plants;

(c) comb honey stored by bees in the cells of freshly built broodless combs, and sold in sealed whole combs or sections of such combs;

(d) extracted honey obtained by centrifuging decapped broodless combs;

(e) pressed honey obtained by pressing broodless combs with or without the application of moderate heat.

Definitions

Lot means an identifiable group of animals or quantity of animal product intended for food use and determined to have common characteristics, such as origin variety, type of packing, packer or consignor, or markings, by the sampling official. Several Lots may make up a consignment.

Consignments means an identifiable group of animals or quantity of animal product intended for food use as described on a particular contractor's shipping document. Lots in a Consignment may have different origins or may be delivered at different times.

Primary sample means a quantity of representative biological material taken from a single animal (or group of animals) or from one place in the Lot. When the quantity is inadequate for residue analysis, samples from more than one animal (or group of animals) or more than one location in the Lot can be combined for the primary sample (such as poultry organs).

Bulk sample means the combined total of all the primary samples taken from the same Lot.

Final laboratory sample means the primary or bulk sample, or a representative portion of the primary or bulk sample, intended for laboratory analysis.

Final laboratory test portion means the representative portion of the final laboratory sample on which an analysis is conducted. The entire laboratory sample may be used for analysis in some cases but typically will be sub-divided into representative test portions for analysis. It is prepared by combining and thoroughly mixing the primary samples.

Lot of honey means a discrete quantity of honey delivered for distribution at one time, and determined to have common characteristics, such as origin, variety, type of packing, packer or consignor, or markings, by the sampling official.

Consignment of honey means discrete quantity of honey as described on a particular contractor's shipping document. A consignment may be made up of different Lots.

Primary honey sample means a quantity of honey taken from one place in the Lot, unless this quantity is inadequate for the residue analysis. When the quantity is inadequate, samples from more than one location can be combined for the primary sample.

Sampling procedures

149. Samples must be collected by those officially authorized for this purpose.

150. Each Lot to be examined must be sampled separately.

151. During collection and processing care must be taken to prevent contamination or other changes in the samples which would alter the residue, affect the analytical determination, or make the laboratory test portion not representative of the bulk or laboratory sample.

152. Detailed instructions for collection of a primary sample of various products are provided in Table A: Meat and Poultry Products) and Table B: (Milk, Eggs, Dairy Products and Aquatic Animal Products). The following are general instructions:

(a) each primary sample should be taken from a single animal (or group of animals) or unit in a Lot, and when possible, be selected randomly;

(b) when several animals are required for adequate sample size of the primary sample (e.g. poultry liver), the samples should be collected consecutively after initial random selection;

(c) frozen product should not be thawed before sampling;

(d) canned or packaged product should not be opened for sampling unless the unit size is at least twice the amount required for the final laboratory sample. The final laboratory sample should contain a representative portion of juices surrounding the product;

(e) Unopened cans or packages which constitute a final laboratory sample should be sent unopened and intact to the laboratory for analysis;

(f) the contents of cans or packages opened by the authorised inspector should be frozen as described in paragraph 170d before dispatch to the laboratory for analysis;

(g) large, bone-containing units of product (i.e. prime cuts) should be sampled by collecting edible product only as the primary sample;

(h) portions remaining of final laboratory samples should be frozen and stored in conditions which will maintain the sample integrity.

153. The number of primary samples collected will depend on if a Lot is considered suspect.

154. A Lot is suspect if there is:

(a) a history of non-compliance with the MRLVD;

(b) evidence of contamination during transport;

(c) signs of toxicosis (systemic poisoning) observed during ante- or post-mortem inspection; or

(d) other relevant information available to the authorised inspection official.

155. A minimum of six to a maximum of thirty primary samples should be collected from a suspect lot. When the suspected residues are is expected to occur throughout the Lot the smaller number of samples is sufficient.

156. Imports from countries that do not run verification programmes for compliance with MRLVDs should be sampled as suspect lots.

Specific sample preparation instructions for honey

(a) Collect 250 mL of liquid or strained honey after the following preparations as applicable;

(b) Liquidise Comb honey: Cut across top of comb, if sealed, and separate completely from comb by straining through a sieve the meshes of which are made by so weaving wire as to form square opening of 0.500 mm by 0.500 mm (ISO 565-1990)[5].

(c) If foreign matter, such as wax, sticks, bees, particles of comb, etc., is present, heat sample to 40°C in water bath and strain through cheesecloth in hot-water-funnel before sampling.

157. When a sample is free from granulation mix thoroughly by stirring or shaking; if granulated, place closed container in water-bath without submerging, and heat for 30 min at 60°C; then if necessary heat at 65°C until liquefied. Occasional shaking is essential. Mix thoroughly and cool rapidly as soon as the sample liquefies.

[5] Such sieve could be replaced by US sieve with No. 40 standard screen (size of opening 0.420 mm).

Statistical concerns

158. For non-suspect Lots a statistically-based, non-biased sampling programme is recommended. Any of the following types of sampling can be used.

Stratified random sampling

159. Where consignments are commingled simple random criteria cannot be applied and stratified random sampling should be considered.

160. In stratified random sampling the consignment is divided into non-overlapping groups or strata, e.g. geographical origin, genders, time. A sample is taken from each stratum.

161. Homogeneity within each stratum is better than in the whole population. Countries or geographic regions are considered natural strata based on uniformity in agricultural practices.

162. Time strata (e.g., month, quarter) are commonly used for convenience, efficiency, and detection of seasonal variability. Random number tables[6] or other objective techniques should be used to ensure that all elements of a population have an equal and independent chance of being included in the sample.

Systematic sampling

163. In systematic sampling units are selected from the population at a regular interval *(*e.g., once an hour, every other Lot, etc.).

164. It may be applied when there is reliable information on product volumes to determine the sampling interval that will provide the desired number of samples over time. However ;

(a) if the sampling system is too predictable, it may be abused;

(b) consignments need to be homogeneous, because systematic sample units are uniformly distributed over the population.

Biased or estimated worst case sampling

165. In biased or estimated worst case sampling, investigators use their judgement and experience regarding the population, Lot, or sampling frame to decide which primary samples to select.

166. The population group anticipated to be at greatest risk may be identified, but no general conclusion should be made about the population sampled from the data collected (non-random samples).

Preparation of laboratory samples

167. The final laboratory sample is sent for analysis.

168. Some national/regional legislation/regulation may require that the final laboratory sample is sub-divided into two or more portions for separate analyses. Each portion should be representative of the final laboratory sample. Precautions indicated under *sampling procedures* should be observed.

169. The laboratory test portion should be prepared from the final laboratory sample by an appropriate method of reduction.

Shipment of laboratory samples

170. Final laboratory samples should be prepared as follows:

(a) each sample should be placed in a clean, thermally insulating, chemically inert container to protect the sample from contamination, defrosting and damage in shipping;

(b) the container should be sealed so that unauthorized opening is detectable;

(c) the container should be sent to the laboratory as soon as possible, after taking precautions against leakage and spoilage;

[6] Random number tables consist of a randomly generated series of digits (0-9). To improve readability there are spaces between every e.g. every 4th digit and between every 10th rows. Reading can begin anywhere (at random) but having started has to continue across the line or down a column and NOT jump about. Example: extract from a table of random sampling numbers: 3680 2231 8846 5418 0498 5245 7071 2597.

(d) for shipping, all perishable samples should be frozen to minus 20°C, immediately after collection, and packed in a suitable container that retards thawing. Freezer packs or other suitable refrigerants should be used to maintain freezer temperatures during shipment. Samples and freezer packs should be fully frozen to minus 20°C prior to dispatch;

(e) replicate portions of the final laboratory sample which may be retained as required by national/regional legislation or as an administrative policy should be placed in a clean, chemically inert container to protect the sample from contamination, sealed so that unauthorized opening is detectable and stored under suitable conditions to prevent a change in the product or any residues it may contain in case future analysis is required for comparison with analytical results obtained on the sample material submitted to the laboratory.

Result interpretation in the laboratory

171. For purposes of control, the MRLVD is applied to the residue concentration found in each laboratory sample taken from a Lot.

172. Lot compliance with a MRLVD is achieved when the mean result for analysis of the laboratory test portions does not indicate the presence of a residue which exceeds the MRLVD.

Sampling records

173. Each primary or bulk sample and each final laboratory sample should be uniquely linked to a record with the type of sample, analyses required, its origin (e.g., country, state, or town), its location of collection, date of sampling, and additional information required for follow-up action if necessary.

174. If there is a deviation from recommended sampling procedures, records accompanying the sample should describe procedures actually followed in detail.

Instructions for collection minimum quantity required for different commodities

Table A: Meat and poultry products

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
I. Group 030 (Mammalian Meats)		
A. Whole carcass or side, unit weight normally 10 kg or more	Collect diaphragm muscle, supplement with cervical muscle, if necessary, from one animal.	500 g
B. Small carcass (e.g. rabbit)		500 g after removal of skin and bone
C. Fresh/chilled parts		
1. Unit minimum weight of 0.5 kg, excluding bone (e.g. quarters, shoulders, roasts)	Collect muscle from one unit.	500 g
2. Unit weighing less than 0.5 kg (e.g. chops, fillets)	Collect the number of units from selected container to meet laboratory sample size requirements.	500 g after removal of bone
D. Bulk frozen parts	Collect a frozen cross-section from selected container, or take muscle from one large part.	500 g
E. Retail packaged frozen/chilled parts, or individually wrapped units for wholesale	For large cuts, collect muscle from one unit or take sample from number of units to meet laboratory sample size requirements.	500 g after removal of bone

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
Ia. Group 030		
(Mammalian Meats where MRL is expressed in carcass fat)		
A. Animals sampled at slaughter	See instructions under II. Group 031.	
B. Other meat parts	Collect 500 g of visible fat, or sufficient product to yield 50-100 g of fat for analysis. (Normally 1.5-2.0 kg of product is required for cuts without trimmable fat).	Sufficient to yield 50-100 g of fat
II. Group 031		
(Mammalian Fats)		
A. Large animals sampled at slaughter, usually weighing at least 10 kg	Collect kidney, abdominal, or subcutaneous fat from one animal.	500 g
B. Small animals sampled at slaughter[(a)]	Collect abdominal and subcutaneous fat from one or more animals.	500 g
C. Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
III. Group 032		
(Mammalian Edible Offal)		
A. Liver	Collect whole liver(s) or portion sufficient to meet laboratory sample size requirements.	400 - 500 g
B. Kidney	Collect one or both kidneys, or kidneys from more than one animal, sufficient to meet laboratory sample size requirement. Do not collect from more than one animal if size meets the low range for sample size.	250 - 500 g
C. Heart	Collect whole heart or ventricle portion sufficient to meet laboratory sample size requirement.	400 - 500 g
D. Other fresh/chilled or frozen, edible offal product	Collect portion derived from one animal unless product from more than one animal is required to meet laboratory sample size requirement. A cross-section can be taken from bulk frozen product.	500 g
IV. Group 036		
(Poultry Meats)		
A. Whole carcass of large bird, typically weighing 2-3 kg or more (e.g. turkey, mature chicken, goose, duck)	Collect thigh, leg, and other dark meat from one bird.	500 g after removal of skin and bone
B. Whole carcass of bird typically weighing between 0.5-2.0 kg (e.g. young chicken, duckling, guinea fowl)	Collect thigh, legs, and other dark meat from 3-6 birds, depending on size.	500 g after removal of skin and bone
C. Whole carcasses of very small birds typically weighing less than 500 g (e.g. quail, pigeon)	Collect at least 6 whole carcasses	250 - 500 g of muscle tissue

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
D. Fresh/chilled or frozen parts		
1. Wholesale package		
a. Large parts	Collect an interior unit from a selected container.	500 g after removal of skin and bone
b. Small parts	Collect sufficient parts from a selected layer in the container	500 g after removal of skin and bone
2. Retail packaged	Collect a number of units from selected container to meet laboratory sample size requirement.	500 g after removal of skin and bone
IVa. Group 036		
(Poultry Meats where MRLVD is expressed in carcass fat)		
A. Birds sampled at slaughter	See instructions under V. Group 037	
B. Other poultry meat	Collect 500 g of fat or sufficient product to yield 50-100 g of fat. (Normally, 1.5-2.0 kg is required.)	500 g of fat or enough tissue to yield 50-100 g of fat
V. Group 037		
(Poultry Fats)		
A. Birds sampled at slaughter	Collect abdominal fat from 3-6 birds, depending on size.	Sufficient to yield 50-100 g of fat
B. Bulk fat tissue	Collect equal size portions from 3 locations in container.	500 g
VI. Group 038		
(Poultry Edible Offal)		
A. Liver	Collect 6 whole livers or a sufficient number to meet laboratory sample requirement.	250 - 500 g
B. Other fresh/chilled or frozen edible offal product	Collect appropriate parts from 6 birds. If bulk frozen, take a cross-section from container.	250 - 500 g
VII. Class E - Type 16		
(Secondary Meat and Poultry Products)		
A. Fresh/chilled or frozen comminuted product of single species origin	Collect a representative fresh or frozen cross-section from selected container or packaged unit.	500 g
B. Group 080(Dried Meat Products)	Collect a number of packaged units in a selected container sufficient to meet laboratory sample size requirements.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
VIII. Class E-Type 18 (Manufactured, single ingredient product of animal origin)		
A. Canned product (e.g. ham, beef, chicken), unit size of 1 kg or more	Collect one can from a lot. When unit size is large (greater than 2 kg), a representative sample including juices may be taken.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
B. Cured, smoked, or cooked product (e.g. bacon slab, ham, turkey, cooked beef), unit size of at least 1 kg	Collect portion from a large unit (greater than 2 kg), or take whole unit, depending on size.	500 g, unless fat content is less than 5% and MRLVD is expressed on a fat basis. Then 1.5-2.0 kg is required.
IX. Class E - Type 19 (Manufactured, multiple ingredient, product of animal origin)		
A. Sausage and luncheon meat rolls with a unit size of at least 1 kg	Collect cross-section portion from a large unit (greater than 2 kg), or whole unit, depending on size.	500 g

(a) When adhering fat is insufficient to provide a suitable sample, the sole commodity without bone, is analysed and the MRL will apply to the sole commodity.

Table B: Milk, eggs, dairy products and aquatic animal products

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
I. Group 033		
(Milks)		
Whole liquid milk raw, pasteurised, UHT & sterilized	In bulk. Mix thoroughly and immediately take a sample by means of a dipper. In retail containers. Take sufficient units to meet laboratory sample size requirements.	500 mL
II. Group 082		
(Secondary Milk Products)		
A. Skimmed milk - skimmed and Semi-skimmed	As for whole liquid milk Bulk containers (barrels, drums). Mix the contents carefully and scrape adhering material from the sides and bottom of the container. Remove 2 to 3 litres, repeat the stirring and take a 500 mL sample.	500 mL
B. Evaporated milk - evaporated full cream & skimmed milk	Small retail containers. Take sufficient units to meet laboratory sample size requirements.	500 mL
C. Milk powders		
1. Whole	Bulk containers. Pass a dry borer tube steadily through the powder at an even rate of penetration. Remove sufficient bores to make up a sample of 500 g. Small retail containers. Take sufficient units to meet laboratory sample size requirements..	500 g
2. Low fat	As for whole milk powders	500 g
III. Group 087		
(Derived Milk Products)		
A. Cream - fresh, frozen & UHT; single, whipping, whipped, double & clotted	Bulk containers. Plunge to ensure thorough mixing moving the plunger from place to place avoiding foaming, whipping and churning. Take a 200 ml sample by means of a dipper. Small containers. Take sufficient units to meet laboratory sample size requirements.	200 mL
B. Butter - including whey butter and low fat spreads containing butterfat	In bulk. Take two cores or more of butter so that the minimum total sample weight is not less than 200 g In pats or rolls. For units weighing over 250 g divide into four and take opposite quarters. For units weighing less than 250 g take one unit as sample.	200 g

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
C. Butter oil - including anhydrous butte roil and anhydrous milk fat	Mix thoroughly and take a 200 g sample.	200 g
IV. Group 090		
(Manufactured Milk Products - single ingredient)		
A. Yoghurt - natural, low fat through to full cream	Select number of units sufficient to meet laboratory requirements.	500 g
B. Cheeses - all varieties	Make two cuts radiating from the centre of the cheese if the cheese has a circular base, or parallel to the sides if the base is rectangular. The piece removed should meet the laboratory sample size requirements. For small cheeses and wrapped portions of cheese take sufficient units to meet laboratory sample requirements.	200 g
V. Group 092		
(Manufactured Milk Products - multi-ingredient)		
A. Dairy ice cream - only ice cream containing 5% or greater of milk fat	Select block or units sufficient to meet laboratory sample size requirements.	500 mL
B. Processed cheese preparations	Select units sufficient to meet laboratory sample size requirements.	200 g
C. Flavoured yoghurt	As for natural yoghurt.	500 g
D. Sweetened condensed Milk	As for evaporated milk.	500 mL
VI. Group 039		
(Eggs and Egg Products)		
A. Liquid and frozen eggs	Use sample schedule. Sub sample size will be 250 mL liquid or 500 mL packed shavings from aseptic drillings into containers.	500 g
B. Dried egg products	Use sample schedule. For containers of 500 g or less or 25 mL or less, collect a minimum of 2 units per sub sample. For containers of 500 g to 10 kg select 1 unit per sub sample. For containers of 10 kg or more collect 1 kg from each unit sampled. Collect with aseptic technique.	500 g
C. Shell eggs		
1. Retail packages	Use sample schedule. Sub sample size is 12 eggs.	500 g or 10 whole eggs
2. Commercial cases	For 15 cases or less collect 12 eggs from each case, minimum of 24 eggs. For 16 or more cases collect 12 eggs from 15 random cases.	500 g or 10 whole eggs

Commodity	Instructions for collection	Minimum quantity required for laboratory sample
VII. Class B - Type 08		
(Aquatic Animal Products)		
A. Packaged fish - fresh, frozen, smoked, cured, or shellfish (except oysters)	Collect 12 sub samples randomly. Minimum sub sample size is 1 kg.	1000 g
B. Bulk fish 0.5 - 1.5 kg	Collect 12 sub samples randomly. Each sub sample should total 500 g of edible fish.	1000 g
C. Bulk fish >1.5kg	Collect 1000 g of edible fish.	1000 g
D. Bulk shellfish	Collect 12 sub samples randomly.	1000 g
E. Other fish and shellfish Products (including oysters)	Collect 12 sub samples	1000 g
VIII. Class E - Type 17		
(Derived Edible Products of Aquatic Animal Origin)		
A. Canned fish and shellfish products (except oysters)	Collect 12 sub samples of 5 cans per sub sample.	1000 g
B. Other fish and shellfish products – fish flour and meal	Use sample schedule. Collect 1 kg per sub sample.	1000 g

General Consideration on Analytical Methods for Residue Control

Introduction

175. Analytical methods used to determine compliance with maximum residue limit for veterinary drugs (MRLVDs) should be suitable for routine use by competent authorities of member governments for their testing programmes for all residues of veterinary drugs and substances which may be used as veterinary drugs. This includes certain pesticides which have veterinary uses and that may be present as residues in commodities. These methods may be used for the analysis of randomly selected survey samples in a national regulatory control programme to determine compliance with established MRLVDs, for the analysis of targeted samples when there is reason to suspect non-compliance with MRLVDs or for the collection of data for use in estimation of intake.

176. Methods may also be required in regulatory control programmes for the detection of residues of substances for which ADIs and MRLVDs have not been established by the Codex Alimentarius Commission. For some substances, the toxicological evaluation leads to the conclusion that an ADI or MRLVD should not be established. For such substances, the determination of the lowest concentration at which the residue can be detected and the identity confirmed in a food is a primary concern in the method validation. Performance characteristics related to quantitative analyses may be less critical for such substances, where detection and confirmation of the presence of the substance as a residue is the major issue. Confirmation of identity of a residue is generally based on the comparison of a set of characteristics of a detected substance with those of a known standard of the suspected residue.

177. Suitably validated methods are not always available for all possible combinations of veterinary drug residues and foods. Competent authorities responsible for designing national residue control programmes should ensure that appropriate residue methods of analysis are used to assure compliance with Codex MRLVDs. This may sometimes require the development and validation of a new analytical method or the extension of the validation of an existing analytical method to include a new combination of analyte and matrix. Appropriate regulatory action may then be taken against adulterated products, consistent with the reliability of the analytical data.

Integrating analytical methods for residue control

178. Analytical methods for veterinary drug residues in foods must reliably detect the presence of an analyte of interest, determine its concentration and correctly identify the analyte. When residues resulting from the use of approved veterinary drugs are detected at concentrations above an established MRLVD, the results should be confirmed before regulatory enforcement actions are taken. In the case of substances which have been banned from use in food-producing animals by a competent authority, or for which an ADI and MRLVDs have not been established for toxicological reasons, the confirmed presence of residues at any concentration in a food may result in regulatory action.

179. The principal performance attributes of analytical methods used in residue control programmes are dependent on whether a method is intended to simply detect, to quantify, or to confirm the presence of a target residue. Completion of a full collaborative study[7] is not a requirement for recognition of a method to be placed in one of these three categories.

[7] Horwitz, W. 1995. Protocol for the design, conduct and interpretation of method performance studies. *Pure and Applied Chemistry*, **67:**331-343.

180. Screening methods are qualitative or semi-quantitative in nature and are used as screening methods to identify the presence (or absence) of samples from a herd or lot which may contain residues which exceed an MRLVD or other regulatory action limit established by a competent authority. These methods may not provide adequate information to accurately define the concentration present or, to confirm the structure of a residue but may be used to quickly determine which products require further testing and which can be released. They may be applied to a sample at the point of entry into the food chain, site of inspection or on receipt of a sample at the laboratory to determine if the sample contains residues which may exceed a regulatory limit. Such methods usually provide greater analytical efficiency, can sometimes be performed in non-laboratory environments and may be less expensive for use in regulatory control programmes than tests conducted within a laboratory. Use of screening methods allows the laboratory resources to be focused on analysis of the presumptive positive (suspect) samples identified using this test. These methods, which should have a defined and low false negative rate, should not be used alone for residue control purposes on official samples without the availability of suitably validated quantitative and/or confirmatory methods to apply to any samples identified as potentially not in compliance with an MRLVD.

181. Quantitative methods provide quantitative information which may be used to determine if residues in a particular sample exceed an MRLVD or other regulatory action limit, but do not provide unequivocal confirmation of the identity of the residue. Such methods which provide quantitative results must perform in good statistical control within the analytical range that brackets the MRLVD or regulatory action limit.

182. Confirmatory methods provide unequivocal confirmation of the identity of the residue and may also confirm the quantity present. Confirmatory methods are the most definitive and frequently are based on combined chromatographic and mass spectrometric techniques, such as liquid chromatography – mass spectrometry (LC/MS). Such methods when used for confirmation of residue identity should provide reliable structural information within established statistical limits. When the confirmatory method does not provide quantitative information, the quantification result of the original quantitative method should be verified by analysis of replicate test portions using the original quantitative method or a suitably validated alternative quantitative method.

183. These three categories of methods – screening, quantitative and confirmatory - often share some performance characteristics. In addition, each category has other specific considerations. Understanding the relationship between these three categories of methods is important in the development and operation of a balanced residue control programme. These three categories of methods may be applied sequentially in a residue control programme.

184. Samples which test "positive" with the screening method are considered as suspect and are usually designated for further laboratory testing using more definitive methods. This could include repeat testing of replicate test portions with a screening method, but typically quantitative and/or confirmatory methods are used in the laboratory to establish that the sample does contain residues in excess of the regulatory limit. Such tests should be conducted on new test portions of the sample material used in the initial screening test to confirm that the analyte detected in the initial test is definitely the suspected compound and that the MRLVD (or other regulatory action limit established by the authority) has indeed been exceeded. The performance attributes, or characteristics, which must be determined during method validation for each type of method – screening, quantitative, confirmatory – are presented in the Chapter "*Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods*" below.

Consideration for selection and validation of analytical methods

Identification of Methods Requirements

Method scope

185. The intended purpose of the method is usually defined in a statement of *scope* which defines the analytes (residues), the matrices (tissues, milk, honey, etc.) and the concentration range to which the method applies. It also states whether the method is intended for screening, quantitative, or confirmatory use. The Competent Authority must establish an appropriate *marker residue* for each drug for which an MRLVD has been established and should also designate a preferred *target tissue* to be sampled for testing.

Marker residue

186. The MRLVD is expressed in terms of the marker residue, which may be the parent drug, a major metabolite, a sum of parent drug and/or metabolites or a reaction product formed from the drug residues during analysis. In some cases, the parent drug or the metabolite may be present in the form of a bound residue which requires chemical or enzymatic treatment or incubation to be released for analysis. It is important that the marker residue should, whenever possible, provide unequivocal evidence of exposure to the drug. In rare situations, it is necessary to use compounds as marker residues which may also result from sources other than exposure to the drug. In such cases, additional information is required to ascertain the probable source of the residue is exposure to the drug. An example of such a situation is the use of semi-carbazide, which may occur from other sources, as a marker residue for the drug nitrofurazone.

Target Tissue

187. The usual target tissue selected by competent authorities to be tested for veterinary drug residues in a residue control programme is the edible tissue in which residues of the marker residue occur at the highest concentrations and are most persistent. For lipophilic substances, the usual target tissue is fat. For most other substances, the target tissue is liver or kidney, depending on the primary route of elimination. One of these tissues is usually the target tissue designated for use in testing of domestically produced foods of animal origin. The organ tissues may not be available for testing imported products, so muscle tissue may be the target tissue for testing of these commodities. In some cases, such as drugs which are normally administered as injectable formulations, testing of muscle tissue from suspected injection sites may be required. The regulatory programme manager and the laboratory managers need to clearly identify the testing objectives and the analytical requirements required in terms of target tissues, marker residues and concentration ranges to ensure suitable methods are used in the regulatory control programme. In certain situations, Competent Authorities may also use biological fluids such as urine or serum to indicate the presence or absence of residues of interest.

Implementing other Codex Alimentarius Commission Guidelines

188. The Codex Alimentarius Commission has issued a guideline for laboratories involved in the import/export testing of foods[8] which recommends that such laboratories should:

(a) use internal quality control procedures which comply with the Harmonised Guidelines for Internal Quality Control in Analytical Chemistry[9];

(b) participate in appropriate proficiency testing schemes designed and conducted in accordance with the International Harmonized Protocol for Proficiency Testing of (Chemical) Analytical Laboratories[10];

(c) become accredited according to ISO/IEC-17025:2005 General requirements for the competence of calibration and testing laboratories[11]; and

(d) whenever available, use methods which have been validated according to the principles laid down by the Codex Alimentarius Commission.

[8] CAC/GL 27-1997. Guidelines for the Assessment of the Competence of Testing Laboratories Involved in the Import and Export Control of Food.

[9] Thompson, M. and Wood, R. 1995. Harmonized Guidelines for Internal Quality Control in Analytical Chemistry Laboratories. *Pure and Applied Chemistry,* **67**: 649-666.

[10] Thompson, M. and Wood, R. 1993. International Harmonized Protocol for Proficiency Testing of (Chemical) Analytical Laboratories. *Pure and Applied Chemistry,* **65**: 2123-2144.

[11] The original guideline CAC/GL 27 referred to ISO/IEC Guide 25: General requirements for the competence of calibration and testing laboratories. International Organization for Standardization, Geneva (1990), which has been superseded by ISO/IEC-17025: General requirements for the competence of calibration and testing laboratories. International Organization for Standardization, Geneva (2005).

189. Methods used for analyses of veterinary drug residues in foods should be capable of detecting the compounds included in the residue control programme. The analytical recovery and precision for the target foodstuffs should meet the criteria stated elsewhere in this document. The methods should be used within an established laboratory quality assurance system which is consistent with the principles in the document on internal quality control referenced above. When methods which have not been subjected to a multi-laboratory performance trial are used in a regulatory programme for control of veterinary drug residues in foods, the quality control and quality assurance procedures applied with these methods require careful definition, implementation, and monitoring. In the case of methods which have been through multi-laboratory trials, performance characteristics, such as recovery and precision, are defined through the results obtained during the study. For a method validated within a single laboratory, data must be generated to define the performance characteristics expected of the method when used by analysts within that laboratory. The on-going performance must be monitored through the quality system in place in the laboratory.

Method Validation and Fitness for Purpose

190. The process of method validation is intended to demonstrate that a method is *fit-for-purpose*. This means that in the hands of a properly trained analyst using the specified equipment and materials, and following the procedures described in the method, reliable and consistent results can be obtained within specified statistical limits for the analysis of a sample. The validation should address the issues of marker residue, target tissue and concentration range identified by the laboratory in consultation with the residue programme manager. When the method protocol is followed, using suitable analytical standards, results within the established performance limits should be obtained on the same or equivalent sample material by a trained analyst in any experienced residue control laboratory.

191. Multi-laboratory method performance studies generally satisfy the analytical requirements for use in a regulatory programme. These methods are subjected to a properly designed inter-laboratory study with analysts in independent laboratories, so that different sources of reagents, materials, and equipment are used by the participants.

192. Quantitative methods studied collaboratively according to the revised harmonized protocol adopted in 1995 by AOAC International, the International Union of Pure and Applied Chemistry (IUPAC), and the International Standards Organization (ISO) have been evaluated in a minimum of 8 laboratories, unless highly complex equipment or other unusual requirements were identified (in such cases, a minimum of 5 participating laboratories is required)[7]. Collaborative studies of qualitative methods currently require a minimum of 10 participating laboratories. Collaborative studies conducted prior to 1995 completed method evaluation in a minimum of six laboratories in an acceptable, statistically designed study. These multi-laboratory method performance studies generally satisfy the analytical requirements for use in a regulatory programme, as information on method performance in the hands of different analysts in different laboratories is obtained through these studies. However, relatively few of the analytical methods currently used in residue control programmes for veterinary drug residues in foods have been validated by such a multi-laboratory study. Collaborative study designs are based on the analyses of coded duplicate test materials which represent the combinations of analytes, matrices, and concentrations included in the scope of the method and include an independent peer-review of both the study design and the results. In some situations, multi-laboratory studies may be conducted which do not have the minimum number of laboratories required to qualify as a collaborative study. Such studies, when conducted using the same scientific principles of design, evaluation, and review as are applied in collaborative studies, can provide useful information on method performance in the hands of multiple analysts in different laboratories, but do not provide the same degree of statistical confidence obtained from the results of a collaborative study.

193. Multi-laboratory and collaborative studies of methods usually do not encompass all possible combinations of residue, tissue and species to which the method may subsequently be applied. Methods may be extended to include related analytes, additional tissues, species or products (or combinations of these not included in the original multi-laboratory study) by completing additional within-laboratory studies. Analytical results from method extension studies may require additional review before use in a regulatory programme. Whenever possible, analytical results obtained using methods that have not been validated by traditional inter-laboratory study should be compared with results obtained using a method which has been validated through a collaborative or multi-laboratory study or tested using sample materials from a recognized proficiency programme. The comparison should be based on a statistically acceptable study design using portions of the same (homogeneous) samples. The data from such studies should be independently reviewed by a qualified third party (such as a QA unit, a peer group of regulatory scientists, auditors of national accreditation body) to determine the comparability of method performance.

194. Some residue control methods that have been demonstrated to be suitable to determine compliance with MRLVDs have a history of use in one or more expert laboratories, but have not been subjected to a formal multi-laboratory study. These methods were demonstrated to be suitable at the time of initial regulatory use and have continued in use over an extended period of time either in the absence of alternative validated methods, or because they remain a preferred choice for reasons which may include use of available technology, cost, reliability and suitability for use within the constraints of a national programme. Although evidence of a formal collaborative or multi-laboratory method trial is lacking, the method performance has been demonstrated through successful use and from quality control data in one or more laboratories over time.

195. Most regulatory laboratories rely on the use of veterinary drug residue methods which have not have been subjected to a multi-laboratory study. Factors which have contributed to this situation include a requirement for specialized expertise or equipment, cost of such studies, lack of suitable collaborating laboratories, analyte and/or sample instability and rapidly changing technologies. While for many years the focus on equivalency of analytical results was based on the use of standardized methods which had performance characteristics defined based on collaborative study, accredited laboratories now operate in an environment where it is the responsibility of the individual laboratory to demonstrate that the methods used and the analytical results produced meet performance criteria established in consultation with a client. In the absence of methods validated through inter-laboratory method trials, regulatory laboratories must frequently use analytical methods which have been subjected to studies conducted within their own laboratory to characterize the method performance.

Single Laboratory Validation – The Criteria Approach

196. A guidance document on single laboratory validation of methods, "Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis", has been published as a technical report by the IUPAC[12]. The Procedural Manual[13] recognizes that inter-laboratory validated methods are not always available or applicable, particularly for multi-analyte/ multi-substrate methods and new analytes. In such cases, methods may be validated in a single laboratory to meet the General Criteria for the Selection of Methods of Analysis, as well as the additional criteria:

(a) the method is validated according to an internationally recognized protocol (for example, the IUPAC Guidelines for Single Laboratory Validation of Methods of Analysis, referenced above);

(b) use of the method is embedded in a quality assurance system in compliance with the ISO/IEC 17025 (2005) Standard or with the Principles of Good Laboratory Practice;

(c) the method should be complemented with information on accuracy demonstrated for instance by:

- regular participation in proficiency schemes, where available;
- calibration using certified reference materials, where applicable;

[12] Thompson, M., Ellison, S.L.R. & Wood, R. (2002) Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis. *Pure and Applied Chem*istry **74**: 835-855.

[13] FAO/WHO. 2006. Codex Alimentarius Commission Procedural Manual, 16th Ed., Food and Agriculture Organization of the United Nations, Rome.

- recovery studies performed at the expected concentration of the analytes;
- verification of result with other validated method where available.

197. The criteria approach, which combines a single laboratory validation model with a requirement that methods meet specific performance specifications, has been adopted by some regulatory authorities.

Attributes of Analytical Methods for Residues of Veterinary Drugs in Foods

Introduction

198. The performance characteristics of analytical methods used to determine compliance with MRLVDs must be defined and proposed methods evaluated accordingly. This will assure reliable analytical results and provide a secure basis for determining residues of veterinary drugs in foods for commodities in international trade. The chapter "*General Considerations of Analytical Methods for Residue Control*" above, presents a discussion of general types or categories of regulatory methods, and provides a scheme for using these analytical methods based upon their intended purpose in a regulatory framework. In the discussion below, attributes common to the three categories of methods (referred to as Confirmatory, Quantitative and Screening methods) for determining compliance with Codex MRLVDs are presented. The additional attributes that are applicable to only one or two categories of methods are also discussed.

Method development considerations

199. The development of an analytical method requires analysts experienced in the analytical techniques to be used, as well as appropriate laboratory space, equipment, and financial support. Before initiating method development activities, the intended use and need for a method in a residue control programme should be established, including the required performance parameters. Other considerations include the required scope of the method (compound or class of compounds of interest and types of sample materials), potential interfering substances, the required performance characteristic of the measurements system, the pertinent physical and chemical properties that may influence method performance, the specificity of the desired testing system and how it will be determined, analyte and reagent stability data and purity of reagents, the acceptable operating conditions for meeting method performance factors, sample preparation guidelines, environmental factors that may influence method performance, safety considerations, and any other specific information pertinent to programme needs. In particular, stability of standards, both under normal conditions of storage and use and during processing of samples, should be assessed. Analyte stability in samples during typical conditions of sample storage prior to analysis should also be determined, including any period for which a sample may be held pending a potential re-analysis for confirmatory purposes.

200. Establishing method performance attributes is essential, as these provide the necessary information for food safety agencies to develop and manage their public health programmes. Performance attributes for analytical methods also provide a basis for good management decisions in future planning, evaluation, and product disposition. For the animal health care industry, it provides a guideline for knowing exactly what performance must be achieved in developing analytical procedures. All will benefit by having well defined analytical method performance factors. Method performance requirements will vary, depending on whether the method is used for the screening, quantification, or confirmation of a residue for which Maximum Residue Limits have been established, or for residues of a drug for which an ADI and MRLVDs have not been recommended. In the latter case, the Competent Authority may establish a minimum performance standard which must be met by analytical methods used for regulatory control purposes. However, when no safe concentrations of these compounds in foods have been established, the Competent Authority may review such limits periodically to ensure they reflect improvements in technology and analytical capability. When such limits have not been formally established by the Competent Authority, they are usually established *de facto* by the detection capabilities of the methods used in the regulatory laboratories.

Analytical performance characteristics

Performance Characteristics of Screening Methods

201. Screening methods are usually either qualitative or semi-quantitative in nature, with the objective being to discriminate samples which contain no detectable residues above a threshold value ("negatives") from those which may contain residues above that value ("positives"). The validation strategy therefore focuses on establishing a threshold concentration above which results are "positive", determining a statistically based rate for both "false positive" and "false negative" results, testing for interferences and establishing appropriate conditions of use.

202. For a screening test, particularly those involving test kit technologies, the term "*sensitivity*" refers to the lowest concentration at which the target analyte may be reliably detected within defined statistical limits. In the AOAC Performance Tested Program ™ for test kits, this is determined experimentally by testing a minimum of 30 residue-free sample materials fortified with the analyte at the target concentration. The sample materials should be from at least six different sources (that is, at least 5 replicates from each of at least 6 sources), all of which should yield a positive result when fortified at the target concentration. Three or more negative results constitute a failure of the sensitivity test. If one or two of the results are negative, the experiment should be repeated and two negative results would then constitute failure. The experiment should be repeated with known incurred material at the target concentration, if such material is available.

203. The "*selectivity"* of a screening method refers to the ability of the test to determine that samples which give a negative response are truly negative. The test must also be able to distinguish the presence of the target compound, or group of compounds, from other substances which may be present in the sample material. It normally is not as great as that of a quantitative method, because screening methods often take advantage of a structural feature common to a group or class of compounds. These methods, which generally fit into the screening methods category, are often based on microbiological growth inhibition, immunoassays, or chromogenic responses which may not unambiguously identify a compound. The selectivity of a screening method may be increased when it is used as a detection system after chromatographic or other separation technique. To demonstrate a selectivity rate of at least 90% with 95% confidence (which is recommended for screening tests), 30 replicate analyses are conducted on representative blank sample matrix materials from a minimum of six different sources. All results should be negative. Additional tests for potential interferences and cross-reactivity may then be conducted by testing blank matrix material fortified with potential interfering substances, such as other drugs which might be used in animal treatment, potential environmental contaminants, drug metabolites, or chemically related compounds. Again, responses should be negative when these compounds are present at concentrations which might reasonably be expected to be present in a sample.

204. The "cut-off" or threshold for the test for a particular compound is established by conducting concentration-response experiments, typically using 30 replicates (from at least six sources) fortified at each of a series of increasing concentrations. Once the concentrations have been established where all 30 replicates give a negative response and all 30 replicates give a positive response, the experiment is repeated using the blank matrix materials fortified at four evenly spaced concentrations between the "all negative" and "all positive" concentrations. An additional set is tested at a concentration 20% above the "all positive" concentration. Statistical analysis of the results enables the user to establish a reliable detection concentration at the required confidence level (usually 95%)[14].

Performance Characteristics for Quantitative Methods

205. *Selectivity*, the ability of an analytical method to detect and discriminate the signal response from a compound in the presence of other compounds which may be present in the sample material, is of particular importance in defining the performance characteristics of methods used in regulatory control programmes for veterinary drug residues in foods. There are two aspects which must be considered – the ability of the method to provide a signal response which is free from interferences from other compounds which may be present in a sample or sample extract and the ability of the method to unequivocally identify a signal response as being exclusively related to a specific compound. For a quantitative method, the requirement is that the signal used for quantification should relate only to the target analyte and not contain contributions for co-extracted materials. Chromatographic analyses based on peaks which are not fully resolved provide less reliable quantitative results. Use of element-specific detectors or detection wavelengths or mass-selective detectors which are more specific to a particular compound or structure, combined with chromatographic separation, improves the selectivity of quantitative methods for veterinary drug residues in foods.

206. In addition to the selectivity of a method, the ability of the method to provide a quantitative result which is reliable must be demonstrated. This consists of two factors:

(a) the closeness of the result to the true or accepted value for the concentration of analyte present in the sample material, expressed in terms of *accuracy*, *trueness,* or *bias*; and

[14] Finney, D.J. (1978) *Statistical Method in Biological Assay, 3rd edition*. MacMillan Publishing Co., New York.

(b) the ability of the method to provide consistent results on replicate determinations, expressed in terms of *precision* (*repeatability* and *reproducibility)*.

207. It is recommended that methods used to support MRLVDs established by the Codex Alimentarius Commission should meet the performance standards for trueness and precision listed in Table 3, where CV_A refers to the coefficient of variation determined by test portions of blank matrix fortified prior to extraction and CV_L is the overall laboratory variability which includes a 10% estimate for variability of sample processing[15].

Table 3. Performance criteria which should be met by methods suitable for use as quantitative analytical methods to support MRLVDs for residues of veterinary drugs in foods[16]

Concentration µg/kg	Coefficient of Variability (CV)				Trueness
	Repeatability (Within-Laboratory, CV_A) %	Repeatability (Within-Laboratory, CV_L) %	Reproducibility (Between-Laboratory, CV_A) %	Reproducibility (Between-Laboratory, CV_L) %	Range of Mean % Recovery
≤ 1	35	36	53	54	50-120
1 to 10	30	32	45	46	60-120
10 to 100	20	22	32	34	70-120
100 to 1000	15	18	23	25	70-110
≥1000	10	14	16	19	70-110

208. The *accuracy* of a method may be determined by analysis of a certified reference material, by comparison of results with those obtained using another method for which the performance parameters have previously been rigorously established (typically, a collaboratively studied method) or, in the absence of reference materials or methods validated by inter-laboratory trial, by determination of the *recovery* of analyte fortified into known blank sample material. The determination of accuracy as recovery is frequently used in validation of methods for veterinary drug residues in foods, as both certified reference materials and methods validated by inter-laboratory trial are often not available. The accuracy of a measurement is closely related to *systematic error* (analytical method bias) and analyte recovery (measured as percent recovery). The accuracy requirements of methods will vary depending upon the planned regulatory use of the results. The accuracy should be carefully characterized at concentrations near the MRLVD or target concentration for regulatory action (typically at concentrations from 0.5 to 2.0 times the target concentration) to ensure that regulatory action is only taken on samples containing residues which can be demonstrated to exceed the regulatory action limit with a defined statistical confidence.

[15] Alder, L, Holland, PT, Lantos, J, Lee, M, MacNeil, JD (chairman), O'Rangers, J, van Zoonen, P, Ambrus, A (scientific secretary). 2000. Report of the AOAC/FAO/IAEA/IUPAC Expert Consultation on Single-Laboratory Validation of Analytical Methods for Trace-Level Concentrations of Organic Chemicals, Miskolc, Hungary, 8-11 November, 1999. Report published on the website of the International Atomic Energy Agency (IAEA) http://www.iaea.org/trc/pest-qa_val2.htm (accessed 18 September, 2007).

[16] *CAC/GL 37-2001* Harmonized IUPAC Guidelines for the use of Recovery Information in Analytical Measurement; see also Thompson, M., Ellison, S., Fajgelj, A., Willetts, P., & Wood, R. (1999) Harmonised Guidelines for the Use of Recovery Information in Analytical Measurement, *Pure Applied Chemistry*, **71:** 337-348.

209. *Recovery* is usually expressed as the percentage of analyte experimentally determined after fortification of sample material at a known concentration and should be assessed over concentrations which cover the analytical range of the method. In interpreting recoveries, it is necessary to recognize that analyte added to a sample may not behave in the same manner as the same biologically incurred analyte (veterinary drug residue). In many situations, the amount of an incurred residue that is extracted (the yield or recovered fraction) is less than the total incurred residues present. This may be due to losses during extraction, intra-cellular binding of residues, the presence of conjugates, or other factors that are not fully represented by recovery experiments conducted with analyte-fortified blank tissues. At relatively high concentrations, analytical recoveries are expected to approach one hundred percent. At lower concentrations, particularly with methods involving extensive extraction, isolation, and concentration steps, recoveries may be lower. Regardless of what average recoveries are observed, recovery with low variability is desirable so that a reliable correction for recovery can be made to the final result, when required. Recovery corrections should be made consistent with the guidance provided by the Codex Alimentarius Commission[16].

210. *Precision*, which quantifies the variation between replicated measurements on test portions from the same sample material, is also an important consideration in determining when a residue in a sample should be considered to exceed an MRLVD or other regulatory action limit. Precision of a method is usually expressed in terms of the within-laboratory variation (*repeatability*) and the between-laboratory variability (*reproducibility*) when the method has been subjected to a multi-laboratory trial. 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. Another useful term is relative standard deviation, or coefficient of variation (the standard deviation, divided by the absolute value of the arithmetic mean). It may be reported as a percentage by multiplying by one hundred.

211. Method variability, achieved in a laboratory developing a method, is usually less than the variability achieved by another laboratory that may later use the method. If a method cannot achieve a suitable standard of performance in the laboratory where it was developed, it cannot be expected to do any better in other laboratories.

212. Quantitative methods are usually based on a comparison of the response from an analyte in a sample with the response from standards of the analyte in solution at known concentrations. In method development and validation, the calibration curve should first be determined to assess the detector response to standards over a range of concentrations. These concentrations (a minimum of five, plus blank) should cover the full range of analytical interest and the resultant curve should be statistically expressed. However, although it is recommended practice to include a suitable blank with the calibration samples, this does not imply that it is acceptable to extrapolate into the region of the curve below the low standard to obtain a quantitative result. The analytical function relates the response for the analyte recovered from sample material at various concentrations throughout the range of analytical interest. For analytes for which an MRLVD or regulatory action limit has been established in a particular sample material (matrix), response is typically determined for known blank sample material and for blank sample material fortified at a range of concentration above and below the MRLVD (use of 6 different sources of blank materials is recommended).

213. The analytical function experiment data can also be used to calculate the analytical recovery at each concentration and is of particular importance when the presence of matrix co-extractives modifies the response of the analyte as compared to analytical standards. The *linearity* is determined from the analytical function experiments and is the statistical expression of the curve obtained for the analysis of sample materials fortified at the target concentrations. It is typically determined from a linear regression analysis of the data, assuming there is a linear response. It is increasingly common in methods for veterinary drug residues in foods to base the quantitative determination on a standard curve prepared by addition of standard to known blank representative matrix material at a range of appropriate concentrations which bracket the target value (the analytical function). Use of such a “tissue standard curve” for calibration incorporates a recovery correction into the analytical results obtained.

214. It is also 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. The *detection limit* may be described in practical terms as the lowest concentration where the analyte can be identified in a sample. It can be estimated using the standard deviation ($s_{y/x}$) from the linear regression analysis of the standard curve generated in the analytical function experiment described above[17]. Using this approach, the limit of detection is calculated using the y-intercept (assuming a positive value) of the curve plus three times $s_{y/x}$. This approach provides a conservative estimate of the detection limit. The detection limit can also be estimated by measurements on representative test materials as the weakest relevant response of the analyte in the blank plus three times its standard deviation. It is often necessary to fortify test materials at a concentration resulting in a barely detectable response to obtain an approximation of the standard deviation of the blank when using this approach.

215. The *limit of quantification* (LOQ), also referred to as limit of quantification or quantification limit may be established from the same experiments using the y-intercept of the curve plus ten times $s_{y/x}$. For methods used to support MRLVDs established by the Codex Alimentarius Commission, the limit of quantification should meet the criteria for precision and accuracy (recovery) in Table 3 and should be equal to or less than one-half the MRLVD. However, when the limit of quantification of a method is lower than the actual concentrations monitored for compliance with a MRLVD, the validation and subsequent application of the method should be based on a *lowest calibrated level* (LCL), which is typically 0.5x the MRLVD. For use in a regulatory programme, the limits of detection and quantification are important parameters when the method will be applied to estimate exposures to residues, where there may be an interest in monitoring residues at concentrations below the MRLVD, or when conducting residue analyses for substances which do not have ADIs or MRLVDs. For monitoring compliance with an MRLVD, it is important that a LCL be included in the analysis which adequately demonstrates that the MRL concentration may be reliably determined. The LCL of a method used to support an MRLVD should not be less than the LOQ. The Procedural Manual recommends the term *determination limit* under "Terms to be Used in the Criteria Approach"[13].

Performance Characteristics for Confirmatory Methods

216. *Selectivity*, the ability of the method to unequivocally identify a signal response as being exclusively related to a specific compound, is the primary consideration for confirmatory methods**.** Certain instrumental techniques such as Fourier transform infrared spectroscopy or mass spectrometry may be sufficiently selective to provide unambiguous identification. These are often the techniques on which confirmatory methods are based.

217. Typically, a minimum of four identification points is required to meet accepted performance criteria for regulatory methods. Methods based on high resolution mass spectrometry are considered to give a higher reliability through more precise measurement of mass than can be obtained using low resolution mass spectrometry techniques. Method performance requirements for confirmatory methods based on low resolution GC/MS and LC/MS, as recently published by an international expert body[18], are given in Table 4.

Table 4: Performance requirements for relative ion intensities (sample compared to standard) using various mass spectrometric analytical techniques[15]

Relative ion intensity (% of base peak)	**GC-MS (EI) (relative)**	**GC-MS (CI), GC-MS/MS LC-MS, LC-MS/MS (relative)**
>50%	≤10%	≤20%
20% to 50%	≤15%	≤25%
10% to 20%	≤20%	≤30%

[17] Miller, J.C., & Miller, J.N. (1993) Statistics for Analytical Chemistry, 3rd Edition, Ellis Horwood Ltd., Chichester.
[18] Bethem, R., Boison, J.O., Gale, J., Heller, D., Lehotay, S., Loo, J., Musser, S., Price, P., and Stein, S. (2003) Establishing the Fitness for Purpose of Mass Spectrometric methods. *Journal of the American Society for Mass Spectrometry* **14:** 528-541.

218. It is considered that one identification point should be assigned to each structurally significant ion fragment detected using a low resolution mass spectrometric method. When a tandem low resolution instrument, such as a "triple quadrupole" mass spectrometer is used, secondary fragments are detected from a primary fragment that is isolated in the first stage of the spectrometer. The fact that these structurally significant fragments are produced from the fragmentation of a major fragment (parent or precursor ion) associated with the molecule provides greater confidence and each such daughter or product ion is assigned a value of 1.5 identification points. A combination of a precursor ion and two product ions provides the 4 required identification points when low resolution MS/MS instruments are used in a confirmatory method.

219. Additional confidence is provided when high resolution mass spectrometers are used in a confirmatory method, as the high resolution provides more precise identification of the mass and may be used to predict the elemental composition of each fragment. For a single high resolution mass spectrometer, each structurally significant fragment detected is assigned a value of two identification points, while product ions generated in high resolution MS/MS experiments are assigned an identification point value of 2.5 each. In addition, at least one ion ratio must also be measured to eliminate the potential for fragments of the same mass arising from isobaric compounds of similar structure.

220. Other techniques, when they are used in combination, may be capable of achieving a comparable degree of selectivity as confirmatory techniques. For example, identification may be verified by combinations of methods such as:

(a) thin layer chromatography;

(b) element-specific gas-liquid chromatography and accompanying detection systems;

(c) formation of characteristic derivatives followed by additional chromatography; or

(d) determining compound specific relative retention times using several chromatographic systems of differing polarity.

221. Such procedures must be applicable at the designated MRLVD of the analyte. When a confirmatory method such as mass spectrometry is not available, information on the selectivity associated with the analysis of a particular veterinary drug residue in a sample may be developed from various sources[19]. This information may be captured in a structured logging document of all the information that leads to the conclusion a method has detected a particular compound in a sample, at a measured concentration as reported. While no single measurement or analysis may provide the unequivocal proof of compound identity and/or quantity present that is desired, the combined information that has been compiled provides evidence that the analyst has made a conscientious effort to arrive at a logical result consistent with the data and other information available. Examples of analytical techniques which may be suitable to meet criteria for confirmatory analytical methods are summarized in Table 5.

Table 5. Examples of detection methods suitable for the confirmatory analysis of substances, as recommended by the Miskolc Consultation[15]

Detection method	*Criterion*
LC or GC and Mass Spectrometry	if sufficient number of fragment ions are monitored
LC-DAD	if the UV spectrum is characteristic
LC – fluorescence	in combination with other techniques
2-D TLC – (spectrophotometry)	in combination with other techniques
GC-ECD, NPD, FPD	only if combined with two or more separation techniques[a]
Derivatisation	if it was not the first choice method
LC-immunogram	in combination with other techniques
LC-UV/VIS (single wavelength)	in combination with other techniques

[a] Other chromatographic systems (applying stationary and/or mobile phases of different selectivity) or other techniques.

[19] Stephany, R.W. (2003). SPECLOG – The Specificity Log. CRD-9, Codex Committee on Residues of Veterinary Drugs in Foods, 14th Session, Arlington, VA., U.S.A., March 4-7.

222. Although confirmatory methods are generally instrumental procedures, observation of a pathologic or other morphologic change that specifically identifies exposure to a class of veterinary drugs, could potentially be a confirmatory method, if it has sufficient sensitivity and precision.

General Performance Characteristics for Methods for Use in a Regulatory Control Programme

223. There are some additional considerations for selection of suitable methods for use in a regulatory control programme for veterinary drug residues in foods. Methods should be rugged (robust), cost effective, relatively uncomplicated, portable, and capable of simultaneously handling a set of samples in a time effective manner. The stability of analytes must also be established.

224. *Ruggedness* testing should be conducted using the standard factorial design approach to determine any critical control points[20]. Typical factors to include 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 of a confirmatory method may be required if the method differs significantly from the quantitative method previously validated (if the method uses different extraction or derivatisation procedures than are used in the quantitative method).

225. *Cost-effectiveness* is the use of reagents and supplies which 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 analysed 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 analysed 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.

226. *Analyte stability* during analysis must be established for both standards and analyte in the presence of sample material, during processing through the complete analysis for all methods used in a regulatory control programme and for typical conditions of storage while a sample is awaiting analysis. The period chosen for stability during storage should cover the expected time when sample material may be stored for all required analyses, including the use of the screening, quantitative, and confirmatory methods. It is prudent to conduct the storage study for a period which extends to at least 90 days beyond the expected time for all screening, quantitative, and confirmatory analyses to be completed and the results reported in case there is a challenge and a request for re-analysis.

Method development and validation considerations for residue control methods

Selection of Appropriate Test Material for Validation

227. Laboratories must demonstrate that the methods in use for analysis of regulatory samples have been suitably validated. Traditionally, the multi-laboratory method validation study has been the preferred approach to provide analytical data to define method performance characteristics. However, other models have been developed which include multi-laboratory trials with smaller numbers of laboratories than are required to conduct a full collaborative study and single laboratory validation based on rigorous in-house evaluation of method performance, supported by a quality system, independent audits and analysis of proficiency or reference materials, when available.

228. In developing and validating a residue control method, data should be derived from three types of sample material. Control test material from non-treated animals provides information about analytical background and matrix interferences. Fortified test material, containing known amounts of the analyte added to the control material, yields information about the method's ability to recover the analyte of interest under controlled conditions. Tissues should be obtained from multiple sources to cover the variations resulting from factors such as different diets, husbandry practices, sex, and breed of animals. A minimum of six different sources of material is recommended.

[20] Youden, W.J., & Steiner, E.H. (1975) *Statistical Manual of the Association of Official Analytical Chemists*, AOAC International, Gaithersburg, VA.

229. In some instances, known drug free sample materials may not be available for use in residue control laboratories. In these instances an equivalent sample material may be used. Equivalent sample materials may consist of either the same matrix as the test sample matrix from an unknown source, or a different matrix from a known drug free source that closely matches the sample matrix. In all cases, the residue control laboratory must demonstrate that the equivalent sample material is free from interferences for the drug and exhibits satisfactory recovery for fortified samples. Additionally, when a material is used from an unknown source for quantitative or screening methods, it is recommended that a second method be used to demonstrate that the matrix does not contain residues of the drug. It is the responsibility of the residue control laboratory to demonstrate fitness for purpose of the equivalent sample material.

230. Finally, analysis of biologically incurred tissue from food producing animals that have been treated with the drug provides information about biological or other interactions that may occur when analysing residue control samples.

Measurement Uncertainty

231. Laboratories should provide their customers on request with information on the measurement uncertainty or statement of confidence associated with the quantitative results produced by each quantitative method. Guidance on estimation of measurement uncertainty is being developed by IUPAC and has been published by other independent scientific bodies[21].

Use of Internal Standards

232. Residue methods are sometimes designed using internal standards for analytical control. A properly used internal standard will compensate for some of the analytical variability of an analysis, improving precision. However, an improperly used internal standard may obscure variables that are an important part of the analytical measurement. If an internal standard is used, it should be added to a sample as early as possible in the procedure, preferably to the test material before analysis begins. The internal standard must reflect the recovery of the target analyte in a uniform and predictable fashion. An internal standard that does not mirror the behaviour of the target analyte in the method will lead to significant errors in calculation of the final result. Caution must be taken in the choice of internal standards to ensure that they do not alter the percent recovery of the analyte of interest or interfere with the measurement process. It is important to know the extent and predictability of the effects of the internal standard on an analytical method. Internal standards can greatly enhance method performance when used properly.

Environmental Considerations

233. If residue control methods may be subjected to widely variable physical test environments, this should be taken into account in the development and validation of these methods. Addressing these issues may help improve method ruggedness. Warmer environments may require reagents to be more thermally stable, while solvents used in the analysis will have to be less volatile and test sample requirements to be more tolerant. Cooler environments may require reagents and solvents to have different physical properties, such as lower freezing point and greater solvating characteristics, to provide effective extraction of an analyte. Environmental temperatures may influence the time required to perform an analysis, as well as influencing reaction rates, gravitational separations, and colour development. These considerations may strain efforts to standardize methods for use in broadly differing environments because of the need to adapt methods to compensate for these factors. It is important when considering the physical environment in which a method will be used to remember that volumetric glassware and many analytical instruments are calibrated to be used at specific temperatures, or within a controlled range of temperature. Operation outside these temperatures may compromise test results.

[21] EURACHEM/CITAC Guide to Quantifying Measurement Uncertainty in Analytical Measurement, http://www.measurementuncertainty.org/mu/guide/index.html, accessed 18 September, 2007.

Choice of Validation Model

234. An analytical method developed and used in only one laboratory may have limited use in a residue control programme unless care is taken to meet the rigorous expectations for single laboratory method validation associated with accreditation under ISO/IEC-17025 or equivalent accreditation procedures for testing laboratories. The reliability of reported values may be a concern even though strong quality control procedures may have been employed, unless supported by data from an on-going proficiency programme, comparison with a suitable method validated in an inter-laboratory trial or other forms of inter-laboratory comparison of results. Ideally, a method should be validated by at least three laboratories. Methods which have been carefully validated in a single laboratory with inclusion of properly designed ruggedness tests should be able to successfully undergo a collaborative study involving at least eight different laboratories.

235. The principles for conducting a single laboratory method validation, a multi-laboratory method trial or a collaborative study of a residue control method are the same. Samples for evaluating method performance should be unknown to the analyst, in randomised replicates, containing the residue near the MRLVD or other target concentration, as well as samples with the analyte above and below the concentration of interest, and test material blanks. All study samples should be analysed over a minimum number of days, preferably with replicate analysis, to improve statistical evaluation of method performance and provide an estimate of inter-day variability. It should be noted that these are only minimal requirements. The establishment of statistically-based performance standards for methods is enhanced by increasing the number of independent analysts and laboratories testing the method, as well as by the number of samples tested. In a single-laboratory validation, it is recommended that the method should be tested by multiple analysts to provide appropriate measures of within-laboratory performance. Expanding the validation to include other laboratories, preferably to the number required for a collaborative study, is recommended. Analyses of blind duplicates, as required in the collaborative study protocol[7] in only eight laboratories, with one or two animal species and tissues, yields limited quality estimates for overall repeatability and reproducibility. The validation of a collaboratively studied method can be extended to include additional tissues and species in a subsequent study conducted by a single expert laboratory, as required.

Quality Control and Quality Assurance

236. Quality control and quality assurance principles are essential components of residue analysis. They provide the basis for ensuring optimum method performance for all methods, regardless of method attributes, whenever they are used. Quality control monitors those factors associated with the analysis of a sample by a tester, while quality assurance provides the oversight by independent reviewers to ensure that the analytical programme is performing in an acceptable manner. Quality control and quality assurance programmes are invaluable to support decision-making for residue control agencies, improving the reliability of analytical results, and providing quality data for residue control programmes to demonstrate food safety to consumers, producers, and law making bodies regarding residues of veterinary drugs in food. The establishment of quality measures consistent with the principles published by IUPAC is recommended for regulatory control laboratories.

Appendix VII

PRIORITY LIST OF VETERINARY DRUGS FOR EVALUATION OR RE-EVALUATION BY JECFA

Name of the Compound	Questions(s) to be answered	Data Availability	Proposed by	Comments
Dexamethasone	Request to recommend MRLs in cattle (tissues, milk); horses (tissues) and pigs (tissues).	Canada will have a method of analysis for the determination of dexamethasone available by the end of 2007.	Canada	Sweden also has a method.
Tylosin	Request to establish ADI and recommend MRLs in poultry (tissues, eggs); pigs (tissues); cattle (tissues); and honey.	The company confirmed they can provide the necessary data by the end of 2007. The Republic of Korea confirmed that they will provide specific data by January 2008.	Germany IFAH	Previously evaluated by JECFA 1968, 1991, 2006.
Avilamycin	Request to establish ADI and recommend MRLs in poultry (tissues); pigs (tissues) and rabbit (tissues).	The company has advised that toxicological and residue data for poultry, pigs and rabbit will be provided by January 2008.	Brazil IFAH	Not previously evaluated by JECFA.
Malachite Green	Request to JECFA to consider a literature review and advise if this substance can be supported for use in food producing animals.	Germany has provided a preliminary literature review on the "Risk assessment of Malachite Green residues" for evaluation by JECFA. A complete literature review will be available by January 2008.	Germany	Not previously evaluated by JECFA.
Tilmicosin	Request to recommend MRLs in sheep (milk), poultry (tissues and eggs).	Company has advised that residue data for cattle milk will be provided as a surrogate for sheep milk. Residue data will be provided by January 2008.	United States	Previously evaluated by JECFA 1996, 2000.
Monensin	Request to establish ADI and recommend MRLs in cattle, goats, sheep (tissues and milk); poultry (tissues and eggs).	Company has advised that toxicological and residue data for these will be provided by January 2008.	United States IFAH	Not previously evaluated by JECFA.
Narasin	Request to establish ADI and recommend MRLs in poultry, pigs and cattle (tissues).	Company has advised that toxicological and residue data for these will be provided by January 2008.	United States IFAH	Not previously evaluated by JECFA.
Triclabendazole	Request to re-evaluate MRLs in cattle and sheep tissues.	Company has advised that new residues data to be made available. To be confirmed by Australia.	Australia	Previously evaluated by JECFA 1992, 2006.
Melengestrol acetate	To address concern raised by the European Community.	January 2008.	European Community	Provided these concerns are submitted with detailed data

Appendix VIII

PROJECT DOCUMENT

Proposal of new work for the development of risk management recommendations/guidance for veterinary drugs for which no ADI and MRL has been recommended by JECFA due to specific human health concerns

Purpose and scope of the standard

To provide risk management advice to national and regional authorities on substances for which acceptable daily intakes (ADI) and maximum residue limits (MRL) cannot be recommended.

Relevance and timeliness

For certain veterinary drugs, JECFA was not able to propose an ADI and MRL due to specific human health concerns (e.g. toxicity to the human consumer, carcinogenicity). It is therefore proposed that CCRVDF should take risk management decisions on those veterinary drugs in order to provide risk management guidance to Codex members. The objective is to protect consumers from residues of these veterinary drugs and to ensure a smoother functioning of international trade.

Various Codex members appreciate the health concerns and thus prohibit the use in food producing animals of respective veterinary drugs. However, discrepancies in application exist between Codex members hampering international food trade. International standardisation would therefore improve consumer protection and facilitate international trade in food. Clear risk management guidance by Codex would be particularly helpful for developing countries.

Main aspects to be covered

The objective of the new work is to develop specific recommendations/guidance on veterinary drugs for which no ADI and MRL has been recommended by JECFA due to specific human health concerns.

The outcome of this proposal is not to establish a negative list, but to develop risk management recommendations. These recommendations may also suggest the use of substances with no ADI/MRL if their unavailability creates animal health concern.

This will consist of:

- identifying the veterinary drugs for which no ADI and MRL has been recommended by JECFA due to specific human health concerns;
- summarising the specific concerns identified by JECFA for each of those veterinary drugs.
- agreeing which veterinary drugs should not be used in food producing animals due to human health concerns related to their residues in food and provide respective guidance to Codex members;
- consider options for communicating risk management recommendations on such substances.

Example:

Chloramphenicol was evaluated by the 42nd and 62nd JECFA meetings. JECFA was unable to set an ADI or recommend an MRL because of specific concerns about human health, i.e. aplastic anaemia and carcinogenicity. Therefore, CCRVDF recommends that chloramphenicol should not be used in food producing animals.

Assessment against the Criteria for the Establishment of Work Priorities

This proposal is consistent with the Criteria for the Establishment of Work Priorities. These recommendations will aim at ensuring better consumer protection from the point of view of health and food safety and fair practices in the international food trade.

In addition, the following criteria are also relevant:

- diversification of national legislations and apparent resultant or potential impediments to international trade;

- such work has not already been undertaken by other international organisations;
- volume of consumption in individual countries and volume and pattern of trade between countries of concerned food products.

Relevance to the Codex Strategic Objectives

This proposal is congruent with the Codex Strategic Objectives 1 and 2.

Objective 1: Promoting Sound Regulatory Framework

This proposal will provide essential guidance for member countries and promote the development of national food control systems based on international principles and criteria for the reduction of health risk along the entire food chain.

Objective 2: Promoting Widest and Consistent Application of Scientific Principles and Risk Analysis

JECFA strictly follows the principles of risk analysis as regards risk assessment of veterinary drugs. Development of international standardisation on veterinary drugs proposed to be prohibited in food producing animals would promote the consistent application of risk analysis principles by Codex members in line with the Working principles for Risk Analysis developed by Codex.

Information on the relation between the proposal and other existing Codex documents

This guidance provided to Codex members will complement the MRL for veterinary drugs already adopted by the CCRVDF.

Identification of any requirement for and availability of expert scientific advice

These risk management recommendations/guidance will take into account evaluations made by JECFA and revised accordingly in the future.

Identification of any need for technical input to the standard from external bodies so that this can be planned for

None.

Proposed time-line for completion of the new work, including the start date, the proposed date for adoption at step 5, and the proposed date for adoption by the Commission

- Circulation of a proposal elaborated by a working group at step 3 after adoption of new work by the CAC;
- Consideration of the proposed draft at the 18th Session of CCRVDF;
- Adoption at Step 5 by the following CAC;
- Consideration of the proposal at the 19th Session of CCRVDF;
- Final adoption by the following CAC.